ACTEMRA®
tocilizumab

Ami 向医生咨询了使用 *ACTEMRA* 治疗类风湿性关节炎 *(RA)* 的事宜。

ACTEMRA 对您的 RA 有什么作用?

无论是否与甲氨蝶呤 (MTX) 联用, ACTEMRA 都可以治疗您的 RA。如需了解更多信息, 请参阅内页。

ACTEMRA 可用于治疗哪些疾病?

ACTEMRA 是一种名为白细胞介素-6 (IL-6) 受体拮抗剂的处方药。

ACTEMRA 用于治疗中度至重度活动性类风湿性关节炎 (RA) 成人患者, 在此药面世之前, 患者至少使用过另一种名为慢作用抗风湿药, 但效果不佳。

重要副作用信息

ACTEMRA 可能导致严重的副作用

严重感染

ACTEMRA 会改变免疫系统的作用方式。这种作用方式可能使您更易受到感染, 或使目前的感染变得更严重。有些人已死于这些感染。您的医疗保健服务提供者应在您开始使用 ACTEMRA 治疗之前、治疗期间及治疗之后评估您是否患有结核病 (TB)。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

ACTEMRA 是否对您适用?

治疗中度至重度类风湿性关节炎 (RA) 是一项挑战。如果您上一次的治疗没有获得预期的效果，本手册将为您提供有关 ACTEMRA 的重要信息，可能对您的下一步治疗有所帮助。

您可以了解在使用或不使用慢作用抗风湿药 (DMARD)（如 MTX）的情况下，ACTEMRA 的治疗效果。

如需了解 ACTEMRA 临床试验结果的信息，请参阅第 16-17 页。

在本手册中，您将了解：

- **ACTEMRA 如何帮助缓解症状**
- **ACTEMRA 的给药方式（输液或注射）**
- **如何使用 ACTPen® 自动注射器**
- **临床试验结果**
- **治疗须知**
- **重要副作用信息**
- **ACTEMRA 费用支付选项**

重要副作用信息（续）

严重感染

ACTEMRA 会改变免疫系统的作用方式。这种作用方式可能使您更易受到感染，或使目前的感染变得更严重。有些人已死于这些感染。您的医疗保健服务提供者应在您开始使用 ACTEMRA 治疗之前、治疗期间及治疗之后评估您是否患有结核病 (TB)。

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如果您的 RA 治疗无效，
请咨询医疗保健专业人员，了解使用 ACTEMRA 的风险和益处。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

ACTEMRA 如何帮助缓解 RA 症状?

您可以看到什么样的效果?

使用 ACTEMRA 治疗中度至重度 RA 有利于:

- **减轻** RA 的体征和症状
- **减轻**关节肿胀和压痛
- 与 DMARD 联合用药时, **减缓**关节损伤
- 使部分 RA 患者的日常生活活动**更轻松**

如需了解 ACTEMRA 临床试验结果的信息, 请参阅第 16-17 页。

"我一直有关节肿胀和疼痛的问题, 在使用 ACTEMRA 几个月后, 发现肿胀减轻了。"

"我发现以前无法弯曲的手指现在又可以弯曲了……这让我备受鼓舞, 尤其是在治疗初期就看到了这些效果。"

"这些效果让我对继续接受 ACTEMRA 治疗充满期待。"

Ami 已使用 *ACTEMRA* 治疗她的 *RA*。
个人疗效可能有所不同。

重要副作用信息(续)

在开始 ACTEMRA 治疗之前, 请告知您的医疗保健服务提供者是否有以下情况:

- 感染, 认为自己可能受到感染, 正在接受感染治疗, 或大量感染复发。感染的症状(伴或不伴发热)包括出汗或发冷; 呼吸急促; 皮肤发热、发红或疼痛, 或身体出现溃疡; 感觉非常疲惫; 肌肉酸痛; 痰中带血; 腹泻或胃痛; 咳嗽; 体重减轻; 排尿时有烧灼感或尿频

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用 ACTEMRA 靶向治疗炎症的关键驱动因素

ACTEMRA 的据信作用方式?

要了解 ACTEMRA 的据信作用方式, 需要先了解什么是白细胞介素-6 (IL-6)。

IL-6 是一种信使, 它向免疫系统传达攻击有害细菌和病毒的信息。当人体产生过多的 IL-6 时, 会导致免疫系统攻击健康细胞, 并可能导致 RA 体征和症状。

ACTEMRA 旨在阻止 IL-6 激活免疫系统进行攻击。

ACTEMRA 靶向一种称为 IL-6 的关键炎症源。

重要副作用信息(续)

如果您有以下情况, 请在开始 ACTEMRA 治疗之前告知医疗保健服务提供者(续):

- 患有以下任何可能会增加感染几率的病症:糖尿病、艾滋病或免疫系统虚弱
- 患有结核病 (TB), 或与结核病患者有过密切接触
- 在美国某些地区居住或有这些地区的居住史或旅行史, 在这些地区感染真菌的几率会增加。这些地区包括俄亥俄河流域、密西西比河流域和西南部地区
- 患有乙型肝炎或曾患乙型肝炎

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

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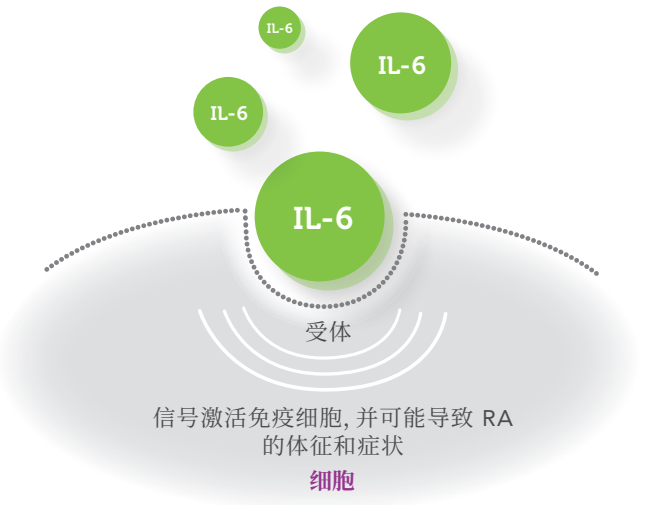
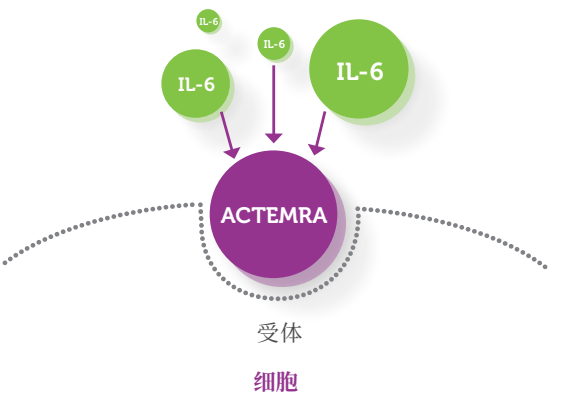
不使用 ACTEMRA

IL-6 结合免疫细胞, 并向它们传达激活信号。当这些细胞激活时, 可能会导致 RA 的体征和症状。



使用 ACTEMRA

ACTEMRA 阻断 IL-6 与细胞的结合。



ACTEMRA 的据信作用方式由早期研究提出。目前尚不清楚它在体内的确切作用原理。

ACTEMRA 有哪些不同的给药方式?

ACTEMRA 针对中度至重度 RA 症状提供了多种治疗选择。这些选择使您能够以最适合您的方式接受药物治疗。

ACTEMRA 的给药方式包括:

静脉 (IV) 输液

液体药物, 通过针头注入静脉。在医疗保健专业人员办公室或输液中心进行给药。

皮下 (SC) 注射

皮下注射药物。由患者本人或看护者居家进行给药。ACTEMRA SC 以预充式注射器或 ACTEMRA ACTPen® 自动注射器的形式提供。

- ACTEMRA 预充式注射器是一种单剂量针头, 可手动注射
- ACTPen 自动注射器是一种预充式、单剂量、笔状自动注射器, 可在注射前保持针尖屏蔽, 并通过按住按钮进行注射

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

ACTEMRA® tocilizumab

无论您倾向于哪种 SC 注射装置, 使用的 ACTEMRA 药物均相同

预充式注射器

非实际尺寸。

ACTPen 自动注射器

非实际尺寸。

针帽 (覆盖针头护罩)　窗口区域　"激活"按钮

医疗保健专业人员将为您提供如何正确注射 ACTEMRA 的培训。您也可以参阅《使用说明》, 逐步了解如何使用预充式注射器或 ACTPen 自动注射器。

如需观看 ACTPen 自动注射器的分步视频指南, 请扫描二维码。

有关如何使用 ACTPen 自动注射器的快速参考指南, 请参阅第 10-13 页。

重要副作用信息(续)

哪些患者不能使用 ACTEMRA?

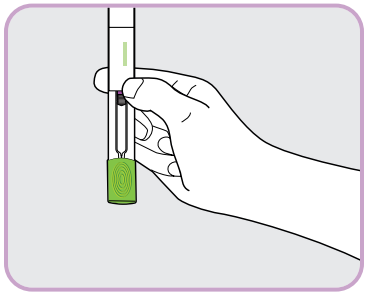
如果您对托珠单抗或 ACTEMRA 中的任何成分过敏, 请勿使用 ACTEMRA。

ACTPen® 自动注射器

快速参考指南

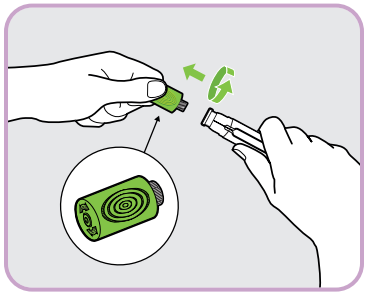
ACTEMRA® tocilizumab

当您熟练掌握使用说明中的步骤后，可在注射前使用本摘要作为快速参考。



1 注射前的准备工作

将 ACTPen 自动注射器从冰箱中取出，预热 45 分钟直至达到室温。检查装置。液体应为澄清的无色至浅黄色液体。如果 ACTPen 自动注射器出现损坏或意外掉落，**请勿**使用。



2 扭动并拔掉针帽

准备注射时取下针帽。ACTPen 自动注射器应在 3 分钟内完成使用或丢弃。开始注射之前，针头会隐藏起来。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

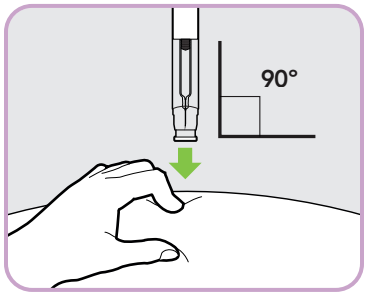
重要副作用信息（续）

如果发现以下严重副作用的迹象，请务必咨询医疗保健服务提供者：

胃或肠撕裂（穿孔）

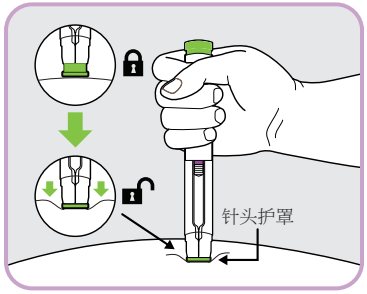
如果您患有憩室炎（大肠部分炎症），请在使用 ACTEMRA 之前咨询您的医疗保健服务提供者。某些患者在使用 ACTEMRA 后，胃壁或肠壁会出现破洞（也称为穿孔）。这种情况最常发生于同时使用非甾体类抗炎药 (NSAID)、皮质类固醇或甲氨蝶呤的患者。

如果您出现以下任何副作用，请立即告知医疗保健服务提供者：发热、新发作的胃部疼痛持续不退，或排便习惯发生变化。



3 提捏进针

选择注射 ACTEMRA 的身体部位。此部位称为注射部位(如需了解推荐的注射部位, 请参阅使用说明中的步骤 2 图 D)。轻轻捏住注射部位的皮肤。将 ACTPen 自动注射器与捏住的皮肤成 90° 角。在进行步骤 5 之前, 请勿按压"激活"按钮。
准备注射时, 请在注射过程中继续捏住皮肤。

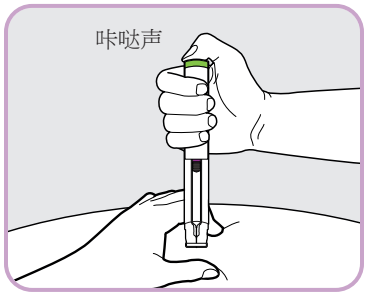


4 按压解锁

在不按住"激活"按钮的情况下, 向下推动 ACTPen 自动注射器, 直到针头护罩完全压紧捏住的皮肤。这将解锁"激活"按钮。请将 ACTPen 自动注射器牢牢固定在此位置。

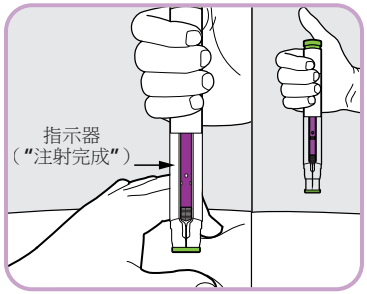
重要副作用信息(续)
肝脏问题(肝毒性)

有些人的肝脏出现严重问题, 危及生命, 需要进行肝移植, 或导致死亡。



5 皮下注射 ACTEMRA

按下"激活"按钮。"咔哒"声表示开始注射。在整个注射过程中按住按钮。注射可能需要 10 秒才能完成。



6 观察并松开

即使听到第二次"咔哒"声, 仍应紧紧握住 ACTPen 自动注射器将其保持在原位, 直到窗口区域的指示器停止移动。将自动注射器从注射部位直接提起并松开"激活"按钮。针头护罩将向下移动, 覆盖针头。

7 丢弃

注射完成后, 请将 ACTPen 自动注射器弃置于锐器容器中。请勿将针帽放回 ACTPen 自动注射器上。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

ACTPen® 自动注射器

给药注意事项

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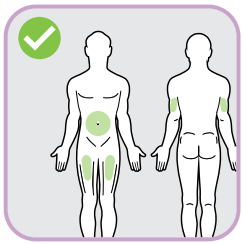
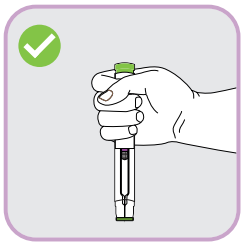
以下提示将帮助您明确如何使用 ACTPen 自动注射器。有关给药的详细信息，请参阅使用说明。

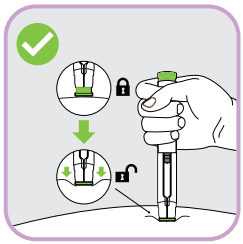
正确操作



每次注射时，**应**选择不同的注射部位。每个新注射部位应距离上次注射部位至少 1 英寸（2.5 厘米）。



应将一只手舒适地握住 ACTPen 自动注射器的上部，以便观察窗口区域。



应将 ACTPen 自动注射器的针头护罩以 90° 角紧贴捏住的皮肤，直到针头护罩完全推入。此操作将解锁“激活”按钮。

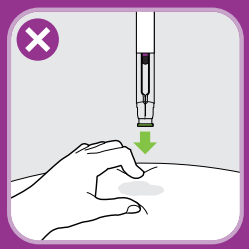
请在 ACTPen 自动注射器紧贴皮肤时按下“激活”按钮。保持自动注射器不动，直到指示器停止移动。

重要副作用信息（续）

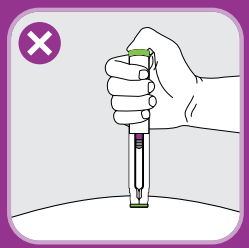
肝脏问题（肝毒性）（续）

如果您在使用 ACTEMRA 治疗期间出现新的或恶化的肝脏问题，医疗保健服务提供者可能会让您停止使用 ACTEMRA。

错误操作

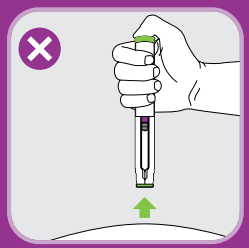


请勿注射到痣、疤痕、瘀伤或皮肤柔嫩、发红、坚硬或不完整的部位。



当自动注射器紧贴皮肤时，**请勿**从自动注射器顶部向下按压或按下**“**激活**”**按钮。

在针头护罩完全紧贴捏住的皮肤之前，**请勿**按下**“**激活**”**按钮。



注射前，**请勿**将针头护罩从皮肤上提起，否则**“**激活**”**按钮将不起作用。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

有证据证明 ACTEMRA 的有效性吗?

在一项临床研究中, 中度至重度 RA 患者接受了 ACTEMRA IV 或 MTX (DMARD) 治疗, 以比较每种治疗减轻症状的效果。

经证实, ACTEMRA IV 可以缓解 RA 症状

接受 ACTEMRA IV 治疗的 10 名患者中, 7 名患者的 RA 症状(也称为 ACR20 反应)**至少改善了 20%** , 包括关节压痛和肿胀的次数减少。

接受 MTX 治疗的 **10 名患者中, 约 5 名患者的**关节压痛和肿胀以及其他 **RA** 症状**至少改善了 20%**。

个人疗效可能有所不同。

重要副作用信息(续)

肝脏问题(肝毒性)(续)

如果出现以下任何症状, 请立即告知医疗保健服务提供者:

- 感到疲惫(疲劳)
- 持续数天或更长时间食欲不振(厌食症)
- 皮肤或眼白发黄(黄疸)
- 腹部肿胀和胃部右侧疼痛
- 浅色大便
- 虚弱
- 恶心和呕吐
- 神志不清
- 尿液呈深"茶色"

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ACTEMRA 有可能迅速改善症状

某些接受 ACTEMRA IV 治疗的患者在短短 2 周内症状就开始改善。

研究证明 ACTEMRA SC 与 ACTEMRA IV 同样有效

在另一项研究中, 联用 ACTEMRA SC 和 DMARD 的患者的症状减轻情况与联用 ACTEMRA IV 和 DMARD 的患者相似。

- 在这两个研究组中, 10 名患者中约有 7 名患者的 RA 症状改善了 20%

此外, 研究还证明 ACTEMRA 对以往接受过生物制剂治疗的患者有效。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

了解您的剂量

ACTEMRA
tocilizumab

如果您和您的医疗保健专业人员决定使用 ACTEMRA, 请务必了解 ACTEMRA 的使用剂量及频率。

ACTEMRA 的推荐剂量是多少?

ACTEMRA IV 输液

每月 1 次

ACTEMRA 的推荐起始剂量为 **4 mg/kg*, 每月一次**

每月 1 次

根据您对治疗的反应, 剂量可能会增加到 **8 mg/kg*, 每月一次**

*1 kg=2.2 lb。

IV 输液将持续约 1 小时。

ACTEMRA SC 注射

每 2 周一次

如果您的体重**低于** 220 lb (100 kg): **每 2 周使用 1 个预充式注射器或 ACTEMRA ACTPen® 自动注射器 (162 mg)**

每周 1 次

如果您的体重**为** 220 lb (100 kg) **或以上: 每周使用 1 个预充式注射器或 ACTPen 自动注射器 (162 mg)**

对于开始每 2 周使用 1 个预充式注射器或 ACTPen 自动注射器的患者, 如果未获得所需的效果, 您和医疗保健专业人员可能需要决定将剂量更改为每周使用 1 个预充式注射器或 ACTPen 自动注射器。

ACTEMRA IV 剂量取决于您的体重

医疗保健专业人员会根据您的情况决定您的适用剂量。

如果我的体征和症状持续存在, 该怎么办?

如果您觉得自己没有得到想要的缓解, 请与您的医疗保健专业人员讨论调整剂量。医疗保健专业人员将监测您的症状和实验室检验结果, 了解您对治疗的反应。剂量调整没有固定的时间。根据实验室检验结果, 医生可能会改变您的 ACTEMRA 剂量。

重要副作用信息(续)

血液检查结果的变化

在您开始接受 ACTEMRA 治疗之前, 医疗保健服务提供者应对您进行血液检查。如果您患有类风湿性关节炎 (RA), 医疗保健服务提供者应在您开始接受 ACTEMRA 治疗后的前 6 个月内, 每 4 到 8 周进行一次血液检查, 之后每 3 个月进行一次。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

治疗须知

如果您之前从未接受过输液或注射治疗，您可能想知道会发生什么。以下是治疗前、治疗期间和治疗后会发生的一些事情。

治疗期间的常规血液检查

为了检测肝功能的变化，您的医疗保健专业人员将在治疗开始后的前 6 个月内，每 4 至 8 周对您进行一次血液检查，然后每 3 个月进行一次。此外，他们还将在治疗开始后的前 6 个月内，每 4 至 8 周进行一次中性粒细胞和血小板计数的血液检查，之后每 3 个月进行一次。在首次 ACTEMRA 输液或注射后的 4 至 8 周，医疗保健专业人员还应通过血液检查来检查您的胆固醇水平。

了解您的治疗

在开始 ACTEMRA IV 输液或 ACTEMRA SC 注射之前，了解所有事实非常重要。请务必查看《ACTEMRA 用药指南》（可从 ACTEMRA.com 获取）。请仔细阅读"关于 ACTEMRA，有哪些重要须知？"和"在接受 ACTEMRA 治疗之前，请向医疗保健专业人员告知您的所有医疗状况"部分。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

就诊前称重

由于 ACTEMRA IV 输液剂量取决于您的体重，因此在每次输液之前都需要称重。如果通过 SC 注射 ACTEMRA，医疗保健专业人员应在每次诊室就诊时为您称重。如果您的体重发生变化，您和医疗保健专业人员将决定是否需要改变剂量。

关于 ACTEMRA IV

当需要输液时，您将坐在或斜倚在舒适的椅子上。输液将持续约一小时。

重要副作用信息（续）

血液检查结果的变化（续）

这些血液检查是为了检查 ACTEMRA 的以下副作用：

- 中性粒细胞计数低：中性粒细胞是一类可帮助身体抵抗感染的白细胞
- 血小板计数低：血小板是一类帮助凝血的血细胞，负责止血
- 肝功能检查水平升高
- 血液胆固醇水平升高：应在开始接受 ACTEMRA 治疗后 4 至 8 周检查您的胆固醇水平。

医疗保健服务提供者将决定您接受后续血液检查的频率。请确保按照医疗保健服务提供者的指示完成所有后续血液检查。

治疗须知(续)

关于 ACTEMRA SC

医疗保健专业人员或护士应为您或您的看护者提供如何使用预充式注射器或 ACTEMRA ACTPen® 自动注射器正确正确进行 ACTEMRA SC 注射的培训。在此培训课程中，您或您的看护者应进行 ACTEMRA SC 的首次注射。只有经过适当培训的患者或看护者才能使用 ACTEMRA 预充式注射器或 ACTPen 自动注射器。

监测副作用

在接受输液治疗期间，医疗保健专业人员或护士将对您进行监测。**如果进行 ACTEMRA SC 注射，请务必留意可能出现的副作用。**ACTEMRA 可能导致过敏反应，包括死亡。任何治疗都可能发生这些情况，即使以前没有发生过。如果注射后出现荨麻疹、皮疹或潮红，请在下次用药前告知医疗保健专业人员。**如果出现以下情况，请立即告知医疗保健专业人员或护士，或立即联系 911：**

- 呼吸急促或呼吸困难
- 嘴唇、舌头或面部肿胀
- 胸痛
- 感觉头晕或昏厥
- 中度或重度腹痛或呕吐

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

重要副作用信息

ACTEMRA 可用于治疗哪些疾病?

ACTEMRA 是一种名为白细胞介素-6 (IL-6) 受体拮抗剂的处方药。
ACTEMRA 用于治疗中度至重度活动性类风湿性关节炎 (RA) 成人患者，在此药面世之前，患者至少使用过另一种名为慢作用抗风湿药，但效果不佳。

ACTEMRA 可能导致严重的副作用

严重感染
ACTEMRA 会改变免疫系统的作用方式。这种作用方式可能使您更易受到感染，或使目前的感染变得更严重。有些人已死于这些感染。您的医疗保健服务提供者应在您开始使用 ACTEMRA 治疗之前、治疗期间及治疗之后评估您是否患有结核病 (TB)。

在开始 ACTEMRA 治疗之前，请告知您的医疗保健服务提供者是否有以下情况：

- 感染，认为自己可能受到感染，正在接受感染治疗，或大量感染复发。感染的症状(伴或不伴发热)包括出汗或发冷；呼吸急促；皮肤发热、发红或疼痛，或身体出现溃疡；感觉非常疲惫；肌肉酸痛；痰中带血；腹泻或胃痛；咳嗽；体重减轻；排尿时有烧灼感或尿频
- 患有以下任何可能会增加感染几率的病症：糖尿病、艾滋病或免疫系统虚弱
- 患有结核病 (TB)，或与结核病患者有过密切接触
- 在美国某些地区居住或有这些地区的居住史或旅行史，在这些地区感染真菌的几率会增加。这些地区包括俄亥俄河流域、密西西比河流域和西南部地区
- 患有乙型肝炎或曾患乙型肝炎

ACTEMRA® tocilizumab

重要副作用信息(续)

ACTEMRA® tocilizumab

哪些患者不能使用 ACTEMRA?

如果您对托珠单抗或 ACTEMRA 中的任何成分过敏, 请勿使用 ACTEMRA。

如果发现以下严重副作用的迹象, 请务必咨询医疗保健服务提供者:

胃或肠撕裂(穿孔)

如果您患有憩室炎(大肠部分炎症), 请在使用 ACTEMRA 之前咨询医疗保健服务提供者。某些患者在使用 ACTEMRA 后, 胃壁或肠壁会出现破洞(也称为穿孔)。这种情况最常发生于同时使用非甾体类抗炎药 (NSAID)、皮质类固醇或甲氨蝶呤的患者。

如果您出现以下任何副作用, 请立即告知医疗保健服务提供者: 发热、新发作的胃部疼痛持续不退, 或排便习惯发生变化。

肝脏问题(肝毒性)

有些人的肝脏出现严重问题, 危及生命, 需要进行肝移植, 或导致死亡。如果您在使用 ACTEMRA 治疗期间出现新的或恶化的肝脏问题, 医疗保健服务提供者可能会让您停止使用 ACTEMRA。如果出现以下任何症状, 请立即告知医疗保健服务提供者:

- 感到疲惫(疲劳)
- 持续数天或更长时间食欲不振(厌食症)
- 皮肤或眼白发黄(黄疸)
- 腹部肿胀和胃部右侧疼痛
- 浅色大便
- 虚弱
- 恶心和呕吐
- 神志不清
- 尿液呈深"茶色"

血液检查结果的变化

在您开始接受 ACTEMRA 治疗之前, 医疗保健服务提供者应对您进行血液检查。如果您患有类风湿性关节炎 (RA), 医疗保健服务提供者应在您开始接受 ACTEMRA 治疗后的前 6 个月内, 每 4 到 8 周进行一次血液检查, 之后每 3 个月进行一次血液检查。这些血液检查是为了检查 ACTEMRA 的以下副作用:

- 中性粒细胞计数低: 中性粒细胞是一类可帮助身体抵抗感染的白细胞
- 血小板计数低: 血小板是一类帮助凝血的血细胞, 负责止血
- 肝功能检查水平升高
- 血液胆固醇水平升高: 应在开始接受 ACTEMRA 治疗后 4 至 8 周检查您的胆固醇水平。

医疗保健服务提供者将决定您接受后续血液检查的频率。请确保按照医疗保健服务提供者的指示完成所有后续血液检查。

如果您的中性粒细胞和血小板计数过低, 或肝功能检查水平过高, 则不应接受 ACTEMRA 治疗。血液检查结果的变化可能会导致医疗保健服务提供者暂时停止您的 ACTEMRA 治疗或改变剂量。

癌症

ACTEMRA 可能会改变您的免疫系统的作用方式, 从而增加您罹患某些癌症的风险。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

重要副作用信息(续)

ACTEMRA® tocilizumab

乙型肝炎感染

如果您患有乙型肝炎或为乙型肝炎病毒(一种影响肝脏功能的病毒)的携带者,当您使用 ACTEMRA 时,该病毒可能会变得活跃。在您开始使用 ACTEMRA 治疗之前及治疗期间,医疗保健服务提供者可能会对您进行血液检查。如果出现以下症状的迹象,请告知医疗保健服务提供者:

- 感觉非常疲惫
- 皮肤或眼睛发黄
- 食欲不振或没有食欲
- 呕吐
- 大便呈粘土色
- 发热
- 发冷
- 胃部不适
- 肌肉酸痛
- 尿液呈深色
- 皮疹

严重过敏反应

ACTEMRA 可能导致严重的过敏反应,包括死亡。任何一次 ACTEMRA 输液或注射都可能发生这些反应,即使之前的输液或注射没有发生。如果您出现以下任何严重过敏反应的迹象,应立即停用 ACTEMRA 并联系您的医疗服务提供者,同时寻求紧急帮助:

- 面部、嘴唇、口腔或舌头肿胀
- 呼吸困难
- 喘息
- 严重瘙痒
- 皮疹、荨麻疹、注射部位以外的皮肤发红或肿胀
- 感到头晕或昏厥
- 心跳加快或胸部有心跳剧烈的感觉(心动过速)
- 出汗

神经系统问题

使用 ACTEMRA 的患者被诊断出患有多发性硬化症的情况虽然罕见,但也有发生。

ACTEMRA 最常见的副作用包括:

- 上呼吸道感染(普通感冒、鼻窦感染)
- 头痛
- 血压升高(高血压)
- 注射部位反应

请告知医务人员任何让您感到不适或持续存在的副作用。这些并非 ACTEMRA 可能引起的所有副作用。

ACTEMRA 与妊娠

如果您正在备孕、已经怀孕、计划母乳喂养或正在母乳喂养,请告知医疗保健服务提供者。您和医疗保健服务提供者应决定是使用 ACTEMRA 进行治疗还是进行母乳喂养。两者之间存在冲突。

如果出现任何副作用,请告知医疗保健服务提供者。您可以致电 1-800-FDA-1088 向 FDA 报告副作用。也可以致电 1-888-835-2555 向 Genentech 报告副作用。

请参阅《处方信息和用药指南》全文,包括严重副作用,了解更多重要的安全信息。

帮助支付 ACTEMRA 费用

ACTEMRA tocilizumab

ACTEMRA Access Solutions 致力于帮助您了解您的保险范围和援助选项*†。这可以帮助您获得医生开具的 ACTEMRA。

1 ACTEMRA 共付额计划

您只需支付

5 美元/处方‡

符合条件的商业保险患者每年最多可获得 **15,000 美元的共付额支持**

‡患者最终的自付额可能低至 5 美元，具体可能因患者的健康保险计划而异。符合条件的商业保险患者如获得可用于 FDA 批准用途的 ACTEMRA 处方，每年最多可获得 15,000 美元的药物费用援助。请参阅每个计划的条款和条件。计划限制适用。

请参阅第 30 页了解 ACTEMRA 共付额计划的条款和条件。

*您和您的医生负责填写并向健康保险计划提交所有必要的文件。Genentech 和 ACTEMRA 不保证您的保险计划承保任何治疗。

†Genentech 为患者提供承保范围和报销服务，帮助他们了解补助金额、承保范围和报销条件。Genentech 仅在医疗保健服务提供者开具 Genentech 处方产品后向患者提供这些服务。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

如何开始

请访问 **RACopay.com**

请致电 **855-RA-COPAY (855-722-6729)§**

如何知道您是否符合条件

如果满足以下条件，则可能符合条件：

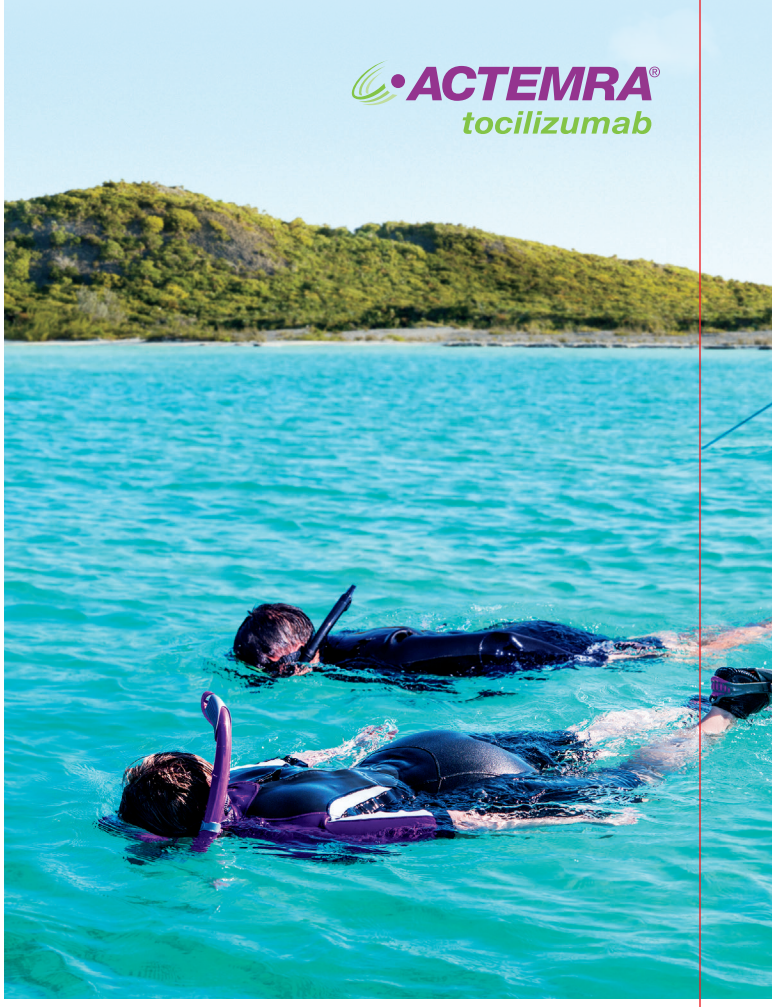
- 正在使用 ACTEMRA 治疗中度至重度 RA
- **年满 18 周岁或有 18 周岁以上的法定监护人来管理该计划**
- 拥有商业（私人或非政府）保险‡
- **没有**使用联邦或州健康保险计划。这包括但不限于 **Medicare、Medicaid、Medigap、VA、DoD 或 TRICARE**
- 目前**没有**从 Genentech 患者基金会 (Genentech Patient Foundation) 或任何独立的共付额援助基金会获得 ACTEMRA 相关帮助
- 在美国或美国领土居住和接受治疗
- **没有**居住在法律禁止该计划的州

§周一至周五，太平洋时间上午 6 点至下午 5 点，重要节假日除外。

†商业保险是您从私人健康保险公司获得的保险计划。可以是您工作单位提供的保险，也可以是您自己购买的保险计划，还可以是健康保险市场（例如 HealthCare.gov）提供的保险。Medicare 和 Medicaid 不属于商业保险。

ACTEMRA 共付额计划可以帮助符合条件的商业保险患者支付药物费用。本计划仅帮助支付 ACTEMRA 的费用。不帮助患者支付与 ACTEMRA 同时使用的其他药物的费用或设施费用。

帮助支付 ACTEMRA 费用（续）



ACTEMRA 共付额计划条款和条件

- 共付额计划仅对拥有商业（私人或非政府）保险且获得用于经美国食品药品监督管理局 (FDA) 批准的 Genentech 药物适应症的有效处方的患者有效。使用 Medicare、Medicaid 或任何其他联邦或州政府计划（统称为“政府计划”）支付其 Genentech 药物费用的患者不符合条件。

- 根据该计划，患者可支付共付额。患者最终支付的 Genentech 药物费用可能低至 0 美元（请参阅该计划的具体细节）。患者自付费用总额取决于患者的健康保险计划。该计划仅对 Genentech 药物的费用进行援助，不帮助支付其他药物、手术或诊病费用。在达到该计划的年度最高补助金额后，患者将自行承担所有剩余的自付费用。该计划补助金额不得超过患者自付的 Genentech 药物相关费用。

- 所有参与者均有责任按照保险公司或法律的要求报告所有该计划补助的领取情况。该计划仅在美国和美国领土有效，在法律禁止的情况下无效，在适用情况下，应遵守各州对 AB 级等效仿制药的相关限制（如马萨诸塞州、加利福尼亚州）。任何一方均不得要求报销通过该计划获得的全部或任何部分补助。该计划面向患者。只有使用该计划的患者才能获得通过该计划提供的资金。该计划不适用于减少患者可用金额或将部分金额用于自身目的的第三方。如果患者的健康计划将 Genentech 计划的援助转用于患者自付费用，则可能需要接受替代的计划补助结构。Genentech 保留随时取消、撤销或修改该计划的权利，恕不另行通知。

- 附加条款和条件适用。请访问 RAcopay.com 查看条款和条件的完整列表。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

帮助支付 ACTEMRA 费用（续）

2 独立的共付额援助基金会*

如果您需要 ACTEMRA 共付额方面的帮助， ACTEMRA Access Solutions 可将您转介给独立的共付额援助基金会。独立的共付额援助基金会为患者提供公共或商业健康保险方面的帮助。

3 Genentech 患者基金会†

Genentech 患者基金会**为没有保险**或有财务问题并符合资格要求**的患者免费提供 ACTEMRA**。

如需了解更多信息：

请致电 **1-800-ACTEMRA (1-800-228-3672)**

请访问 **Genentech-Access.com/ACTEMRA/patients**

*独立的共付额援助基金会有自己的资格评定规则。Genentech 不参与或影响独立的基金会决策或资格评定标准，也不清楚基金会是否能够为您提供帮助。我们只能将您转介给支持您疾病状态的基金会。Genentech 不宣传或偏向任何特定基金会。我们将您转介给的基金会可能不是唯一能够为您提供帮助的基金会。

†如果您拥有健康保险，应尝试获得其他类型的经济援助（如有）。您还需要满足收入要求。如果您没有保险，或者您使用的 Genentech 药物不属于您所购买保险的承保范围，则必须满足一组不同的收入要求。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

请致电 1-800-ACTEMRA (1-800-228-3672), 获取免费的 ACTEMRA 旅行包和锐器容器

旅行包包括一个可冷冻的冰袋和一张 TSA 卡, 在您携带 ACTEMRA 旅行时可能会有所帮助。

ACTEMRA® tocilizumab

向您的医生咨询具有十多年应用历史的治疗选择

ACTEMRA 已在数千名患者身上进行了长达十多年的研究, 这些患者服用 ACTEMRA 来治疗美国 FDA 批准的多种疾病。

10+
年的研究

20+
项关键临床研究*

1,600,000+
全球治疗人数†

*包括 FDA 批准的用于 RA 以外疾病的使用途径。
†根据托珠单抗定期收益-风险评估报告 (PBRER)。1,600,000+ 这一数字包括截至 2020 年 4 月 10 日, 在临床试验期间和市场环境中接受治疗的患者。在市场环境中接受治疗的患者数量根据产品销量估算得出。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息, 请参阅随附的《处方信息和用药指南》全文。

立即向医生咨询，了解 ACTEMRA 是否有助于缓解您的 RA 症状

如需了解有关 ACTEMRA 的更多信息，请访问 **ACTEMRA.com**，或致电 **1-800-ACTEMRA**。

重要副作用信息

ACTEMRA 可能导致严重的副作用
严重感染
ACTEMRA 会改变免疫系统的作用方式。这种作用方式可能使您更易受到感染，或使目前的感染变得更严重。有些人已死于这些感染。您的医疗保健服务提供者应在您开始使用 ACTEMRA 治疗之前、治疗期间及治疗之后评估您是否患有结核病 (TB)。

请参阅第 23-27 页的重要副作用信息。如需了解其他安全信息，请参阅随附的《处方信息和用药指南》全文。

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PHONE (818) 794-4512 • FAX (818) 332-1976

Certificate of Translation

I, Angel Ayala, Translations Project Manager at N1 Translations, declare under penalty of perjury that an expert translator fluent in both English and Chinese, upon review and validation, confirmed that **M-US-00023060(v2.0) ACTEMRA RA In Office Patient Digital Brochure - Simplified Chinese copy is an accurate representation of the M-US-00007196(v5.0) English copy**.

Translations may not always be verbatim to account for nuances and geographical idioms, however it remains consistent with the intent of the original piece.

The translation of the attached document is hereby certified; no judgment whatsoever is made concerning the contents thereof.

Date: January 28, 2025

Signed:

Angel Ayala

ACTEMRA®
tocilizumab

Ami *spoke to her doctor about ACTEMRA for her rheumatoid arthritis (RA).*

WHAT COULD ACTEMRA DO FOR YOUR RA?

ACTEMRA may be able to treat your RA with or without methotrexate (MTX). See inside for more information.

WHAT DOES ACTEMRA TREAT?

ACTEMRA is a prescription medicine called an interleukin-6 (IL-6) receptor antagonist. ACTEMRA is used to treat adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a disease modifying antirheumatic drug (DMARD) has been used and did not work well.

IMPORTANT SIDE EFFECT INFORMATION

ACTEMRA can cause serious side effects
Serious Infections
ACTEMRA changes the way your immune system works. This can make you more likely to get infections or make any current infection worse. Some people have died from these infections. Your healthcare provider should assess you for TB before starting, during, and after treatment with ACTEMRA.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

COULD ACTEMRA BE RIGHT FOR YOU?

Managing your moderate to severe rheumatoid arthritis (RA) can be challenging. If your last treatment didn't give you the results you were looking for, this brochure will give you important information about ACTEMRA, a possible next step for you that could help.

You may be able to see results on ACTEMRA with or without disease-modifying antirheumatic drugs (DMARDs) like MTX.

Please see pages 16-17 for information on the ACTEMRA clinical trial results.

In this brochure, you'll learn about:

- **How ACTEMRA may help ease your symptoms**
- **How ACTEMRA is taken (infusion or injection)**
- **How to use the ACTPen® autoinjector**
- **Clinical trial results**
- **What to expect with treatment**
- **Important Side Effect Information**
- **Options to help you pay for ACTEMRA**

Important Side Effect Information (continued)

Serious Infections
ACTEMRA changes the way your immune system works. This can make you more likely to get infections or make any current infection worse. Some people have died from these infections. Your healthcare provider should assess you for TB before starting, during, and after treatment with ACTEMRA.

ACTEMRA® tocilizumab

If your RA treatment isn't working, **talk to your healthcare professional about the risks and benefits of taking ACTEMRA.**

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

HOW COULD ACTEMRA HELP EASE RA SYMPTOMS?

What kind of results could you see?

Treating your moderate to severe RA with ACTEMRA could help you:

- **Reduce** the signs and symptoms of RA
- **Reduce** swollen and tender joints
- **Decrease** the progression of joint damage when taken with DMARDs
- **Ease** some daily living activities for some people with RA

Please see pages 16-17 for information on the ACTEMRA clinical trial results.

"I had been dealing with swelling and painful joints, and after being on ACTEMRA for a couple of months I actually noticed a reduction in the swelling.

"I found that, while before I couldn't really bend my fingers, I could bend them again...so that really encouraged me, particularly seeing those effects early in the treatment.

"It really gave me hope as to what I would be able to continue to see by taking ACTEMRA."

Ami *has treated her RA with ACTEMRA.*

Individual results may vary.

Important Side Effect Information (continued)

Before starting ACTEMRA, tell your healthcare provider if you have:

- an infection, think you may have an infection, are being treated for an infection, or get a lot of infections that return. Symptoms of an infection, with or without a fever, include sweating or chills; shortness of breath; warm, red or painful skin or sores on your body; feeling very tired; muscle aches; blood in phlegm; diarrhea or stomach pain; cough; weight loss; burning when you urinate or urinating more than normal

ACTEMRA® tocilizumab

TARGETING A KEY DRIVER OF INFLAMMATION WITH ACTEMRA

How is ACTEMRA believed to work?

To understand how ACTEMRA is believed to work, let's start with learning what interleukin-6 (IL-6) is.

IL-6 is a messenger that tells the immune system to attack harmful bacteria and viruses. When your body produces too much IL-6, it causes the immune system to attack healthy cells and may contribute to the signs and symptoms of RA.

ACTEMRA is designed to block IL-6 from activating the immune system to attack.

ACTEMRA targets a key source of inflammation called IL-6.

Important Side Effect Information (continued)

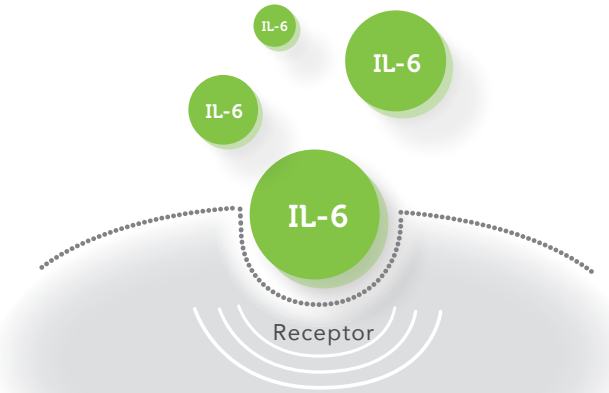
Before starting ACTEMRA, tell your healthcare provider if you have (continued):

- any of the following conditions that may give you a higher chance of getting infections: diabetes, HIV, or a weak immune system
- tuberculosis (TB), or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the United States where there is an increased chance of getting fungal infections. These parts include the Ohio and Mississippi River valleys and the Southwest
- hepatitis B or have had hepatitis B

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

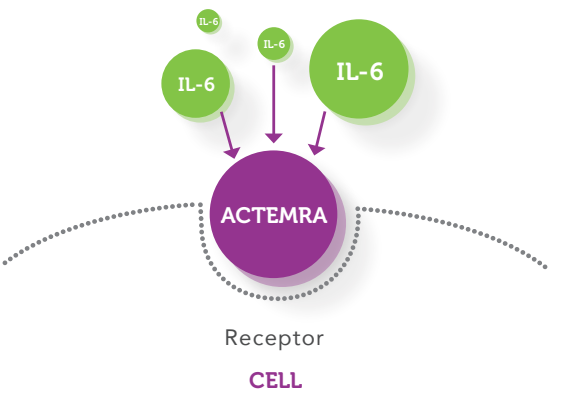
Without ACTEMRA

IL-6 connects to immune cells and tells them to activate. When these cells activate, this may contribute to the signs and symptoms of RA.



With ACTEMRA

ACTEMRA blocks IL-6 from connecting to the cell.



The way ACTEMRA is believed to work was suggested in early research. It is not known exactly how it works in the body.

WHAT ARE THE DIFFERENT WAYS I CAN TAKE ACTEMRA?

ACTEMRA offers several options for your moderate to severe RA symptoms. These options give you the ability to take your medicine in a way that works best for you.

ACTEMRA is available as:

An intravenous (IV) infusion

This medicine is a liquid solution placed into your vein with a needle. It is given at your healthcare professional's office or an infusion center.

A subcutaneous (SC) injection

This medicine is injected under your skin. It is given at home by you or a caregiver. ACTEMRA SC is available in a prefilled syringe or the ACTEMRA ACTPen® autoinjector.

- The ACTEMRA prefilled syringe is a single-dose needle that is manually injected
- The ACTPen autoinjector is a prefilled, single-dose, pen-like autoinjector that keeps the needle tip shielded before the injection, allowing you to inject by holding down a button

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

Whichever SC injection device you prefer, the ACTEMRA you take is the same

Prefilled syringe

Not actual size.

ACTPen autoinjector

Not actual size.

Cap (covers needle shield) | Window area | Activation button

Your healthcare professional will train you on how to properly inject ACTEMRA. You may also refer to the Instructions for Use step-by-step guidance on how to use your prefilled syringe or ACTPen autoinjector.

To watch a step-by-step video guide to the ACTPen autoinjector, scan the QR code.

For a quick reference guide on how to use ACTPen autoinjector, please see pages 10-13.

Important Side Effect Information (continued)

Who should not take ACTEMRA?

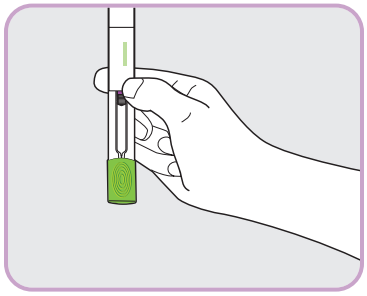
Do not take ACTEMRA if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA.

ACTPen® AUTOINJECTOR

QUICK REFERENCE GUIDE

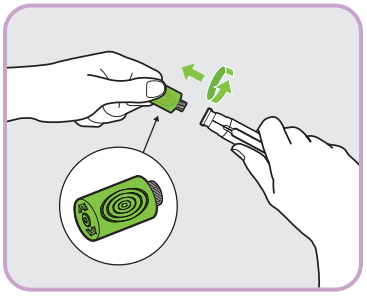
ACTEMRA® tocilizumab

Once you have become comfortable with the steps shown in the Instructions for Use, you may use this summary as a quick reference before injecting.



1 Prepare for your injection

Remove the ACTPen autoinjector from the refrigerator and let it warm up for 45 minutes until it reaches room temperature. Inspect the device. The liquid should be clear and colorless to pale yellow. **Do not** use the ACTPen autoinjector if it appears to be damaged or if it has accidentally been dropped.



2 Twist and pull off cap

Remove the cap when you are ready to inject. The ACTPen autoinjector should be used within 3 minutes or thrown away. The needle will be hidden until you begin your injection.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

Important Side Effect Information (continued)

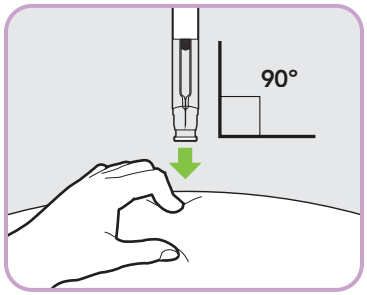
Be sure to talk to your healthcare provider if you see any signs of these serious side effects:

Tears (perforation) of the Stomach or Intestines

If you have diverticulitis (inflammation in parts of the large intestine), talk to your healthcare provider before taking ACTEMRA. Some people taking ACTEMRA may develop a hole in the wall of their stomach or intestines (also known as a perforation). This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

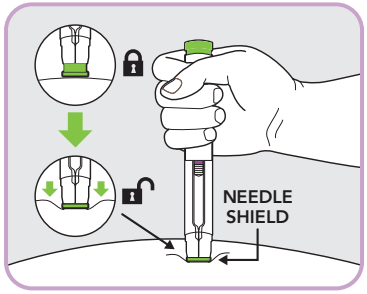
Tell your healthcare provider right away if you see any of these side effects: fever, new onset stomach-area pain that does not go away, or if you see a change in your bowel habits.

QUICK REFERENCE GUIDE (CONTINUED)



3 Pinch skin

Choose an area of the body where you will inject ACTEMRA. This is known as the injection site (refer to Step 2, Figure D in the Instructions for Use for recommended injection sites). Gently pinch the skin in this area. Place the ACTPen autoinjector against your pinched skin at a 90° angle. Do not press the Activation button until you get to Step 5. **When you're ready to inject, remember to continue to pinch your skin as you go.**

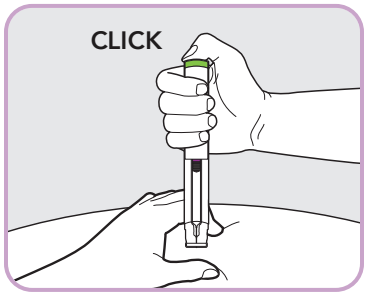


4 Compress to unlock

Without holding the Activation button, push the ACTPen autoinjector down until the needle shield is fully compressed against your pinched skin. This will unlock the Activation button. Hold the ACTPen autoinjector firmly in this position.

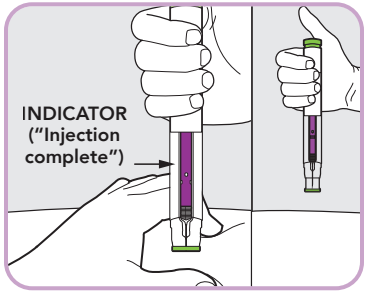
Important Side Effect Information (continued)
Liver problems (Hepatotoxicity)

Some people have experienced serious life-threatening liver problems, which required liver transplant or led to death.



5 Inject ACTEMRA SC

Press the Activation button. A "click" sound indicates the start of the injection. Keep the button pressed throughout the injection. The injection may take up to 10 seconds to complete.



6 Watch and release

Hold the ACTPen autoinjector in place until the indicator in the window area has stopped moving, even if you hear a second "click." Lift the device straight off your skin and release the Activation button. The needle shield will move down to cover the needle.

7 Discard

Once finished, throw away the ACTPen autoinjector in a sharps container. Do not put the cap back on the ACTPen autoinjector.

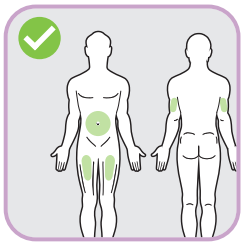
Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

ACTPen® AUTOINJECTOR

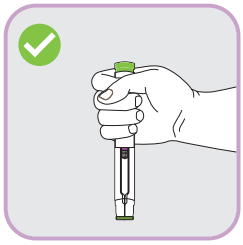
ADMINISTRATION DO'S AND DON'TS

The tips below will help clarify how you should use the ACTPen autoinjector. For full details about administration, please refer to the Instructions for Use.

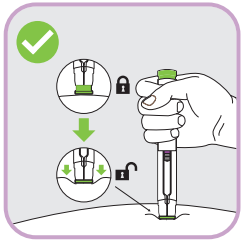
DO



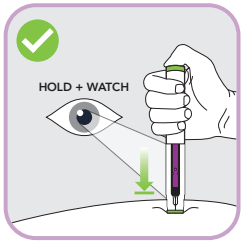
DO choose a different injection site each time you inject. Each new site should be at least 1 inch (2.5 cm) away from the area you last injected.



DO hold the upper part of the ACTPen autoinjector comfortably in one hand so that you can see the window area.



DO place the needle shield of the ACTPen autoinjector firmly against your pinched skin at a 90° angle until the needle shield is completely pushed in. This will unlock the Activation button.



DO press the Activation button once the ACTPen autoinjector is firmly held in place against your skin. Hold the device still until the indicator stops moving.

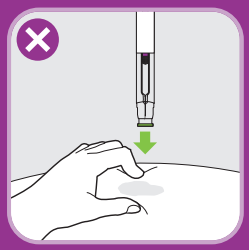
Important Side Effect Information (continued)

Liver problems (Hepatotoxicity) (continued)

Your healthcare provider may tell you to stop taking ACTEMRA if you develop new or worsening liver problems during treatment with ACTEMRA.

ACTEMRA® tocilizumab

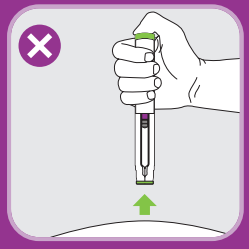
DON'T



DO NOT inject into moles, scars, bruises, or areas where the skin is tender, red, hard, or not intact.

DO NOT push down from the top of the device or on the Activation button when you are positioning the device against your skin.

DO NOT push the Activation button until the needle shield is fully pressed against your pinched skin.



DO NOT lift the needle shield from your skin before you inject, otherwise the Activation button will not work.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

IS THERE PROOF ACTEMRA CAN WORK?

In a clinical study, people with moderate to severe RA were given either ACTEMRA IV **OR** MTX (a DMARD) to compare how well each treatment reduced symptoms.

ACTEMRA IV was proven to ease RA symptoms

7 out of 10 people on **ACTEMRA IV saw at least a 20% improvement** in their RA symptoms (also known as an ACR20 response), including the number of tender and swollen joints.

About **5 out of 10 people** on **MTX saw at least a 20% improvement** in their tender and swollen joint counts and other RA symptoms.

Individual results may vary.

Important Side Effect Information (continued)
Liver problems (Hepatotoxicity) (continued)

Tell your healthcare provider right away if you have any of the following symptoms:

- feeling tired (fatigue)
- lack of appetite for several days or longer (anorexia)
- yellowing of your skin or the whites of your eyes (jaundice)
- abdominal swelling and pain on the right side of the stomach-area
- light colored stools
- weakness
- nausea and vomiting
- confusion
- dark "tea-colored" urine

ACTEMRA® tocilizumab

ACTEMRA may improve symptoms quickly

Some people taking ACTEMRA IV started to see an improvement in as little as 2 weeks.

ACTEMRA SC was proven to be as effective as ACTEMRA IV

In another study, people taking ACTEMRA SC along with DMARDs experienced a reduction of symptoms similar to those taking ACTEMRA IV along with DMARDs.

- About 7 out of 10 people in both study groups saw a 20% improvement in their RA symptoms

ACTEMRA was also proven to work in patients who have been on previous biologics.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

UNDERSTANDING YOUR DOSE

ACTEMRA® tocilizumab

If you and your healthcare professional decide on ACTEMRA, it's important to understand how much ACTEMRA you will receive, and how often you will receive it.

What's the recommended ACTEMRA dosage?

ACTEMRA IV infusions

1x month — The recommended starting dose of ACTEMRA is **4 mg/kg* once a month**

1x month — Based on your response to treatment, your dose may be increased to **8 mg/kg* once a month**

*1 kg=2.2 lb.

Your IV infusion will last about 1 hour.

ACTEMRA SC injections

every 2 weeks — If you weigh **less than** 220 lb (100 kg): **1 prefilled syringe or ACTEMRA ACTPen® autoinjector every 2 weeks (162 mg)**

1x week — If you weigh 220 lb (100 kg) **or more: 1 prefilled syringe or ACTPen autoinjector once a week (162 mg)**

For patients starting on 1 prefilled syringe or ACTPen autoinjector every 2 weeks, you and your healthcare professional may decide to change your dose to 1 prefilled syringe or ACTPen autoinjector every week if you aren't getting the results you need.

Your ACTEMRA IV dose is based on your weight

It's up to your healthcare professional to determine what dose is right for you.

What if my signs and symptoms persist?

If you feel like you aren't getting the level of relief you want, talk to your healthcare professional about adjusting your dose. Your healthcare professional will monitor your symptoms and lab test results to see how you're responding to treatment. There is no set time for dose adjustment. Depending on your lab test results, your doctor may change your dosage of ACTEMRA.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

Important Side Effect Information (continued)

Changes in Blood Test Results

Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA) your healthcare provider should do blood tests 4 to 8 weeks after you start receiving ACTEMRA for the first 6 months and then every 3 months after that.

WHAT TO EXPECT WITH TREATMENT

ACTEMRA® tocilizumab

If you've never had an infusion or injection therapy before, you may be wondering what to expect. Here are a few things that will happen before, during, and after your treatment.

Routine blood tests during treatment

To check for changes in your liver function tests, your healthcare professional will take blood tests every 4 to 8 weeks for the first 6 months following the start of treatment and then every 3 months after. They will also take blood tests 4 to 8 weeks after the start of treatment and every 3 months after to check for changes in neutrophil and platelet counts. Your healthcare professional should also do blood tests to check your cholesterol levels 4 to 8 weeks after your first ACTEMRA infusion or injection.

Getting to know your treatment

Before you start on ACTEMRA IV infusions or ACTEMRA SC injections, it's important to know all the facts. Make sure you review the ACTEMRA Medication Guide, available at ACTEMRA.com. Especially take note of the "What is the most important information I should know about ACTEMRA?" and "Before you receive ACTEMRA, tell your healthcare professional about all of your medical conditions" sections.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

Weighing in before appointments

Your ACTEMRA IV infusion dose is based on your weight, so before every infusion, you'll be weighed. If taking ACTEMRA by SC injection, your healthcare professional should weigh you at each in-office appointment. If your weight changes, you and your healthcare professional will decide if a change in dose is necessary.

If you are on ACTEMRA IV

When it's time for your infusion, you will sit or recline in a comfortable chair. The infusion will last about an hour.

Important Side Effect Information (continued)
Changes in Blood Test Results (continued)

These blood tests are to check for the following side effects of ACTEMRA:

- Low neutrophil count: neutrophils are white blood cells that help the body fight infection
- Low platelet count: platelets are blood cells that help with clotting, which stops bleeding
- Increase in liver function test levels
- Increase in blood cholesterol levels: your cholesterol levels should be checked 4 to 8 weeks after you start receiving ACTEMRA.

Your healthcare provider will determine how often you will have follow-up blood tests. Make sure you get all your follow-up blood tests done as ordered by your healthcare provider.

WHAT TO EXPECT WITH TREATMENT (CONTINUED)

If you are on ACTEMRA SC

Your healthcare professional or nurse should train you or your caregiver on how to properly inject ACTEMRA SC with either the prefilled syringe or the ACTEMRA ACTPen® autoinjector. During this training session, you or your caregiver should inject ACTEMRA SC for the first time. Only patients or caregivers who have been properly trained should use the ACTEMRA prefilled syringe or ACTPen autoinjector.

Monitoring for side effects

While receiving your treatment by infusion, a healthcare professional or nurse will monitor you. **If you are injecting ACTEMRA SC, make sure to keep an eye out for possible side effects.** ACTEMRA may lead to allergic reactions, including death. These events may happen with any treatment, even if they have not happened before. If you had hives, rash, or flushing after an injection, tell your healthcare professional before your next dose. **Let your healthcare professional or nurse know right away, or contact 911 immediately, if you're experiencing:**

- Shortness of breath or trouble breathing
- Swelling of the lips, tongue, or face
- Chest pain
- Feeling dizzy or faint
- Moderate or severe abdominal pain or vomiting

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

IMPORTANT SIDE EFFECT INFORMATION

What does ACTEMRA treat?

ACTEMRA is a prescription medicine called an interleukin-6 (IL-6) receptor antagonist. ACTEMRA is used to treat adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a disease modifying antirheumatic drug (DMARD) has been used and did not work well.

ACTEMRA can cause serious side effects

Serious Infections
ACTEMRA changes the way your immune system works. This can make you more likely to get infections or make any current infection worse. Some people have died from these infections. Your healthcare provider should assess you for TB before starting, during, and after treatment with ACTEMRA.

Before starting ACTEMRA, tell your healthcare provider if you have:

- an infection, think you may have an infection, are being treated for an infection, or get a lot of infections that return. Symptoms of an infection, with or without a fever, include sweating or chills; shortness of breath; warm, red or painful skin or sores on your body; feeling very tired; muscle aches; blood in phlegm; diarrhea or stomach pain; cough; weight loss; burning when you urinate or urinating more than normal
- any of the following conditions that may give you a higher chance of getting infections: diabetes, HIV, or a weak immune system
- tuberculosis (TB), or have been in close contact with someone with TB
- live or have lived, or have traveled to certain parts of the United States where there is an increased chance of getting fungal infections. These parts include the Ohio and Mississippi River valleys and the Southwest
- hepatitis B or have had hepatitis B

ACTEMRA® tocilizumab

IMPORTANT SIDE EFFECT INFORMATION (CONTINUED)

ACTEMRA® tocilizumab

Who should not take ACTEMRA?

Do not take ACTEMRA if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA.

Be sure to talk to your healthcare provider if you see any signs of these serious side effects:

Tears (perforation) of the Stomach or Intestines

If you have diverticulitis (inflammation in parts of the large intestine), talk to your healthcare provider before taking ACTEMRA. Some people taking ACTEMRA may develop a hole in the wall of their stomach or intestines (also known as a perforation). This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.

Tell your healthcare provider right away if you see any of these side effects: fever, new onset stomach-area pain that does not go away, or if you see a change in your bowel habits.

Liver problems (Hepatotoxicity)

Some people have experienced serious life-threatening liver problems, which required liver transplant or led to death. Your healthcare provider may tell you to stop taking ACTEMRA if you develop new or worsening liver problems during treatment with ACTEMRA. Tell your healthcare provider right away if you have any of the following symptoms:

- feeling tired (fatigue)
- lack of appetite for several days or longer (anorexia)
- yellowing of your skin or the whites of your eyes (jaundice)
- abdominal swelling and pain on the right side of the stomach-area
- light colored stools
- weakness
- nausea and vomiting
- confusion
- dark "tea-colored" urine

Changes in Blood Test Results

Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA) your healthcare provider should do blood tests 4 to 8 weeks after you start receiving ACTEMRA for the first 6 months and then every 3 months after that. These blood tests are to check for the following side effects of ACTEMRA:

- Low neutrophil count: neutrophils are white blood cells that help the body fight infection
- Low platelet count: platelets are blood cells that help with clotting, which stops bleeding
- Increase in liver function test levels
- Increase in blood cholesterol levels: your cholesterol levels should be checked 4 to 8 weeks after you start receiving ACTEMRA.

Your healthcare provider will determine how often you will have follow-up blood tests. Make sure you get all your follow-up blood tests done as ordered by your healthcare provider.

You should not receive ACTEMRA if your neutrophil and platelet counts are too low or your liver function test levels are too high. Changes in blood test results may cause your healthcare provider to stop your ACTEMRA treatment for a time or change your dose.

Cancer

ACTEMRA may increase your risk of certain cancers by changing the way your immune system works.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

IMPORTANT SIDE EFFECT INFORMATION (CONTINUED)

ACTEMRA® tocilizumab

Hepatitis B Infection

If you have or are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. Your healthcare provider may do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any signs of these symptoms:

- feel very tired
- skin or eyes look yellow
- little or no appetite
- vomiting
- clay-colored bowel movements
- fevers
- chills
- stomach discomfort
- muscle aches
- dark urine
- skin rash

Serious Allergic Reactions

Serious allergic reactions, including death, can happen with ACTEMRA. These reactions can happen with any infusion or injection of ACTEMRA, even if they did not occur with an earlier infusion or injection. Stop taking ACTEMRA, contact your healthcare provider, and get emergency help right away if you have any of the following signs of a serious allergic reaction:

- swelling of the face, lips, mouth, or tongue
- trouble breathing
- wheezing
- severe itching
- skin rash, hives, redness, or swelling outside of the injection site area
- dizziness or fainting
- fast heartbeat or pounding in your chest (tachycardia)
- sweating

Nervous System Problems

While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA.

The most common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)
- injection site reactions

Tell your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of ACTEMRA.

ACTEMRA & Pregnancy

Tell your healthcare provider if you are planning to become pregnant, are pregnant, plan to breast-feed, or are breast-feeding. You and your healthcare provider should decide if you will take ACTEMRA or breast-feed. You should not do both.

Tell your healthcare provider if you have any side effects. You may report side effects to the FDA at 1-800-FDA-1088. You may also report side effects to Genentech at 1-888-835-2555.

Please see full Prescribing Information and the Medication Guide, including Serious Side Effects, for more Important Safety Information.

HELP PAYING FOR ACTEMRA

ACTEMRA tocilizumab

ACTEMRA Access Solutions is dedicated to helping you understand your insurance coverage and assistance options.*† This can help you get the ACTEMRA your doctor prescribed.

1 ACTEMRA Co-pay Program

You pay as little as

$5 per prescription‡

with up to **$15,000 in co-pay support annually** for eligible, commercially insured patients

‡The final amount owed by patients may be as little as $5, but may vary depending on the patient's health insurance plan. Eligible commercially insured patients who are prescribed ACTEMRA for an FDA-approved use can receive up to $15,000 in assistance annually for drug costs. See terms and conditions for each program. Program limits apply.

Please see page 30 for the ACTEMRA Co-pay Program terms and conditions.

*You and your doctor are responsible for completing and submitting all required paperwork to your health insurance plan. Genentech and ACTEMRA cannot guarantee your plan will cover any treatments.

†Genentech provides coverage and reimbursement services to patients to help them understand benefits, coverage and reimbursement. Genentech provides these services to patients only after a healthcare provider has prescribed a Genentech product.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

How to get started

Visit **RACopay.com**

Call **855-RA-COPAY (855-722-6729)§**

How to know if you are eligible

You may be eligible if:

- You are taking ACTEMRA for moderate to severe RA
- **You are 18 years of age or older or have a legal guardian over the age of 18 to manage the program**
- You have commercial (private or non-governmental) insurance‡
- You do **not** use a federal or state health insurance program. This includes, but is not limited to, **Medicare, Medicaid, Medigap, VA, DoD or TRICARE**
- You do **not** currently receive help for ACTEMRA from the Genentech Patient Foundation or any independent co-pay assistance foundations
- You live and are treated in the United States or U.S. Territories
- You do **not** live in any state where the program is prohibited by law

§Monday through Friday, from 6 am - 5 pm PT, except major holidays.

‡Commercial insurance is an insurance plan you get from a private health insurance company. This can be insurance from your job, from a plan you bought yourself or from a Health Insurance Marketplace (for example, from HealthCare.gov). Medicare and Medicaid are not considered commercial insurance.

The ACTEMRA Co-pay Program may help eligible commercially insured patients with their drug costs. This program helps with the cost of ACTEMRA only. It does not help with the cost of other medicines the patient takes at the same time as ACTEMRA or with facility fees.

HELP PAYING FOR ACTEMRA (CONTINUED)

ACTEMRA Co-pay Program Terms and Conditions

- The Co-pay Program is valid ONLY for patients with commercial (private or non-governmental) insurance who have a valid prescription for a Food and Drug Administration (FDA)-approved indication of a Genentech medicine. Patients using Medicare, Medicaid or any other federal or state government program (collectively, "Government Programs") to pay for their Genentech medicine are not eligible.
- Under the Program, the patient may pay a co-pay. The final amount owed by a patient may be as little as $0 for the Genentech medicine (see Program specific details). The total patient out-of-pocket cost is dependent on the patient's health insurance plan. The Program assists with the cost of the Genentech medicine only. It does not assist with the cost of other medicines, procedures or office visit fees. After reaching the maximum annual Program benefit amount, the patient will be responsible for all remaining out-of-pocket expenses. The Program benefit amount cannot exceed the patient's out-of-pocket expenses for the cost associated with the Genentech medicine.
- All participants are responsible for reporting the receipt of all Program benefits as required by any insurer or by law. The Program is only valid in the United States and U.S. Territories, is void where prohibited by law and shall follow state restrictions in relation to AB-rated generic equivalents (e.g., MA, CA) where applicable. No party may seek reimbursement for all or any part of the benefit received through the Program. The Program is intended for the patient. Only the patient using the Program may receive the funds made available through the Program. The Program is not intended for third parties who reduce the amount available to the patient or take a portion for their own purposes. Patients with health plans that redirect Genentech Program assistance intended for patient out-of-pocket costs may be subject to alternate Program benefit structures. Genentech reserves the right to rescind, revoke or amend the Program without notice at any time.
- Additional terms and conditions apply. Please visit RAcopay.com for the full list of Terms and Conditions.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

HELP PAYING FOR ACTEMRA (CONTINUED)

2 Independent Co-pay Assistance Foundations*

If you need help with the co-pay for your ACTEMRA, ACTEMRA Access Solutions can refer you to an independent co-pay assistance foundation. Independent co-pay assistance foundations help patients with public or commercial health insurance.

3 Genentech Patient Foundation†

The Genentech Patient Foundation gives **free ACTEMRA to people who don't have insurance coverage** or who have financial concerns and meet eligibility requirements.

To learn more:

Call **1-800-ACTEMRA (1-800-228-3672)**

Visit **Genentech-Access.com/ACTEMRA/patients**

*Independent co-pay assistance foundations have their own rules for eligibility. Genentech has no involvement or influence in independent foundation decision-making or eligibility criteria and does not know if a foundation will be able to help you. We can only refer you to a foundation that supports your disease state. Genentech does not endorse or show preference for any particular foundation. The foundations we refer you to may not be the only ones that might be able to help you.

†If you have health insurance, you should try to get other types of financial assistance, if available. You also need to meet income requirements. If you do not have insurance, or if your insurance does not cover your Genentech medicine, you must meet a different set of income requirements.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

GET YOUR FREE ACTEMRA TRAVEL PACK AND SHARPS CONTAINER BY CALLING 1-800-ACTEMRA (1-800-228-3672)

The Travel Pack includes a freezable ice pack and a TSA card, which may be helpful when you take ACTEMRA with you when you travel.

ACTEMRA® tocilizumab

Ask your doctor about the treatment option with over a decade of experience

ACTEMRA has been studied for over a decade in thousands of people taking ACTEMRA for multiple FDA-approved uses.

10+
YEARS OF STUDIES

20+
KEY CLINICAL STUDIES*

1,600,000+
PEOPLE TREATED WORLDWIDE†

*Includes FDA-approved uses for conditions other than RA.
†According to the tocilizumab Periodic Benefit-Risk Evaluation Report (PBRER). The 1,600,000+ number includes patients treated during clinical trials and in market setting through April 10, 2020. Patients treated in the market setting is estimated based on the volume of product sold.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

Ask your doctor today if ACTEMRA could help ease your RA symptoms

To learn more about ACTEMRA, visit **ACTEMRA.com,** or call **1-800-ACTEMRA.**

IMPORTANT SIDE EFFECT INFORMATION

ACTEMRA can cause serious side effects
Serious Infections
ACTEMRA changes the way your immune system works. This can make you more likely to get infections or make any current infection worse. Some people have died from these infections. Your healthcare provider should assess you for TB before starting, during, and after treatment with ACTEMRA.

Please see Important Side Effect Information on pages 23-27. For additional safety information, please see the full Prescribing Information and Medication Guide enclosed.

M-US-00007196(v5.0) 10/24

处方信息要点

这些要点不包括安全有效地使用 ACTEMRA 所需的所有信息。参见 ACTEMRA 的完整处方信息。

ACTEMRA®（托珠单抗）注射液，供静脉或皮下注射用

美国首次批准：2010

警告：存在严重感染风险

请参阅完整处方信息以获取完整黑框警告信息。

- **接受 ACTEMRA 治疗的患者已发生过导致住院或死亡的严重感染，包括结核病 (TB)、细菌、侵袭性真菌、病毒和其他机会性感染。(5.1)**
- **如发生严重感染，应中断 ACTEMRA 治疗，直至感染得到控制。(5.1)**
- **接受潜伏性结核病检查（COVID-19 患者除外）；如检测结果呈阳性，请在 ACTEMRA 治疗前进行结核病治疗。(5.1)**
- **即使初始潜伏性结核病检查结果为阴性，也应在治疗期间进行活动性结核病监测 (5.1)**

----------近期重大变更----------

警告与注意事项 (5.6) 2024 年 9 月

----------适应症与用法----------

ACTEMRA®（托珠单抗）是一种白介素 6 (IL-6) 受体拮抗剂，适用于治疗：

类风湿性关节炎 (RA) (1.1)

- 本品用于治疗对改善病情的抗风湿药物 (DMARDs) 治疗应答不足的中到重度活动性类风湿性关节炎的成人患者。

巨细胞动脉炎 (GCA) (1.2)

- 本品用于治疗巨细胞动脉炎的成人患者。

系统性硬化症相关间质性肺病 (SSc-ILD) (1.3)

- 本品用于减缓系统性硬化症相关间质性肺病 (SSc-ILD) 成人患者肺功能下降的速度。

多关节型幼年特发性关节炎 (PJIA) (1.4)

- 本品用于治疗 2 岁及以上活动性多关节型幼年特发性关节炎患者。

全身型幼年特发性关节炎 (SJIA) (1.5)

- 本品用于治疗 2 岁及以上活动性全身型幼年特发性关节炎患者。

细胞因子释放综合征 (CRS) (1.6)

- 本品用于治疗由嵌合抗原受体 (CAR) T 细胞引起的重度或危及生命的细胞因子释放综合征 (CRS) 的成人和 2 岁及以上儿童患者。

2019 冠状病毒病 (COVID-19) (1.7)

- 本品用于治疗正在接受全身性皮质类固醇治疗，并需要辅助供氧、无创或有创机械通气或体外膜肺氧合 (ECMO) 的 2019 冠状病毒病 (COVID-19) 成人住院患者。

---------- 剂量与给药----------

RA、pJIA 和 sJIA 患者可接受 ACTEMRA 单药或与甲氨蝶呤联合用药；RA 患者可接受其他非生物 DMARDs 治疗。(2)

一般给药和剂量信息 (2.1)

- *RA*、*GCA*、*SSc-ILD*、*PJIA* 和 *SJIA* 患者 – 建议绝对中性粒细胞计数 (ANC) 低于 2000/mm^3、血小板计数低于 100,000/mm^3，或 ALT 或 AST 超过正常值上限 (ULN) 1.5 倍的患者不要接受 ACTEMRA 治疗 *(5.3, 5.4)*。
- *COVID-19* 患者 – 建议绝对中性粒细胞计数 (ANC) 低于 1000/mm^3、血小板计数低于 50,000 /mm^3，或 ALT 或 AST 超过 10 倍 ULN 的患者不要接受 ACTEMRA 治疗 *(5.3, 5.4)*。
- *RA*、*CRS* 或 *COVID-19* 患者 – 不建议每次输注 ACTEMRA 的剂量超过 800 mg。(2.2, 2.7, 12.3)
- *GCA* 患者 – 不建议每次输注 ACTEMRA 的剂量超过 600 mg。(2.3, 12.3)

类风湿性关节炎 (2.2)

成人静脉给药的推荐剂量：

当与非生物 DMARDs 联用或单药治疗时，起始推荐剂量为 4 mg/kg，每 4 周一次，随后根据临床应答情况增加至 8 mg/kg，每 4 周一次。

成人皮下给药的推荐剂量：

患者体重 < 100 kg	162 mg，皮下给药，隔周一次，随后根据临床应答情况增加至每周一次
患者体重 ≥ 100 kg	162 mg，皮下给药，每周一次

巨细胞动脉炎 (2.3)

成人静脉给药的推荐剂量：

在逐渐减少糖皮质激素用量的同时，推荐剂量为 6 mg/kg，每 4 周一次。可在糖皮质激素停用后接受 ACTEMRA 单药治疗。

成人皮下给药的推荐剂量：

在逐渐减少糖皮质激素用量的同时，皮下注射，每周一次，推荐剂量为 162 mg。

根据临床考虑，可在逐渐减少糖皮质激素用量的同时，皮下注射，隔周一次，推荐剂量为 162 mg。

可在糖皮质激素停用后接受 ACTEMRA 单药治疗。

系统性硬化症相关间质性肺病 (SSc-ILD) (2.4)

成人皮下给药的推荐剂量：

成人 SSc-ILD 患者 ACTEMRA 的推荐剂量为 162 mg，皮下注射，每周一次。

多关节型幼年特发性关节炎 (2.5)

PJIA 患者每 4 周静脉给药的推荐剂量	
患者体重 < 30 kg	10 mg/kg
患者体重 ≥ 30 kg	8 mg/kg

PJIA 患者皮下给药的推荐剂量	
患者体重 < 30 kg	162 mg，每 3 周一次
患者体重 ≥ 30 kg	162 mg，每 2 周一次

全身型幼年特发性关节炎 (2.6)

SJIA 患者每 2 周静脉给药的推荐剂量	
患者体重 < 30 kg	12 mg/kg
患者体重 ≥ 30 kg	8 mg/kg

SJIA 患者皮下给药的推荐剂量	
患者体重 < 30 kg	每 2 周 162 mg
患者体重 ≥ 30 kg	每周 162 mg

细胞因子释放综合征 (2.7)

CRS 患者静脉给药的推荐剂量	
患者体重 < 30 kg	12 mg/kg
患者体重 ≥ 30 kg	8 mg/kg
单药治疗或与皮质类固醇联合用药。	

2019 冠状病毒病 (2.8)

成人 COVID-19 患者的 ACTEMRA 推荐剂量为 8 mg/kg，60 分钟静脉输注给药。

静脉制剂给药 (2.9)

- 体重 ≥ 30 kg 的 RA、GCA、COVID-19、CRS、PJIA 和 SJIA 患者，使用 0.9% 或 0.45% 氯化钠注射液 (USP) 稀释至 100 mL，在无菌条件下进行静脉输注。
- 体重 < 30 kg 的 PJIA、SJIA 和 CRS 患者，使用 0.9% 或 0.45% 氯化钠注射液 (USP) 稀释至 50 mL，在无菌条件下进行静脉输注。
- 单次静脉滴注时间 1 小时以上；请勿以团注或推注方式给药。

皮下制剂给药 (2.10)

- 遵循预充式注射器和预充式 ACTPen® 自动注射器的使用说明

剂量调整 (2.11)

- 推荐用于处理某些与剂量相关的实验室指标变化，包括肝酶升高、中性粒细胞减少症和血小板减少症。

---------- 剂型和规格 ----------

静脉注射液

注射液：80 mg/4 mL (20 mg/mL)、200 mg/10 mL (20 mg/mL)、400 mg/20 mL (20 mg/mL) 单剂量药瓶，用于在静脉输注前进一步稀释 (3)

皮下注射液

注射液：162 mg/0.9 mL，装在单剂量预充式注射器或单剂量预充式 ACTPen® 自动注射器中 (3)

---------- 禁忌症----------

已知对 ACTEMRA 有过敏反应的患者。(4)

---------- 警告与注意事项----------

- 严重感染 – 在活动性感染包括局部感染期间请勿接受 ACTEMRA 治疗。如发生严重感染，应中断 ACTEMRA 治疗，直至感染得到控制。(5.1)
- 胃肠道 (GI) 穿孔 – 风险较高的患者应谨慎使用。(5.2)
- 肝毒性 – 监测患者肝功能损伤的体征和症状。如果肝脏检查异常持续或恶化，或者出现肝病的临床体征和症状，则调整 ACTEMRA 剂量或中断治疗。(2.10, 5.3)
- 实验室监测 – 由于可能会发生与治疗相关的中性粒细胞、血小板、血脂和肝功能变化，建议进行实验室监测。(2.10, 5.4)
- 超敏反应，包括过敏性反应甚至死亡。ACTEMRA 还可能导致严重的皮肤反应，如伴随嗜酸性粒细胞增多和全身症状的药物反应 (DRESS)。如果出现此类反应，应立即停用 ACTEMRA，尽早进行治疗，并在反应未完全消失前持续监测患者状况。(5.6)
- 活疫苗—避免与 ACTEMRA 联用。(5.9, 7.3)

----------不良反应----------

最常见的不良反应（发生率至少 5%）：上呼吸道感染、鼻咽炎、头痛、高血压、ALT 升高、注射部位反应。(6)

如需报告疑似不良反应，请致电 1-888-835-2555 联系 Genentech，或致电 1-800-FDA-1088 或访问 www.fda.gov/medwatch 联系 FDA

---------- 特殊人群用药----------

- **妊娠期：** 根据动物数据，可能会对胎儿造成伤害。(8.1)
- **哺乳期：** 考虑到药物对母亲产生的重要影响，请停止用药或停止哺乳。(8.2)

有关“患者咨询信息和用药指南”，请参阅第 17 节

修订日期：2024 年 9 月

完整处方信息：目录*

*未列出完整处方信息中省略的章节或小节。

完整处方信息

警告：存在严重感染风险

接受 ACTEMRA 治疗的患者发生严重感染的风险升高，可导致住院或死亡*[*参见警告和注意事项 *(5.1)*，不良反应 *(6.1)]*。发生这类感染的患者大多合并使用氨蝶呤或皮质类固醇等免疫抑制剂。

如发生严重感染，应中断 ACTEMRA 治疗，直至感染得到控制。

报告的感染包括：

- **活动性结核病，可表现为肺部疾病或肺外疾病。除 COVID-19 外，患者在接受 ACTEMRA 治疗前和治疗期间应接受潜伏性结核病检测。应在接受 ACTEMRA 治疗前进行潜伏感染治疗。**
- **侵袭性真菌感染，包括念珠菌病、曲霉病和肺孢子虫感染。侵袭性真菌感染患者可能会出现播散性而非局部性疾病。**
- **由机会性病原体引起的细菌感染、病毒感染和其他感染。**

在慢性或复发性感染患者开始治疗前，应仔细评估 ACTEMRA 治疗的风险和益处。

在接受 ACTEMRA 治疗期间和治疗后，应密切监测患者是否出现感染体征和症状，包括在开始治疗前潜伏性结核感染测试为阴性的患者可能发生的结核病*[*参见警告和注意事项 *(5.1)]*。

1 适应症与用法

1.1 类风湿性关节炎 (RA)

ACTEMRA®（托珠单抗）适用于治疗对一种或多种改善病情的抗风湿药物 （DMARDs） 治疗应答不足的中度至重度活动性类风湿性关节炎成人患者。

1.2 巨细胞动脉炎 (GCA)

ACTEMRA®（托珠单抗）适用于治疗巨细胞动脉炎 (GCA) 成人患者。

1.3 系统性硬化症相关间质性肺病 (SSc-ILD)

ACTEMRA®（托珠单抗）适用于减缓系统性硬化症相关间质性肺病成人患者肺功能下降的速度。

1.4 多关节型幼年特发性关节炎 (PJIA)

ACTEMRA®（托珠单抗）适用于治疗 2 岁及以上活动性多关节型幼年特发性关节炎患者。

1.5 全身型幼年特发性关节炎 (SJIA)

ACTEMRA®（托珠单抗）适用于治疗 2 岁及以上活动性全身型幼年特发性关节炎患者。

1.6 细胞因子释放综合征 (CRS)

ACTEMRA®（托珠单抗）适用于治疗由嵌合抗原受体 (CAR) T 细胞引起的重度或危及生命的细胞因子释放综合征的成人和 2 岁及以上儿童患者。

1.7 2019 冠状病毒病 (COVID-19)

ACTEMRA®（托珠单抗）适用于治疗正在接受全身性皮质类固醇治疗并需要辅助供氧、无创或有创机械通气或体外膜肺氧合 (ECMO) 的冠状病毒病住院成年患者。

2 剂量与给药

2.1 一般给药注意事项

<u>不建议与生物 DMARDs 联合用药</u>

考虑到联合用药可能增加免疫抑制和感染风险，尚未进行过 ACTEMRA 与生物 DMARDs 联合用药（例如 TNF 拮抗剂、IL-1R 拮抗剂、抗 CD20 单克隆抗体和选择性共刺激调节剂）的研究。请避免 ACTEMRA 与生物 DMARDs 联合用药。

治疗前的基线实验室评估

治疗前获取并评估基线全血细胞计数 (CBC) 和肝功能检查结果。

- *RA*、*GCA*、*SSc-ILD*、*PJIA* 和 *SJIA* 患者 – 建议绝对中性粒细胞计数 (ANC) 低于 2000/mm^3、血小板计数低于 100,000/mm^3 或 ALT 或 AST 超过正常值上限 (ULN) 1.5 倍的患者不要接受 ACTEMRA 治疗*[*参见警告和注意事项 *(5.3, 5.4)]*。
- *CRS* 患者 – 患有严重或危及生命的 CRS 的患者经常因淋巴细胞耗竭性化疗或 CRS 而出现血细胞减少或 ALT 或 AST 升高。进行 ACTEMRA 给药的决定应考虑治疗 CRS 的潜在益处与使用 ACTEMRA 短期治疗的风险。
- *COVID-19* 患者 – 建议绝对中性粒细胞计数 (ANC) 低于 1000/mm^3、血小板计数低于 50,000/mm^3 或 ALT 或 AST 高于 ULN 10 倍的患者不要接受 ACTEMRA 治疗*[*参见警告和注意事项 *(5.3, 5.4)]*。

2.2 类风湿性关节炎的推荐剂量

ACTEMRA 可单药治疗，也可与甲氨蝶呤或其他非生物 DMARDs 通过静脉输注或皮下注射联合用药。

静脉给药的推荐方案：

成人患者 ACTEMRA 的推荐剂量为 4 mg/kg，每 4 周一次，每次静脉滴注 60 分钟，随后根据临床应答情况增加至 8 mg/kg，每 4 周一次。

- 为了处理某些与剂量相关的实验室指标变化，包括肝酶升高、中性粒细胞减少症和血小板减少症，建议将剂量从 8 mg/kg 减少至 4 mg/kg*[*参见剂量与给药方法 *(2.11)*，警告和注意事项 *(5.3, 5.4)*，和不良反应 *(6.1)]*。
- 不建议 RA 患者每次的输注剂量超过 800 mg*[*参见临床药理学 *(12.3)]*。

皮下给药的推荐方案：

患者体重 < 100 kg	162 mg，皮下给药，隔周一次，随后根据临床应答情况增加至每周一次
患者体重 ≥ 100 kg	162 mg，皮下给药，每周一次

从 ACTEMRA 静脉给药治疗过渡到皮下给药治疗时，应使用首次皮下给药剂量，而非下一个预定的静脉给药剂量。

建议中断治疗或将皮下给药频率从每周给药改为隔周给药，以处理某些与剂量相关的实验室指标变化，包括肝酶升高，中性粒细胞减少症和血小板减少症*[*参见剂量与给药 *(2.11)*，警告和注意事项 *(5.3*、*5.4)* 和不良反应 *(6.2)]*。

2.3 巨细胞动脉炎的推荐剂量

静脉给药的推荐方案：

在逐渐减少糖皮质激素用量的同时，成人患者 ACTEMRA 的推荐剂量为 6 mg/kg，每 4 周一次， 每次静脉滴注 60 分钟。

可在糖皮质激素停用后接受 ACTEMRA 单药治疗。

- 可能需要中断治疗以处理与剂量相关的实验室异常，包括肝酶升高、中性粒细胞减少症和血小板减少症*[*参见剂量与给药 *(2.11)]*。
- 不建议 GCA 患者每次输注的剂量超过 600 mg*[*参见临床药理学 *(12.3)]*。

皮下给药的推荐方案：

在逐渐减少糖皮质激素用量的同时，成人 GCA 患者 ACTEMRA 的推荐剂量为 162 mg，皮下注射，每周一次。

根据临床考虑，可在逐渐减少糖皮质激素用量的同时，推荐剂量为 162 mg，皮下注射，隔周一次。

可在糖皮质激素停用后接受 ACTEMRA 单药治疗。

当从 ACTEMRA 静脉给药过渡到皮下给药时，应使用首次皮下给药剂量，而非下一个预定的静脉给药剂量。

建议中断治疗或将皮下给药频率从每周给药改为隔周给药，以处理与剂量相关的实验室异常，包括肝酶升高，中性粒细胞减少症和血小板减少症*[参见剂量与给药 (2.11)]*。

2.4 系统性硬化症相关间质性肺病的推荐剂量

成人 SSc-ILD 患者 ACTEMRA 的推荐剂量为 162 mg，皮下注射，每周一次。

- 可能需要中断治疗以处理与剂量相关的实验室异常，包括肝酶升高、中性粒细胞减少症和血小板减少症*[参见剂量与给药 (2.11)]*。
- 尚未对 SSc-ILD 患者使用预充式 ACTPen® 自动注射器进行皮下给药进行研究。
- 静脉给药未被批准用于 SSc-ILD 患者。

2.5 多关节型幼年特发性关节炎的推荐剂量

ACTEMRA 可以静脉输注或皮下注射的方式进行单药治疗，或与甲氨蝶呤联合用药。考虑到体重的波动性，不能仅根据一次就诊时的体重测量指标来调整剂量。

静脉给药的推荐方案：

PJIA 患者，每 4 周一次 60 分钟单次静脉滴注 ACTEMRA 的推荐剂量为：

PJIA 患者每 4 周静脉给药的推荐剂量	
患者体重 < 30 kg	10 mg/kg
患者体重 ≥ 30 kg	8 mg/kg

皮下给药的推荐方案：

PJIA 患者皮下给药的推荐剂量	
患者体重 < 30 kg	162 mg，每 3 周一次
患者体重 ≥ 30 kg	162 mg，每 2 周一次

当从 ACTEMRA 静脉给药过渡到皮下给药时，应使用首次皮下给药剂量，而非下一个预定的静脉给药剂量。

可能需要中断治疗以处理与剂量相关的实验室异常，包括肝酶升高、中性粒细胞减少症和血小板减少症*[参见剂量与给药 (2.11)]*。

2.6 全身型幼年特发性关节炎的推荐剂量

ACTEMRA 可以静脉输注或皮下注射的方式进行单药治疗，或与甲氨蝶呤联合用药。考虑到体重的波动性，不能仅根据一次就诊时的体重测量指标来调整剂量。

静脉给药的推荐方案：

SJIA 患者每 2 周一次 60 分钟单次静脉滴注 ACTEMRA 的推荐剂量为：

SJIA 患者每 2 周静脉给药的推荐剂量	
患者体重 < 30 kg	12 mg/kg
患者体重 ≥ 30 kg	8 mg/kg

皮下给药的推荐方案：

SJIA 患者皮下给药的推荐剂量	
患者体重 < 30 kg	162 mg，每 2 周一次
患者体重 ≥ 30 kg	162 mg，每周一次

从 ACTEMRA 静脉给药过渡到皮下给药时，应在预定的下一剂静脉给药结束时进行首次皮下给药。

可能需要中断治疗以处理与剂量相关的实验室异常，包括肝酶升高、中性粒细胞减少症和血小板减少症 *[参见剂量与给药 (2.11)]*。

2.7 细胞因子释放综合征 (CRS) 的推荐剂量

仅使用静脉给药途径治疗 CRS 患者。以 60 分钟静脉输注方式治疗 CRS 患者的 ACTEMRA 推荐剂量为：

CRS 患者静脉给药的推荐剂量	
患者体重 < 30 kg	12 mg/kg
患者体重 ≥ 30 kg	8 mg/kg
单药治疗或与皮质类固醇联合用药	

- 如果首次给药后 CRS 患者的体征和症状没有得到临床改善，则可以额外给予最多 3 剂次 ACTEMRA。连续给药间隔至少为 8 小时。
- 不建议 CRS 患者每次的输注剂量超过 800 mg。
- 皮下给药未获批准用于 CRS 治疗。

2.8 2019 冠状病毒病 （COVID-19）

仅通过静脉输注进行 ACTEMRA 治疗。

ACTEMRA 用于治疗成人 COVID-19 患者的推荐剂量为 8 mg/kg，单次 60 分钟静脉输注给药。如果首次给药后患者临床体征或症状恶化或未改善，可在首次输注 8 小时后再进行一次 ACTEMRA 输注治疗。

- 不建议 COVID-19 患者每次的输注剂量超过 800 mg。
- 皮下给药未获批准用于治疗 COVID-19。

2.9 静脉输注制剂的制备及给药说明

用于静脉输注的 ACTEMRA 应由医护人员在无菌条件下进行如下稀释：

- 使用无菌针头和注射器来制备 ACTEMRA。
- **体重 < 30 kg** 的患者：使用 **50 mL** 的装有 0.9% 或 0.45% 的氯化钠注射液 (USP) 的输液袋或输液瓶，然后按照下列步骤 1 和 2 进行操作。
- **体重 30 kg** 的患者：使用 **100 mL** 的输液袋或输液瓶，然后按照下列步骤 1 和 2 进行操作。
- 步骤 1。从输液袋或输液瓶中抽取与患者所需 ACTEMRA 治疗剂量相等的 0.9% 或 0.45% 氯化钠注射液 (USP) *[参见剂量与给药 (2.2, 2.5, 2.6, 2.7)]*。

供静脉注射用：每千克体重的 ACTEMRA 注射液用量		
剂量	**适应症**	**每千克体重的 ACTEMRA 注射液用量**
4 mg/kg	成人 RA 患者	0.2 mL/kg
6 mg/kg	成人 GCA 患者	0.3 mL/kg
8 mg/kg	成人 RA 患者 成人 COVID-19 患者 SJIA、PJIA 和 CRS（体重 ≥ 30 kg）患者	0.4 mL/kg
10 mg/kg	PJIA 患者（体重 < 30 kg）	0.5 mL/kg
12 mg/kg	SJIA 和 CRS 患者（体重 < 30 kg）	0.6 mL/kg

- 步骤 2。从药瓶中抽取用于静脉输注的 ACTEMRA 量，缓慢加入 0.9% 或 0.45% 氯化钠注射液 (USP) 输液袋或输液瓶中。混合溶液时，请轻轻翻转袋子，以免起泡。
- 使用 0.9% 氯化钠注射液 (USP) 充分稀释的 ACTEMRA 溶液可在 36°F 至 46°F（2°C 至 8°C）或室温下避光储存长达 24 小时。
- 使用 0.45% 氯化钠注射液 (USP) 完全稀释的 ACTEMRA 溶液可在 36°F 至 46°F（2°C 至 8°C）下避光储存长达 24 小时，或在室温下避光储存长达 4 小时。
- ACTEMRA 溶液不含防腐剂；因此，残留在药瓶中的未使用的产品不应继续使用。
- 输注前，完全稀释的 ACTEMRA 溶液需达到室温。
- 输注时间应超过 60 分钟，且必须使用输液器进行输注。请勿以静脉推注或团注的方式给药。
- ACTEMRA 不应与其他药物在同一静脉管线中同时输注。尚未进行物理或生化相容性研究来评估 ACTEMRA 与其他药物的联合治疗方式。
- 只要溶液和容器允许，在给药前应检查肠外药品是否有颗粒物和变色。如果发现颗粒物和变色，则不应使用该产品。
- 完全稀释的 ACTEMRA 溶液与聚丙烯、聚乙烯和聚氯乙烯输液袋以及聚丙烯、聚乙烯和玻璃输液瓶兼容。

2.10 皮下注射剂的制备和给药说明

- 用于皮下注射的 ACTEMRA 不适用于静脉滴注。
- 评估患者是否适合居家皮下注射，并告知患者若出现任何过敏反应症状，需在注射下一剂量之前告知医护人员。如果患者出现严重过敏反应症状，应立即就医。ACTEMRA 皮下注射剂应在医护人员指导下使用。经过适当的皮下注射技术培训后，如果医护人员确定合适，患者可以自行注射 ACTEMRA，或患者的照料者可以帮忙注射 ACTEMRA。在医护人员和父母/法定监护人都认为合适的情况下，PJIA 和 SJIA 患者可以用 ACTEMRA 预充式注射器或 ACTPen® 自动注射器自行注射，或患者的照料者可以帮忙注射 ACTEMRA *[参见特殊人群用药 (8.4)]*。应指导患者或其照料者遵循“用药说明” (IFU)，了解有关给药的更多详细信息。
- 给药前应检查肠外药品是否有颗粒物和变色。请勿使用出现颗粒物、混浊或变色的 ACTEMRA 预充式注射器 (PFS) 或预充式 ACTPen® 自动注射器。用于皮下注射的 ACTEMRA 应为透明、无色至淡黄色。如果 PFS 或 ACTPen® 自动注射器的任何部件出现损坏，请勿使用。
- 应指导进行 ACTEMRA 皮下给药的患者根据 IFU 中提供的说明，在注射器中注射全部量 (0.9 mL) 或在 ACTPen® 自动注射器中注射全部量 (0.9 mL)，该注射器提供 162 mg ACTEMRA。
- 每次注射时应轮换注射部位，切勿注射到痣、疤痕或皮肤柔软、瘀伤、发红、坚硬或不完整的区域。

2.11 因严重感染或实验室异常而调整剂量

严重感染

如果患者出现严重感染，请暂停 ACTEMRA 治疗，直至感染得到控制。

实验室异常

类风湿性关节炎、巨细胞动脉炎和系统性硬化症-间质性肺病

肝酶异常*[参见警告和注意事项 (5.3, 5.4)]*		
实验室值	**针对 RA 和 SSc-ILD 患者的建议**	**针对 GCA 患者的建议**
大于 1 至 3 倍 ULN	酌情调整联合用药中 DMARDs 的剂量 如果在此范围内持续升高： • 接受静脉注射 ACTEMRA 的患者，需将剂量减少至 4 mg/kg 或暂停 ACTEMRA 给药直至 ALT 或 AST 恢复正常 • 接受皮下 ACTEMRA 给药的患者，需将注射频率减少至隔周一次或暂停治疗直至 ALT 或 AST 恢复正常。恢复 ACTEMRA 治疗，隔周一次，并根据临床应答情况将频率增加至每周一次。	酌情调整免疫调节剂的剂量 如果在此范围内持续升高： • 接受静脉注射 ACTEMRA 的患者，需暂停 ACTEMRA 给药直至 ALT 或 AST 恢复正常 • 接受皮下 ACTEMRA 给药的患者，需将注射频率减少至隔周一次或暂停治疗直至 ALT 或 AST 恢复正常。恢复 ACTEMRA 治疗，隔周一次，并根据临床应答情况将频率增加至每周一次
大于 3 至 5 倍 ULN （经重复测试证实）	暂停 ACTEMRA 给药直至低于 3 倍 ULN，高于 1 至 3 倍 ULN 时，请遵循上述建议 如果持续升高，超过 3 倍 ULN，则停止 ACTEMRA 给药	暂停 ACTEMRA 给药直至低于 3 倍 ULN，高于 1 至 3 倍 ULN 时，请遵循上述建议 如果持续升高，超过 3 倍 ULN，则停止 ACTEMRA 给药
大于 5 倍 ULN	停止 ACTEMRA 给药	停止 ACTEMRA 给药

绝对中性粒细胞计数 (ANC) 低*[参见警告和注意事项 (5.4)]*		
实验室值（细胞数/mm^3）	**针对 RA 和 SSc-ILD 患者的建议**	**针对 GCA 患者的建议**
ANC 大于 1000	维持剂量	维持剂量
ANC 500 至 1000	暂停 ACTEMRA 给药 当 ANC 大于 1000/mm^3 时： • 接受静脉 ACTEMRA 给药的患者，需以 4 mg/kg 的剂量恢复 ACTEMRA 给药，并根据临床应答情况增加至 8 mg/kg 的剂量 • 接受皮下 ACTEMRA 给药的患者，恢复每 2 周一次的 ACTEMRA 给药，并根据临床应答情况将频率增加至每周一次	暂停 ACTEMRA 给药 当 ANC 大于 1000/mm^3 时： • 接受静脉 ACTEMRA 给药的患者，需以 6 mg/kg 的剂量恢复 ACTEMRA 给药 • 接受皮下 ACTEMRA 给药的患者，恢复每 2 周一次的 ACTEMRA 给药，并根据临床应答情况将频率增加至每周一次
ANC 低于 500	停止 ACTEMRA 给药	停止 ACTEMRA 给药

血小板计数低*[参见警告和注意事项 (5.4)]*		
实验室值（细胞数/mm^3）	**针对 RA 和 SSc-ILD 患者的建议**	**针对 GCA 患者的建议**
50,000 至 100,000	暂停 ACTEMRA 给药 当血小板计数大于 100,000/mm^3 时： • 接受静脉 ACTEMRA 给药的患者，需以 4 mg/kg 的剂量恢复 ACTEMRA 给药，并根据临床应答情况增加至 8 mg/kg 的剂量 • 接受皮下 ACTEMRA 给药的患者，恢复每 2 周一次的 ACTEMRA 给药，并根据临床应答情况将频率增加至每周一次	暂停 ACTEMRA 给药 当血小板计数大于 100,000/mm^3 时： • 接受静脉 ACTEMRA 给药的患者，需以 6 mg/kg 的剂量恢复 ACTEMRA 给药 • 接受皮下 ACTEMRA 给药的患者，恢复每 2 周一次的 ACTEMRA 给药，并根据临床应答情况将频率增加至每周一次
少于 50,000	停止 ACTEMRA 给药	停止 ACTEMRA 给药

多关节和全身型幼年特发性关节炎

尚未在 PJIA 和 SJIA 患者中进行 ACTEMRA 剂量减少的研究。对于肝酶异常、中性粒细胞计数低和血小板计数低的 PJIA 和 SJIA 患者，建议中断 ACTEMRA 给药，其水平与上述 RA 和 GCA 患者的水平相似。如有需要，应酌情调整剂量或停止甲氨蝶呤和/或其他药物联合用药，并暂停 ACTEMRA 给药，直至直至临床情况得到评估。在 PJIA 和 SJIA 患者中，因实验室异常而停止 ACTEMRA 给药的决定应基于个体患者的医疗评估而定。

3 剂型和规格

静脉注射液

注射液：80 mg/4 mL、200 mg/10 mL、400 mg/20 mL 为透明、无色至浅黄色溶液，装在 20 mg/mL 单剂量药瓶中，供静脉输注前进一步稀释。

皮下注射液

注射液：162 mg/0.9 mL 澄清、无色至微黄色溶液，装在单剂量预充式注射器或单剂量预充式 ACTPen® 自动注射器中。

4 禁忌症

已知对 ACTEMRA 过敏的患者禁用 ACTEMRA*[参见警告和注意事项 (5.6)]*。

5 警告与注意事项

5.1 严重感染

有报告称，接受 ACTEMRA 等免疫抑制剂治疗的患者会因细菌、分枝杆菌、侵袭性真菌、病毒、原虫或其他机会性病原体而发生严重甚至致命的感染。最常见的严重感染包括肺炎，尿路感染，蜂窝织炎，带状疱疹，胃肠炎，憩室炎，败血症和细菌性关节炎*[参见不良反应 (6.1)]*。在机会性感染中，有报告称 ACTEMRA 引起了结核病、隐球菌病、曲霉病、念珠菌病和肺囊虫病。临床研究中未报告的其他严重感染也可能发生（例如组织胞浆菌病、球孢子菌病、李氏杆菌病）。患者表现为播散性而非局限性疾病，并且常与甲氨蝶呤或皮质类固醇等免疫抑制剂联合使用，这些药物和类风湿性关节炎可能使患者易受感染。

请勿对有活动性感染（包括局部感染）的患者进行 ACTEMRA 给药。在对下列患者进行 ACTEMRA 给药之前应考虑治疗的风险和益处：

- 患有慢性或反复感染；
- 结核病接触史；
- 有严重或机会性感染史；
- 结核病或真菌病疫区居住或旅行史；或者
- 患有可能使他们易受感染的潜在疾病。

在 ACTEMRA 治疗期间和治疗后，应密切监测患者是否出现感染体征和症状，因为急性炎症体征和症状可能由于抑制急性期反应物而减轻*[*参见剂量与给药 *(2.8)*，不良反应 *(6.1)* 和患者咨询信息 *(17)]*。

如果患者出现严重感染、机会性感染或败血症，应暂停 ACTEMRA 给药。在进行 ACTEMRA 治疗期间出现新感染的患者，应立即进行适合免疫功能低下患者的完整诊断检查，开始适当的抗菌治疗，并进行密切监测。

COVID-19

对于 COVID-19 患者，在进行 ACTEMRA 治疗期间和治疗后，应监测患者是否出现新感染的体征和症状。有关 COVID-19 患者同时患有活动性严重感染时使用 ACTEMRA 的信息有限。应评估对并发其他感染的 COVID-19 患者使用 ACTEMRA 治疗的风险和益处。

结核病

在进行 ACTEMRA 给药之前，应评估患者的结核病危险因素并进行潜在感染检查。对于 COVID-19 患者，在进行 ACTEMRA 治疗之前无需检接受潜伏感染检查。

对于既往有潜伏性或活动性结核病史且无法确定是否接受过适当治疗的患者，以及潜伏性结核病检测阴性但具有结核感染危险因素的患者，在进行 ACTEMRA 给药之前，应考虑进行抗结核治疗。建议咨询具有结核病治疗专业知识的医生，以帮助决定开始抗结核治疗是否适合个别患者。

应密切监测患者是否出现结核病体征和症状，包括在开始治疗前潜伏性结核感染检测呈阴性的患者。

全球临床开发项目中结核病的发病率为 0.1%。潜伏性结核病患者在进行 ACTEMRA 给药之前应接受标准抗分枝杆菌治疗。

病毒再激活

有报告称，免疫抑制生物疗法会导致病毒再激活，并且在 ACTEMRA 的临床研究中观察到带状疱疹恶化的病例。试验中没有观察到乙型肝炎再激活的病例；然而，肝炎筛查呈阳性的患者未纳入试验中。

5.2 胃肠穿孔

临床试验中已报告胃肠道穿孔事件，主要是接受 ACTEMRA 治疗的患者出现憩室炎并发症。对于胃肠道穿孔风险增加的患者，请谨慎使用 ACTEMRA。及时评估出现发烧、新发腹部症状和排便习惯改变的患者，以便早期识别胃肠道穿孔*[*参见不良反应 *(6.1)]*。

5.3 肝毒性

在接受静脉或皮下 ACTEMRA 治疗的患者中观察到严重肝功能损伤病例。其中一些病例导致肝移植或死亡。开始托珠单抗治疗后，病例发病时间从数月到数年不等。虽然大多数病例表现为转氨酶显着升高（大于 5 倍 ULN），但有些病例表现为肝功能障碍的体征或症状，且转氨酶仅轻度升高。

在随机对照研究期间，进行 ACTEMRA 治疗与转氨酶升高较高发生率相关*[*参见不良反应 *(6.1, 6.2, 6.6, 6.8)]*。当潜在肝毒性药物（例如 MTX）与 ACTEMRA 联合用药时，升高的频率和幅度都会增加。

RA、GCA 和 SSc-ILD 患者应在开始进行 ACTEMRA 治疗之前进行肝脏检查（血清丙氨酸氨基转移酶 [ALT]、天门冬氨酸氨基转移酶 [AST]、碱性磷酸酶和总胆红素），在开始治疗后的前 6 个月内每 4 到 8 周进行一次肝脏检查，之后每 3 个月进行一次。不建议转氨酶 ALT 或 AST 升高超过 1.5 倍 ULN 的 RA、GCA 或 SSc-ILD 患者接受 ACTEMRA 治疗。ALT 或 AST 升高超过 5 倍 ULN 的患者，应停止 ACTEMRA 治疗。基于转氨酶增加的剂量调整，参见剂量与给药 *(2.11)*。

COVID-19 住院患者的 ALT 或 AST 水平可能升高。累及肝脏的多器官衰竭被认为是重度 COVID-19 的并发症之一。ACTEMRA 的给药决定应基于治疗 COVID-19 潜在益处与 ACTEMRA 急性治疗潜在风险的平衡。不建议 ALT 或 AST 升高超过 10 倍 ULN 的 COVID-19 患者接受 ACTEMRA 治疗。治疗期间应监测 ALT 和 AST。

如果患者出现疲劳、厌食、右上腹部不适、尿色深或黄疸等可能提示肝功能损伤的症状，应立即进行肝脏检查。在这种临床背景下，如果发现患者肝脏检查异常（例如，ALT 大于参考范围上限的三倍，血清总胆红素大于参考范围上限的两倍），则应中断 ACTEMRA 治疗，并进行检查以确定可能的原因。ACTEMRA 仅可在因其他原因导致肝脏检查异常且肝脏检查正常化后对患者重新启用。

在接受 ACTEMRA 治疗的 PJIA 和 SJIA 患者中也发现了类似的肝酶升高情况。在第二次给药时监测肝脏检查结果，PJIA 患者此后每 4 ~ 8 周监测 1 次，SJIA 患者此后每 2 ~ 4 周监测 1 次。

5.4 实验室参数变化

类风湿性关节炎、巨细胞动脉炎、系统性硬化症相关间质性肺病和 *2019* 新型冠状病毒肺炎患者

中性粒细胞减少症

ACTEMRA 治疗会增加中性粒细胞减少症发生率。在长期扩展研究和上市后临床经验中，与治疗相关的中性粒细胞减少症有关的感染报道较少。

- 不建议中性粒细胞计数较低（即绝对中性粒细胞计数 (ANC) 低于 2000/mm^3 的 RA、GCA 和 SSc-ILD 患者接受 ACTEMRA 治疗。不建议绝对中性粒细胞计数低于 500/mm^3 的患者接受 ACTEMRA 治疗。
- 治疗开始后 4 至 8 周监测中性粒细胞，此后每 3 个月检测一次*[*参见临床药理学 *(12.2)]*。基于 ANC 结果的推荐调整剂量，参见剂量与给药 *(2.11)*。
- 不建议 ANC 低于 1000/mm^3 的 COVID-19 患者接受 ACTEMRA 治疗。应监测中性粒细胞计数。

血小板减少症

ACTEMRA 治疗能够降低血小板计数。临床试验显示治疗相关的血小板减少与严重出血事件无关*[*参见不良反应 *(6.1, 6.2)]*。

- 不建议血小板计数低于 100,000/mm^3 的 RA、GCA 和 SSc-ILD 患者接受 ACTEMRA 治疗。不建议血小板计数低于 50,000/mm^3 的患者接受 ACTEMRA 治疗。
- 治疗开始后 4 至 8 周监测一次血小板，此后每 3 个月监测一次。基于血小板计数的推荐调整剂量，参见剂量与给药 *(2.11)*。
- 不建议血小板计数低于 50,000/mm^3 的 COVID-19 患者接受 ACTEMRA 治疗。应监测血小板。

肝酶升高

参见 5.3 肝毒性。关于推荐的调整剂量*[*参见剂量与给药 *(2.11)]*

血脂异常

使用 ACTEMRA 治疗能够升高总胆固醇、甘油三酯、低密度脂蛋白胆固醇和/或高密度脂蛋白胆固醇等血脂参数*[参见不良反应 (6.1, 6.2)]*。

– ACTEMRA 治疗开始后约 4 至 8 周评估血脂参数。

– 随后，根据临床指南 [例如美国国家胆固醇教育计划 (NCEP)] 对患者进行高脂血症管理。

多关节和全身型幼年特发性关节炎患者

在接受 ACTEMRA 治疗的 PJIA 和 SJIA 患者中，也出现了类似的肝酶升高、中性粒细胞计数低、血小板计数低和血脂升高的情况。在第二次给药时监测中性粒细胞、血小板、ALT 和 AST，此后 PJIA 患者每 4 至 8 周监测一次；SJIA 患者每 2 至 4 周监测一次。按照上述已批准的成人适应症监测血脂*[参见剂量与给药 (2.11)]*。

5.5 免疫抑制

ACTEMRA 治疗对恶性肿瘤发生的影响尚不清楚，但在临床研究中观察到恶性肿瘤*[见不良反应 (6.1)]*。ACTEMRA 是一种免疫抑制剂，免疫抑制剂治疗可能会导致恶性肿瘤风险增加。

5.6 超敏反应，包括过敏性反应

研究报告称超敏反应，包括过敏性反应与 ACTEMRA 相关，且静脉输注 ACTEMRA 已报告可导致过敏性事件并造成致命后果。在静脉注射 ACTEMRA 的 6 个月对照试验中，需要停止治疗的过敏性反应和其他超敏反应的发生率为 0.1% (3/2644)，在静脉注射全暴露 RA 患者中的发生率为 0.2% (8/4009)，在 6 个月的皮下注射对照试验中的发生率为 0.7% (8/1068)，在皮下全暴露患者中的发生率为 0.7% (10/1465)。SJIA 患者静脉注射 ACTEMRA 对照试验中，需要停止治疗的超敏反应发生率为 0.9% (1/112)。PJIA 患者静脉注射 ACTEMRA 的对照试验中，全暴露患者中需要停止治疗的超敏反应发生率为 0% (0/188)。需要停止治疗的反应包括全身红斑、皮疹和荨麻疹。注射部位反应单独分类*[参见不良反应 (6)]*。

上市后，接受不同剂量静脉注射 ACTEMRA 治疗（单药或联合治疗）的患者均发生了超敏反应事件，包括过敏性反应和死亡。术前用药的患者中曾发生过此类事件。超敏反应，包括过敏性反应事件，在既往有无超敏反应和首次输注 ACTEMRA 时均有发生*[参见不良反应(6.12)]*。此外，在接受 ACTEMRA 治疗的自身炎症疾病患者中，已有报告出现严重的皮肤反应，包括嗜酸性粒细胞增多及系统性症状的药物反应 (DRESS)。

ACTEMRA 静脉注射给药只能由医护人员在有医疗保障的情况下进行，以应对过敏性反应。ACTEMRA 皮下注射给药时，如果患者出现任何超敏反应症状，请立即就医。如果发生超敏反应，应立即停止使用 ACTEMRA，并及时进行治疗和监测，直至症状消失。

5.7 脱髓鞘疾病

ACTEMRA 治疗对脱髓鞘疾病的影响尚不清楚，但在 RA 临床研究中很少报道多发性硬化症和慢性炎症性脱髓鞘性多发性神经病。监测患者是否出现脱髓鞘疾病的潜在体征和症状。处方医生在考虑对既往存在或近期发病的脱髓鞘疾病患者使用 ACTEMRA 时应谨慎。

5.8 活动期肝病和肝功能损伤

不推荐在有活动期肝病或肝功能损伤患者中使用 ACTEMRA 治疗*[参见不良反应 (6.1)*，特殊人群用药*(8.6)]*。

5.9 疫苗接种

考虑临床安全性未知，应避免与 ACTEMRA 同时使用活疫苗。目前尚无关于接种活疫苗的患者向接受 ACTEMRA 治疗的患者继发感染传播的数据。

目前尚无关于接受 ACTEMRA 治疗的患者同时接种疫苗的疗效数据。由于 IL-6 抑制可能会干扰对新抗原的正常免疫反应，因此建议所有患者，特别是儿童或老年患者，在开始接受 ACTEMRA 给药之前，尽可能按照现行免疫指南进行所有免疫接种。活疫苗接种和开始 ACTEMRA 治疗之间的间隔时间应符合现行有关免疫抑制剂的疫苗接种指南。

6 不良反应

标签说明中其他地方描述了以下严重不良反应：

- 严重感染*[参见警告和注意事项 (5.1)]*
- 胃肠穿孔*[参见警告和注意事项 (5.2)]*
- 实验室参数*[参见警告和注意事项 (5.4)]*
- 免疫抑制*[参见警告和注意事项 (5.5)]*
- 超敏反应，包括过敏性反应*[参见警告和注意事项 (5.6)]*
- 脱髓鞘疾病*[参见警告和注意事项 (5.7)]*
- 活动期肝病和肝功能损伤*[参见警告和注意事项 (5.8)]*

由于临床研究是在具有广泛差异的条件下进行的，因此在一种药物的临床研究中观察到的不良反应率不能直接与另一种药物的临床研究中的不良反应率进行比较，并且无法预测在临床实践中在更广泛的患者群体中观察到的不良反应率。

6.1 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗类风湿性关节炎患者的临床试验经验

类风湿性关节炎 (RA) 的 ACTEMRA-IV 数据包括 5 项双盲、对照、多中心研究。在这些研究中，患者接受 ACTEMRA-IV 8 mg/kg 单药治疗 (n=288)、ACTEMRA-IV 8 mg/kg 与 DMARDs （包括甲氨蝶呤）联合用药治疗 (n=1582)，或 ACTEMRA-IV 4 mg/kg 与甲氨蝶呤联合用药治疗 (n=774)。

全暴露人群包括注册研究中接受至少 1 剂 ACTEMRA-IV 的所有患者。在该人群的 4009 例患者中，3577 例接受了至少 6 个月的治疗，3309 例接受了至少一年的治疗； 2954 例接受了至少 2 年的治疗，2189 例接受了 3 年的治疗。

这些研究中的所有患者均患有中至重度活动性类风湿性关节炎。研究人群的平均年龄为 52 岁，其中 82% 为女性，74% 为白种人。

最常见的严重不良反应是严重感染*[参见警告和注意事项 (5.1)]*。在长达 24 周的对照研究中，最常见的不良反应是上呼吸道感染、鼻咽炎、头痛、高血压和 ALT 升高（在接受 ACTEMRA-IV 单药给药或与 DMARDs 联合用药的患者中，至少 5% 的患者会出现这些不良反应）。

在双盲、安慰剂对照研究期间，因任何不良反应而停止治疗的患者比例为，接受 ACTEMRA-IV 的患者为 5%，接受安慰剂治疗的患者为 3%。需要停用 ACTEMRA-IV 治疗的最常见不良反应是肝转氨酶值升高（根据方案要求）和严重感染。

总体感染情况

在为期 24 周的对照临床研究中，ACTEMRA-IV 单药给药组的患者感染率为 119/100 患者年，与甲氨蝶呤单药给药组相似。ACTEMRA-IV 4 mg/kg 和 8 mg/kg 与 DMARD 联合用药组的感染率分别为 133/100 患者年和 127/100 患者年，安慰剂与 DMARD 联合用药组的感染率为 112/100 患者年。最常见的感染（占患者的 5% 至 8%）是上呼吸道感染和鼻咽炎。

全暴露人群中 ACTEMRA-IV 的总体感染率与研究对照期间的感染率保持一致。

严重感染

在为期 24 周的对照临床研究中，ACTEMRA-IV 单药给药组的严重感染率为 3.6/100 患者年，而甲氨蝶呤组为 1.5/100 患者年。ACTEMRA-IV 4 mg/kg 和 8 mg/kg 与 DMARD 联合用药组的严重感染率分别为 4.4/100 患者年和 5.3/100 患者年，而安慰剂与 DMARD 联合用药组为 3.9/100 患者年。

在全暴露人群中，严重感染的总体发生率与研究对照期间的发生率保持一致。最常见的严重感染包括肺炎、尿路感染、蜂窝组织炎、带状疱疹、胃肠炎、憩室炎、败血症和细菌性关节炎。已有机会性感染病例报告*[*参见警告和注意事项 *(5.1)]*。

在心血管结局研究 WA25204 中，ACTEMRA IV 每 4 周 8 mg/kg 治疗组，无论是否与 DMARD 联合用药，严重感染的发生率为 4.5/100 患者年；依那西普 SC 每周 50 mg 治疗组，严重感染的发生率为 3.2/100 患者年 *[*参见临床研究 *(14.1)]*。

胃肠穿孔

在为期 24 周的对照临床试验中，ACTEMRA-IV 治疗组的胃肠道穿孔总体发生率为 0.26/100 患者年。

在全暴露人群中，胃肠道穿孔的总体发生率与研究对照期间的发生率保持一致。胃肠道穿孔的报告主要是憩室炎的并发症，包括全身化脓性腹膜炎、下消化道穿孔、瘘管和脓肿。大多数发生胃肠道穿孔的患者同时服用非甾体类抗炎药 (NSAIDs)、皮质类固醇或甲氨蝶呤 *[*参见警告和注意事项 *(5.2)]*。与 ACTEMRA-IV 相比，这些联合用药对胃肠道穿孔的相对影响尚不清楚。

输注反应

在为期 24 周的对照临床研究中，ACTEMRA-IV 4 mg/kg 和 ACTEMRA-IV 8 mg/kg 与 DMARD 联合用药组中，分别有 8% 和 7% 的患者报告了与输液相关的不良事件（发生在输液期间或输液开始后 24 小时内），而安慰剂与 DMARD 联合用药组仅有 5% 的患者报告了此类不良事件。输注期间，4 mg/kg 和 8 mg/kg 剂量组中最常报告的事件是高血压（两种剂量均为 1%），而输注结束 24 小时内最常报告的事件是头痛（两种剂量均为 1%）和皮肤反应（两种剂量均为 1%），包括皮疹、瘙痒和荨麻疹。此类事件不限制治疗。

过敏性反应

在为期 24 周的对照试验中，与 ACTEMRA-IV 相关的需要停止治疗的超敏反应（包括过敏性反应）发生率为 0.1% (3/2644)；在全暴露人群中，与 ACTEMRA-IV 相关的需要停止治疗的超敏反应发生率为 0.2% (8/4009)。这些反应通常发生在第二次至第四次 ACTEMRA-IV 输注期间。如果发生严重的超敏反应，应立即采取适当的医疗治疗*[*参见警告和注意事项 *(5.6)]*。

实验室异常

中性粒细胞减少症

在为期 24 周的对照临床研究中，ACTEMRA-IV 4 mg/kg 与 8 mg/kg 与 DMARD 联合用药组中，患者中性粒细胞计数低于 1000/mm^3 比例分别为 1.8% 和 3.4%，而安慰剂与 DMARD 联合用药组中，这一比例仅为 0.1%。大约一半的 ANC 低于 1000/mm^3 的病例发生在开始治疗后 8 周内。在 ACTEMRA-IV 4mg/kg 和 8mg/kg 与 DMARD 联合用药组中，患者中性粒细胞计数减少至低于 500/mm^3 的比例分别为 0.4% 和 0.3%，而在安慰剂与 DMARD 联合用药组中，这一比例为 0.1%。中性粒细胞减少到 1000/mm^3 以下与严重感染的发生之间没有明确的关系。

在全暴露人群中，中性粒细胞计数减少的模式和发生率与 24 周对照临床研究中观察到的情况一致*[*参见警告和注意事项 *(5.4)]*。

血小板减少症

在为期 24 周的对照临床研究中，ACTEMRA-IV 4 mg/kg 和 8 mg/kg 与 DMARD 联合用药组中，患者血小板计数低于 100,000/mm^3 的比例分别为 1.3% 和 1.7%，而安慰剂与 DMARD 联合用药组中，这一比例为 0.5%，同时未发生相关出血事件。

在全暴露人群中，血小板计数减少的模式和发生率与 24 周对照临床研究中观察到的保持一致*[*参见警告和注意事项 *(5.4)]*。

肝酶升高

表 1 概述了肝酶异常情况。在肝酶升高的患者中，调整治疗方案，如减少 DMARD 联合用药的剂量、中断 ACTEMRA-IV 治疗或减少 ACTEMRA-IV 的剂量，可使肝酶降低或恢复正常*[*参见剂量与给药 *(2.11)]*。肝酶升高与直接胆红素的临床相关增加无关，也与肝炎或肝功能不全的临床证据无关*[*见警告和注意事项 *(5.3, 5.4)]*。

表 1　　在为期 24 周的对照研究 I 至研究 V* 中，肝酶异常的发生率

	ACTEMRA 8 mg/kg 单药给药 N = 288 (%)	**甲氨蝶呤 N = 284 (%)**	**ACTEMRA 4 mg/kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)**	**安慰剂+ DMARDs N = 1170 (%)**
AST (U/L)					
> 1 - 3 倍 ULN	22	26	34	41	17
> 3 - 5 倍 ULN	0.3	2	1	2	0.3
> 5 倍 ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> 1 - 3 倍 ULN	36	33	45	48	23
> 3 - 5 倍 ULN	1	4	5	5	1
> 5 倍 ULN	0.7	1	1.3	1.5	0.3

ULN = 正常上限

*有关这些研究的描述，请参阅第 14 节中“临床研究”。

在全暴露人群中，ALT 和 AST 的升高与 24 周对照临床试验中观察到的情况一致。

在 WA25204 研究中，接受托珠单抗治疗的 1538 例中度至重度 RA 患者中[参见临床研究 (14.1)]，分别有 5.3% 和 2.2% 的患者出现 ALT 或 AST 大于 3 倍 ULN 的情况。研究报告了一起与托珠单抗相关的药物性肝炎伴高胆红素血症的严重事件。

血脂

在为期 24 周的对照临床试验中，在开始接受 ACTEMRA-IV 给药 6 周后首次评估血脂参数（总胆固醇、LDL、HDL、甘油三酯）的升高情况。在此时间点观察到水平升高，此后保持稳定。很少观察到甘油三酯增加至 500 mg/dL 以上的水平。对从基线到第 24 周的其他血脂参数的变化进行了评估，总结如下：

- 在 ACTEMRA 4 mg/kg + DMARD 组、ACTEMRA 8 mg/kg + DMARD 组和 ACTEMRA 8 mg/kg 单药治疗组中，平均 LDL 分别增加了 13 mg/dL、20 mg/dL 和 25 mg/dL。
- 在 ACTEMRA 4 mg/kg + DMARD 组、ACTEMRA 8 mg/kg + DMARD 组和 ACTEMRA 8 mg/kg 单药治疗组中，平均 HDL 分别增加了 3 mg/dL、5 mg/dL 和 4 mg/dL。
- 在 ACTEMRA 4 mg/kg + DMARD 组、ACTEMRA 8 mg/kg + DMARD 组和 ACTEMRA 8 mg/kg 单药治疗组中，平均 LDL/HDL 比值分别增加了 0.14、0.15 和 0.26。
- 接受 ACTEMRA 治疗的患者， ApoB/ApoA1 比值基本没有变化。

血脂水平升高对降脂药物有反应。

在全暴露人群中，血脂参数的升高与 24 周对照临床试验中观察到的情况保持一致。

免疫原性

与所有治疗性蛋白质一样，存在潜在的免疫原性。抗体形成的检测高度依赖于检测方法的灵敏度和特异性。此外，检测中观察到的抗体（包括中和抗体）阳性发生率可能受到多种因素的影响，包括检测方法、样品处理、样品采集时间、伴随药物和潜在疾病。由于这些原因，将下述研究中托珠单抗抗体发生率与其他研究或其他产品中抗体发生率进行比较可能会产生误导。

在为期 24 周的对照临床研究中，共有 2876 例患者接受了抗托珠单抗抗体检测。46 例患者 (2%) 出现抗托珠单抗抗体阳性，其中 5 例患者出现相关的、具有医学意义的超敏反应，导致治疗中止。30 例患者 (1%) 产生了中和抗体。

恶性肿瘤

在为期 24 周的对照研究期间，接受 ACTEMRA-IV 给药的患者诊断出 15 种恶性肿瘤，对照组诊断出 8 种。暴露调整后的发病率在 ACTEMRA-IV 组（1.32/100 患者年）和安慰剂与 DMARD 联合用药组（1.37/100 患者年）相似。

在全暴露人群中，恶性肿瘤的发生率与 24 周对照期观察到的发生率保持一致[见警告和注意事项 (5.5)]。

其他不良反应

表 2 总结了接受 ACTEMRA-IV 4 或 8mg/kg 与 DMARD 联合用药的患者中，不良反应发生率为 2% 或以上，至少比安慰剂与 DMARD 联合用药的患者中观察到的不良反应发生率高 1%。

表 2　　接受 ACTEMRA 4 或 8mg/kg 与 DMARD 联合用药的患者中，不良反应发生率为 2% 或以上，至少比安慰剂与 DMARD 联合用药的患者中观察到的不良反应发生率高 1%

24 周第 3 期对照研究人群					
首选术语	**ACTEMRA 8 mg/kg 单药给药 N = 288 (%)**	**甲氨蝶呤 N = 284 (%)**	**ACTEMRA 4 mg/kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg/kg + DMARDs N = 1582 (%)**	**安慰剂 + DMARDs N = 1170 (%)**
上呼吸道感染	7	5	6	8	6
鼻咽炎	7	6	4	6	4
头痛	7	2	6	5	3
高血压	6	2	4	4	3
ALT 升高	6	4	3	3	1
头晕	3	1	2	3	2
支气管炎	3	2	4	3	3
皮疹	2	1	4	3	1
口腔溃疡	2	2	1	2	1
上腹部疼痛	2	2	3	3	2
胃炎	1	2	1	2	1
转氨酶升高	1	5	2	2	1

在对照试验中，接受 ACTEMRA-IV 治疗的类风湿性关节炎患者中，发生率低于 2% 的其他罕见且医学相关的不良反应包括：

感染及侵染类疾病：口腔单纯疱疹
胃肠道疾病：口腔炎、胃溃疡
检查：体重增加，总胆红素增加

血液和淋巴系统疾病：白细胞减少症
一般疾病和给药部位状况：外周水肿
呼吸、胸部和纵隔疾病：呼吸困难、咳嗽
眼部疾病：结膜炎
肾脏疾病：肾结石
内分泌失调：甲状腺功能减退症

6.2 皮下 ACTEMRA (ACTEMRA-SC) 给药治疗类风湿性关节炎患者的临床试验经验

ACTEMRA-SC 类风湿性关节炎 (RA) 数据包括 2 项双盲、对照、多中心研究。SC-I 研究是一项非劣效性研究，在 1262 例患有类风湿性关节炎的成人受试者中比较了 162 mg 托珠单抗每周皮下给药和 8 mg/kg 托珠单抗每 4 周静脉给药的疗效和安全性。SC-II 研究是一项安慰剂对照优效性研究，在 656 例患者中比较了 162 mg 托珠单抗隔周皮下给药或安慰剂给药的安全性和疗效。两项研究中的所有患者均接受了非生物 DMARDs 治疗。

皮下 ACTEMRA-SC 给药观察到的安全性与静脉 ACTEMRA 给药的已知安全性一致；但注射部位反应 (ISR) 除外，与安慰剂 SC 注射（IV 组）相比，ACTEMRA-SC 注射部位反应更常见。

注射部位反应

在为期 6 个月的 SC-I 对照研究中，ACTEMRA-SC 每周组和安慰剂 SC（IV 组）每周组的 ISR 发生率分别为 10.1% (64/631) 和 2.4% (15/631) 。在 SC-II 研究中，ACTEMRA-SC 隔周组和安慰剂隔周组的 ISR 发生率分别为 7.1% (31/437) 和 4.1% (9/218)。此类 ISRs （包括红斑、瘙痒、疼痛和血肿）的严重程度为轻度至中度。大多数患者无需任何治疗即可痊愈，无需停药。

免疫原性

在为期 6 个月的 SC-I 对照研究中，ACTEMRA-SC 组 0.8% (5/625) 和 IV 组 0.8% (5/627) 的患者产生了抗托珠单抗抗体；所有患者都产生了中和抗体。在 SC-II 研究中，ACTEMRA-SC 组 1.6% (7/434) 和安慰剂组 1.4% (3/217) 的患者产生了抗托珠单抗抗体；其中，ACTEMRA-SC 组 1.4% (6/434) 和安慰剂组 0.5% (1/217) 的患者产生了中和抗体。

在全暴露组中，共有 1454 例 ACTEMRA-SC 的患者 (>99%) 接受了抗托珠单抗抗体测试。13 例患者 (0.9%) 产生了抗托珠单抗抗体，其中 12 例患者 (0.8%) 产生了中和抗体。

该比例与之前的静脉给药发生率一致。尚未观察到抗体产生与不良事件或临床应答丧失的相关性。

实验室异常

中性粒细胞减少症

在为期 6 个月的临床对照试验的常规实验室监测期间，ACTEMRA-SC 每周和隔周给药组中，分别有 2.9% 和 3.7% 的患者中性粒细胞计数下降至低于 1×10^9/L。

中性粒细胞减少至 1 x 10^9/L 以下与发生严重感染之间没有明确关系。

血小板减少症

在为期 6 个月的 ACTEMRA-SC 临床对照试验的常规实验室监测期间，未观察到患者血小板计数下降至低于 50,000/mm^3。

肝酶升高

在为期 6 个月的临床对照试验中的常规实验室监测期间， ACTEMRA-SC 每周给药组中，分别有 6.5% 和 1.4% 的患者出现 ALT 或 AST 升高 ≥3 倍 ULN；ACTEMRA-SC 隔周给药组中，分别有 3.4% 和 0.7% 的患者出现 ALT 或 AST 升高 ≥3 倍 ULN。

血脂参数升高

在为期 6 个月的 ACTEMRA-SC 临床试验的常规实验室监测期间，19% 每周给药的患者，19.6% 隔周给药的患者以及 10.2% 安慰剂给药的患者出现总胆固醇持续升高 > 6.2 mmol/l (240 mg/dL)，其中分别有 9%、10.4% 和 5.1% 的每周、隔周和安慰剂给药患者出现了低密度脂蛋白持续升高至 4.1 mmol/l (160 mg/dL)。

6.3 皮下 ACTEMRA (ACTEMRA-SC) 给药治疗巨细胞动脉炎患者的临床试验经验

对 251 例 GCA 患者进行了皮下 ACTEMRA（托珠单抗）给药的 III 期安全性研究 (WA28119) 。在为期 12 个月的双盲、安慰剂对照研究期间，接受 ACTEMRA-SC 给药的 GCA 患者，全暴露人群的总患者年持续时间为 138.5 患者年。在 ACTEMRA-SC 治疗组中观察到的总体安全性与 ACTEMRA 已知的安全性基本一致。相对于 RA 患者，GCA 患者的感染发生率总体较高。ACTEMRA-SC 每周给药组和隔周给药组中，感染/严重感染事件发生率分别为 200.2/9.7/100 患者年和 160.2/4.4/100 患者年；安慰剂 + 26 周泼尼松减量给药组和安慰剂 + 52 周泼尼松减量给药组中，感染/严重感染事件发生率分别为 156.0/4.2/100 患者年和 210.2/12.5/100 患者年 。

6.4 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗巨细胞动脉炎患者的临床试验经验

一项开放标签的 PK-PD 和安全性研究中，对 24 例 GCA 患者接受 ACTEMRA-IV 给药的安全性进行了评估。患者每 4 周接受 ACTEMRA 7 mg/kg 给药，持续 20 周，随后每 4 周接受 6 mg/kg 给药，持续 20 周。患者接受治疗的总患者年为 17.5 年。在 GCA 患者中观察到的 ACTEMRA 静脉给药的总体安全性与 ACTEMRA 给药的已知安全性一致。

6.5 皮下 ACTEMRA (ACTEMRA-SC) 给药治疗系统性硬化症相关间质性肺病患者的临床试验经验

在两项双盲、安慰剂对照、多中心研究（WA29767 和 WA27788）中，对皮下 ACTEMRA 给药的安全性进行了评估。在 WA29767 的 3 期研究中，212 例 SSc 患者被随机分配至每周一次 162 mg 托珠单抗皮下给药组或安慰剂组，持续 48 周，随后进行开放式标签研究，接受每周一次 162 mg 托珠单抗皮下给药，持续 48 周。在 WA27788 的 2/3 期研究中，87 例患者被随机分配至每周一次 162 mg 托珠单抗皮下给药组或安慰剂组，持续 48 周，随后进行开放式标签研究，接受每周一次 162 mg 托珠单抗皮下给药，持续 48 周。

在 WA29767 研究中，ACTEMRA 在第 48 周的安全性对于 SSc-ILD 和 SSc 患者总体上具有可比性，并且在这两项研究中与 ACTEMRA 给药已知的安全性一致。

免疫原性

在 WA29767 和 WA27788 这两项临床研究中，第 96 周时因治疗诱导的抗 TCZ 抗体的发生率较低 (3/169, 1.8%)。这些抗药物抗体具有中和潜力，所有患者均未发生超敏反应。

6.6 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗多关节型幼年特发性关节炎患者的临床试验经验

在对甲氨蝶呤临床应答不足或不耐受的 188 例 2 ~ 17 岁 PJIA 患儿中进行了 ACTEMRA-IV 的安全性研究。ACTEMRA-IV 全暴露人群（定义为接受了至少一剂 ACTEMRA-IV 的患者）中的患者总暴露量为 184.4 患者年。基线时，约有一半的患者口服皮质类固醇，近 80% 的患者服用甲氨蝶呤。一般而言，PJIA 患者的药物不良反应类型与 RA 和 SJIA 患者中观察到的药物不良反应类型一致*[参见不良反应 (6.1* 和 *6.8)]*。

感染

ACTEMRA-IV 全暴露人群的感染率为 163.7/100 患者年。最常见事件是鼻咽炎和上呼吸道感染。与体重 ≥ 30 kg、接受 8 mg/kg 托珠单抗治疗的患者相比（4.0/100 患者年），体重 < 30 kg、接受 10 mg/kg 托珠单抗治疗的患者的发生严重感染的比例更高（12.2/100 患者年）。与体重 ≥ 30 kg、接受 8 mg/kg 托珠单抗治疗的患者 (8%) 相比，体重 < 30 kg 、接受 10 mg/kg 托珠单抗治疗的患者发生导致剂量中断的感染比例更高 (21%)。

输注反应

在 PJIA 患者中，输注相关反应定义为输注期间或输注后 24 小时内发生的所有事件。在 ACTEMRA-IV 全暴露人群中，11 例 (6%) 在输注期间出现不良事件，38 例 (20.2%) 在输注后 24 小时内出现不良事件。输注期间最常见发生的事件是头痛、恶心和低血压，输注 24 小时内最常见发生的事件是头晕和低血压。一般而言，输注期间或输注 24 小时内观察到的药物不良反应性质上与 RA 和 SJIA 患者中观察到的相似*[参见不良反应(6.1* 和 *6.8)]*。

未报告与托珠单抗相关的、需要中断治疗的临床严重超敏反应。

免疫原性

10 mg/kg、体重 < 30 kg 组中的一例患者出现了抗托珠单抗抗体阳性，但未出现超敏反应，随后退出了研究。

实验室异常

中性粒细胞减少症

在对 ACTEMRA-IV 全暴露人群进行的常规实验室监测期间，3.7% 的患者中性粒细胞计数减少至 < 1 × 10^9/L。

中性粒细胞减少至 < 1 x 10^9/L 与严重感染的发生之间没有明确的关系。

血小板减少症

在对 ACTEMRA-IV 全暴露人群进行的常规实验室监测期间，1% 的患者血小板计数减少至 ≤ 50,000/mm^3，但未出现出血事件。

肝酶升高

在对 ACTEMRA-IV 全暴露人群进行的常规实验室监测期间，分别有 4% 和不到 1% 的患者出现 ALT 或 AST 升高至 ≥ 3 倍 ULN。

血脂

在对托珠单抗全暴露人群进行的常规实验室监测期间，一例患者 (0.5%) 的总胆固醇升高超过 1.5-2 倍 ULN，一例患者 (0.5%) 的 LDL 升高超过 1.5-2 倍 ULN。

6.7 皮下 ACTEMRA (ACTEMRA-SC) 给药治疗多关节型幼年特发性关节炎患者的临床试验经验

对甲氨蝶呤临床应答不足或不耐受的 52 例 1 ~ 17 岁 PJIA 患者进行了 ACTEMRA-SC 的安全性研究。PJIA ACTEMRA-SC 人群中的总患者暴露量（定义为接受了至少一剂 ACTEMRA-SC 并考虑治疗中断的患者）为 49.5 患者年。一般来说，皮下 ACTEMRA 给药观察到的安全性与静脉 ACTEMRA 给药的已知安全性一致，但注射部位反应 (ISR) 和中性粒细胞减少症除外。

注射部位反应

在为期 1 年的研究中，在接受 ACTEMRA-SC 治疗的 PJIA 患者中出现 ISR 发生率为 28.8% (15/52)。与体重 < 30 kg 的患者 (14.8%) 相比，体重 ≥ 30 kg 的患者 (44.0%) 发生此类 ISR 的比例更高。所有 ISR 的严重程度均为轻度，均不需要患者退出或中断治疗。与成人 RA 或 GCA 患者相比，接受 ACTEMRA-SC 治疗的 PJIA 患者 ISR 发生率较高*[参见不良反应(6.2* 和 *6.3)]*。

免疫原性

3 例（1 例体重 < 30 kg 的患者和 2 例体重 ≥ 30 kg 的患者）出现了具有中和潜力的抗托珠单抗抗体阳性，但未出现严重或有临床意义的超敏反应。一例患者随后退出研究。

中性粒细胞减少症

在对 ACTEMRA-SC 全暴露人群的常规实验室监测期间，中性粒细胞计数减少至 1 × 10^9/L 的发生率为 15.4%，并且在体重 < 30 kg 的患者中 (25.9%) 较体重 ≥ 30 kg 的患者 (4.0%) 更常见。中性粒细胞减少至 < 1 x 10^9/L 与严重感染的发生之间没有明确的关系。

6.8 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗全身型幼年特发性关节炎患者的临床试验经验

下面描述的数据反映了一项随机、双盲、安慰剂对照试验中 ACTEMRA-IV 的暴露情况，该试验纳入了 112 例 2 至 17 岁因毒性或缺乏疗效而对非甾体抗炎药 (NSAIDs) 或皮质类固醇临床应答不足的 SJIA 儿童患者。基线时，约有一半的患者每天服用 ≥ 0.3 mg/kg 的皮质类固醇，约 70% 的患者服用甲氨蝶呤。其包括为期 12 周的对照和开放标签扩展期。在为期 12 周的双盲对照临床研究中，75 例患者接受了 ACTEMRA-IV 治疗（根据体重，给药 8 或 12 mg/kg）。12 周后或因病情恶化而放弃治疗时，患者在开放标签扩展期接受了 ACTEMRA-IV 治疗。

在为期 12 周的对照研究中，接受 ACTEMRA-IV 治疗的患者最常见的不良反应（至少 5%）是：上呼吸道感染、头痛、鼻咽炎和腹泻。

感染

在为期 12 周的对照期，ACTEMRA-IV 组的所有感染率为 345/100 患者年，安慰剂组为 287/100 患者年。在平均为期 73 周的的开放标签扩展治疗期间，总体感染率为 304/100 患者年。

在为期 12 周的对照期，ACTEMRA-IV 组的严重感染率为 11.5/100 患者年。在平均为期 73 周的的开放标签扩展治疗期间，严重感染的总体发生率为 11.4/100 患者年。最常见的严重感染包括肺炎、胃肠炎、水痘和中耳炎。

巨噬细胞激活综合征

在为期 12 周的对照研究中，所有治疗组中的患者都未在接受指定治疗期间出现巨噬细胞活化综合征 (MAS)；每 112 例中有 3 例 (3%) 在 ACTEMRA-IV 开放标签治疗期间出现 MAS。安慰剂组中的一例患者由于严重的疾病活动而在第 2 周转而接受 ACTEMRA-IV 12 mg/kg 治疗，并最终在第 70 天出现 MAS。另外两例在长期扩展期间出现 MAS。3 例患者都因 MAS 事件而中断 ACTEMRA-IV 给药 (n=2) 或停药 (n=1)，随后接受治疗，MAS 得到缓解，无后遗症。基于有限数量的病例，在 ACTEMRA-IV SJIA 临床开发经验中，MAS 的发生率似乎并未升高；但无法得出明确的结论。

输注反应

患者未接受术前用药，但大多数患者同时服用皮质类固醇，作为 SJIA 背景治疗的一部分。输注相关反应定义为输注期间或输注后 24 小时内发生的所有事件。在为期 12 周的对照期，ACTEMRA-IV 组 4% 的患者，安慰剂组 0% 的患者在输注期间经历过事件。其中血管性水肿被认为是严重事件且危及生命，因此患者停止了研究治疗。

在输注后 24 小时内，ACTEMRA-IV 治疗组 16% 的患者和安慰剂组 5%的患者发生了不良事件。ACTEMRA-IV 组发生的事件包括皮疹、荨麻疹、腹泻、上腹不适、关节痛和头痛。其中荨麻疹被认为是严重事件。

过敏性反应

在对照和开放标签扩展研究期间接受 ACTEMRA-IV 治疗的 112 例患者，有 1 例出现过敏性反应 （小于 1%）*[参见警告和注意事项 (5.6)]*。

免疫原性

112 例患者均在基线时接受了抗托珠单抗抗体检测。两例患者的抗托珠单抗抗体呈阳性：其中一例出现了与过敏性反应一致的荨麻疹和血管性水肿等严重不良反应，因此退出了研究；另一例在接受替换治疗时出现了巨噬细胞活化综合征，因此退出了研究。

实验室异常

中性粒细胞减少症

在为期 12 周对照阶段的常规监测期间， ACTEMRA-IV 组 7% 的患者，安慰剂组 0% 的患者中性粒细胞减少至 < 1×10^9/L。在平均为期 73 周的开放标签扩展治疗期间，ACTEMRA-IV 组 17% 的患者中性粒细胞计数减少。中性粒细胞减少至 < 1 x 10^9/L 与严重感染的发生之间没有明确的关系。

血小板减少症

在为期 12 周对照阶段的常规监测期间，ACTEMRA-IV 组 1% 的患者，安慰剂组 3% 的患者血小板计数减少至 <100,000/mm^3。

在平均为期 73 周的开放标签扩展治疗期间，ACTEMRA-IV 组 4% 的患者血小板计数减少，且未出现相关出血。

肝酶升高

在为期 12 周对照阶段的常规监测期间，ACTEMRA-IV 组 5% 的患者和 3% 的患者发生了 ALT 或 AST 升高至 ≥3 倍 ULN 的情况，安慰剂组为 0%。

在平均为期 73 周的开放标签扩展治疗期间，接受 ACTEMRA-IV 治疗的患者中分别有 13% 和 5% 的患者 ALT 或 AST 升高至 ≥3 倍 ULN。

血脂

在为期 12 周对照阶段的常规监测期间，ACTEMRA-IV 组 1.5% 的患者，安慰剂组 0% 的患者总胆固醇升高超过 1.5-2 倍 ULN。ACTEMRA-IV 组 1.9% 的患者，安慰剂组 0% 的患者 LDL 升高超过 1.5-2 倍 ULN。

在平均为期 73 周的开放标签扩展研究中，血脂参数升高的模式和发生率与 12 周对照研究数据保持一致。

6.9 皮下 ACTEMRA (ACTEMRA-SC) 给药治疗全身型幼年特发性关节炎患者的临床试验经验

在 51 例 1 至 17 岁对 NSAID 和皮质类固醇的临床应答不足的 SJIA 儿童患者中进行了 ACTEMRA-SC 的安全性研究。一般来说，观察到的皮下 ACTEMRA 给药的安全性与静脉 ACTEMRA 给药的已知安全性一致，但与 PJIA 患者和成人 RA 或 GCA 患者相比，接受 ACTEMRA-SC 治疗的 SJIA 患者 ISR 发生率更高*[*参见不良反应*(6.2*、*6.3* 和 *6.7)]*。

注射部位反应 *(ISR)*

共 41.2% (21/51) 的 SJIA 患者出现 ACTEMRA-SC 相关 ISR。最常见的 ISR 是注射部位红斑、瘙痒、疼痛和肿胀。报告的大多数 ISR 均为 1 级事件，报告的所有 ISR 均不严重，患者无需退出或中断治疗。

免疫原性

在基线时接受抗托珠单抗抗体检测的 51 例患者中，有 46 例 (90.2%) 患者至少有一项基线后筛查检测结果。基线后所有患者未出现抗托珠单抗抗体阳性。

6.10 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗细胞因子释放综合征患者的临床试验经验

在对多项临床试验汇总结果数据的回顾性分析中，45 例患者接受托珠单抗 8 mg/kg（体重小于 30 kg 的患者为 12 mg/kg）治疗，联合或不联合额外的大剂量皮质类固醇，用于治疗重度或危及生命的 CAR T-细胞诱导的 CRS。本试验给予的托珠单抗中位剂量为 1 剂（范围，1 ~ 4 剂）。未报告与托珠单抗相关的不良反应*[*见临床研究*(14.10)]*。

6.11 静脉 ACTEMRA (ACTEMRA-IV) 给药治疗 COVID-19 患者的临床试验经验

在纳入 EMPACTA、COVACTA 和 REMDACTA 患者的汇总安全性人群中，对 ACTEMRA 在 COVID-19 住院患者中的安全性进行了评估。不良反应分析包括总共 974 例接受 ACTEMRA 治疗的患者。患者接受 ACTEMRA 8 mg/kg 给药，单次 60 分钟静脉输注（最大剂量 800 mg）。如果临床体征或症状恶化或没有得到改善，可在首次给药后 8-24 小时内再次给药，剂量为 ACTEMRA 8 mg/kg。

表 3 中总结的不良反应发生在至少 3% 接受 ACTEMRA 治疗的患者中，并且在汇总的安全性人群中，发生率高于安慰剂组患者。

表 3　从汇总的 COVID-19 安全性人群中发现的不良反应 [1]

不良反应	**ACTEMRA 8 mg/kg** **N = 974 (%)**	**安慰剂** **N = 483 (%)**
肝转氨酶升高	10%	8%
便秘	9%	8%
尿路感染	5%	4%
高血压	4%	1%
低钾血症	4%	3%
焦虑	4%	2%
腹泻	4%	2%
失眠	4%	3%
恶心	3%	2%

[1] 不考虑不良反应数量，每个类别的患者均记录一次

在汇总的安全性人群中，ACTEMRA 组患者的感染/严重感染事件发生率为 30%/19%，而安慰剂组为 32%/23%。

实验室异常

在 EMPACTA、COVACTA 和 REMDACTA 汇总的安全性人群中，ACTEMRA 组患者中性粒细胞计数 <1000/mcl 的发生率为 3.4%，而安慰剂组为 0.5%。ACTEMRA 组患者血小板计数 <50,000/mcl 的发生率为 3.2%，而安慰剂组为 1.5%。ACTEMRA 组患者 ALT 或 AST ≥ 5 倍 ULN 的发生率为 11.7%，而安慰剂组为 9.9%。

6.12 上市后经验

ACTEMRA 在批准后应用中发现以下不良反应。由于这些反应由不确定规模的人群自愿报告，因此不一定能够可靠地估计其发生率或建立与药物暴露的因果关系。

- 超敏反应：可能发生致命的过敏性反应、史蒂文斯-约翰逊综合征、以及伴随嗜酸性粒细胞增多和系统性症状的药物反应 (DRESS)。*[参见警告和注意事项 (5.6)]*
- 胰腺炎
- 药物性肝损伤、肝炎、肝功能衰竭、黄疸*[参见警告和注意事项 (5.3)]*

7 药物相互作用

7.1 治疗成人适应症的联合用药

在 RA 患者中，群体药代动力学分析未检测到甲氨蝶呤 (MTX)、非甾体类抗炎药或皮质类固醇对托珠单抗清除率有任何影响。单次静脉 ACTEMRA 10 mg/kg 给药与 10-25 mg MTX 联合用药，每周一次，对 MTX 暴露无临床显着影响。尚未对 ACTEMRA 与生物 DMARDs 如 TNF 拮抗剂联合用药进行研究*[*参见剂量与给药 *(2.2)]*。

在 GCA 患者中，尚未观察到与皮质类固醇联合用药对托珠单抗暴露的影响。

7.2 与 CYP450 底物的相互作用

肝脏中的细胞色素 P450 会受到感染和炎症刺激（包括 IL-6 等细胞因子）的下调。在接受托珠单抗治疗的 RA 患者中，抑制 IL-6 信号传导可能会将 CYP450 活性恢复到比没有托珠单抗时更高的水平，从而导致作为 CYP450 底物的药物代谢增加。体外研究表明，托珠单抗有可能影响多种 CYP 酶的表达，包括 CYP1A2、CYP2B6、CYP2C9、CYP2C19、CYP2D6 和 CYP3A4。托珠单抗对 CYP2C8 或转运蛋白的影响尚不清楚。体内研究显示，接受单剂量 ACTEMRA 一周后，奥美拉唑（由 CYP2C19 和 CYP3A4 代谢）和辛伐他汀（由 CYP3A4 代谢）的暴露量分别减少了 28% 和 57%。托珠单抗对 CYP 酶的影响可能与治疗指数较窄的 CYP450 底物具有临床相关性，其剂量需单独调整。正在接受此类药物治疗的患者在开始或停止接受 ACTEMRA 时，应进行疗效监测（如华法林）或药物浓度监测（如环孢素或茶碱），并酌情调整药物的个体剂量。ACTEMRA 与 CYP3A4 底物药物（例如口服避孕药、洛伐他汀、阿托伐他汀等）联合用药时需谨慎，从而确保疗效。托珠单抗对 CYP450 酶活性的影响可能在停止治疗后持续数周*[*参见临床药理学 *(12.3)]*。

7.3 活疫苗

避免与 ACTEMRA 联合使用活疫苗*[*参见警告和注意事项 *(5.9)]*。

8 特殊人群用药

8.1 妊娠期

风险总结

从妊娠暴露登记、回顾性队列研究、药物警戒和已发表文献中获得的有关 ACTEMRA 的现有数据不足以得出与药物相关的重大出生缺陷、流产或其他不良孕产妇或胎儿结局风险的结论。这些研究在方法上存在局限性，包括托珠单抗暴露组的样本量小、暴露和结果信息缺失，以及缺乏对共因子的调整。托珠单抗等单克隆抗体在妊娠晚期被主动转运穿过胎盘，可能影响子宫内暴露婴儿的免疫应答*[*参见临床考虑*]*。 在动物生殖研究中，给处于器官形成期的食蟹猴静脉注射托珠单抗会导致流产/胚胎死亡，剂量为 1.25 倍，高于每 2 ~ 4 周静脉给药 8 mg/kg 的最大推荐人体剂量。动物研究表明，抑制 IL-6 信号传导可能会干扰宫颈成熟、扩张以及子宫肌层收缩活动，从而导致潜在的分娩延迟*[*参见数据*]*。根据动物数据，胎儿可能存在潜在风险。

该人群严重出生缺陷和流产的预估背景风险尚不清楚。所有妊娠都有出生缺陷、流产或其他不良后果的背景风险。在美国普通人群的临床确诊妊娠中，严重出生缺陷和自然流产的背景风险估计分别为 2% ~ 4% 和 15% ~ 20%。

临床考虑

胎儿/新生儿不良反应

随着妊娠的进展，单克隆抗体越来越多地通过胎盘转运，其中在妊娠晚期转运的量最大。在给子宫内暴露于 ACTEMRA 的婴儿施用活疫苗或减毒活疫苗之前应考虑风险和益处*[*参见警告和注意事项*(5.9)]*。

疾病相关的孕产妇风险

已发表的数据表明，类风湿关节炎女性的不良妊娠结局风险与疾病活动性增加有关。不良妊娠结局包括早产（妊娠 37 周前）、低出生体重（低于 2500 克）婴儿以及出生时小于胎龄儿。

数据

动物数据

在妊娠期 (GD) 20-50 天的器官形成过程中，对妊娠食蟹猴进行性静脉托珠单抗给药，每日剂量为 2、10 或 50 mg/kg，进行了胚胎-胎儿发育毒性研究。尽管没有证据表明托珠单抗具有致畸/畸形发生效应，但托珠单抗剂量为 1.25 倍时流产/胎死宫内的发生率增加，产妇静脉给药剂量为 10 mg/kg 和 50 mg/kg 时的 MRHD 更高。在小鼠中进行的托珠单抗类似物试验中，有证据表明，从植入 (GD 6) 至产后第 21 日（断乳），每 3 日静脉给药 50 mg/kg 的托珠单抗对子代在出生前后的发育期未产生任何危害。没有证据表明后代的发育和行为、学习能力、免疫能力和生育能力有任何功能障碍。

分娩与子宫颈和子宫肌层中 IL-6 的显着增加有关。研究表明，抑制 IL-6 信号传导可能会干扰宫颈成熟、扩张以及子宫肌层收缩活动，从而导致潜在的分娩延迟。与野生型小鼠 ($Il6^{+/+}$) 相比，缺乏 IL-6 的小鼠（$Il6^{-/-}$缺陷型小鼠）分娩时间会推迟。给 $Il6^{-/-}$缺陷型小鼠进行重组 IL-6 给药可恢复正常的分娩时间。

8.2 哺乳期

风险总结

目前尚无关于母乳中是否含有托珠单抗、药物对母乳喂养婴儿的影响或药物对乳汁分泌的影响的信息。母体免疫球蛋白 G (IgG) 存在于母乳中。如果托珠单抗转移到母乳中，婴儿胃肠道局部暴露和潜在的有限全身暴露的影响尚不清楚。由于缺乏哺乳期的临床数据，无法明确确定 ACTEMRA 对哺乳期婴儿的风险；因此，在考虑母乳喂养的发育和健康益处的同时，还应考虑母亲对 ACTEMRA 的临床需求，以及托珠单抗或母亲基础疾病对母乳喂养婴儿的潜在不良影响。

8.4 儿童用药

ACTEMRA 静脉给药适用于治疗患有以下疾病的儿童患者：

- 2 岁及以上活动性全身型幼年特发性关节炎患者
- 2 岁及以上活动性多关节型幼年特发性关节炎患者
- 2 岁及以上出现严重或危及生命的 CAR T 细胞诱导的细胞因子释放综合征 (CRS) 的患者。

ACTEMRA 皮下给药适用于治疗患有以下疾病的儿童患者：

- 2 岁及以上活动性多关节型幼年特发性关节炎患者
- 2 岁及以上活动性全身型幼年特发性关节炎患者

ACTEMRA 在 PJIA、SJIA 或 CRS 以外疾病的儿童患者中的安全性和疗效尚未确定。ACTEMRA 在 2 岁以下 PJIA、SJIA 或 CRS PJIA、SJIA 和 CRS 患者中的安全性和疗效尚未确定。

全身型幼年特发性关节炎 – 静脉给药

采用多中心、开放、单臂研究方法，评估了 ACTEMRA 治疗 2 岁以下 SJIA 患者 (N=11) 12 周的 PK、安全性、探索性 PD 和疗效。患者接受了 ACTEMRA 静脉给药，每 2 周一次，剂量为 12 mg/kg。允许与皮质类固醇、MTX 和/或非类固醇抗炎药联合用药进行稳定背景治疗。完成 12 周治疗期的患者可继续进行可选的延长治疗期（共 52 周或至 2 岁，以较长的一项为准）。

本研究中 ACTEMRA 稳态下的主要 PK 终点（C_{max}、C_{trough} 和 AUC_{2weeks}）均在 2 ~ 17 岁 SJIA 患者的上述参数范围内。

对 2 岁以下 SJIA 患者接受 ACTEMRA 治疗的安全性和免疫原性进行了描述性评估。27.3%、36.4% 和 81.8% 的患者分别报告了 SAE、导致停药的 AE 和感染性 AE。6 例 (54.5%) 出现超敏反应，其定义为输注期间或输注后 24 小时内发生的所有不良事件，被认为与 ACTEMRA 给药相关。其中三例患者出现严重的超敏反应并退出研究。三例出现超敏反应的患者（其中两例为严重超敏反应）在事件发生后产生了治疗诱导的抗托珠单抗抗体。根据方案规定的标准，无 MAS 病例，但根据 Ravelli 标准，有 2 例疑似 MAS 病例[1]。

细胞因子释放综合征 - 静脉给药

在对接受 ACTEMRA 治疗 CAR T 细胞诱导的 CRS 的患者的汇总结果数据进行回顾性分析时，25 例患者是儿童（2 岁至 12 岁），17 例患者是青少年（12 岁至 18 岁）。儿童患者和成人之间的安全性或疗效没有差异。

8.5 老年患者用药

在研究 I 至研究 V 中，接受 ACTEMRA 治疗的 2644 例患者中*[参见临床研究 (14)]*，65 岁及以上的类风湿性关节炎患者共计 435 例，其中 75 岁及以上患者 50 例。在 SC-I 和 SC-II 研究中，接受 ACTEMRA-SC 治疗的 1069 例患者中，65 岁及以上的患者共计 295 例，其中 75 岁及以上患者 41 例。65 岁及以上接受 ACTEMRA 治疗的受试者中严重感染的发生率高于 65 岁以下受试者。由于老年患者的感染发生率普遍较高，因此在治疗老年患者时应谨慎用药。

ACTEMRA 治疗 CRS 患者的临床研究没有纳入足够数量的 65 岁及以上患者，无法确定其疗效是否与年轻患者不同。

在 EMPACTA、COVACTA 和 REMDACTA 研究中，接受 ACTEMRA 治疗的 974 例 COVID-19 患者中，65 岁或以上患者 375 例 (39%)。在这些研究中 65 岁及以上患者和 65 岁以下患者之间没有观察到 ACTEMRA 给药安全性或疗效的总体差异*[参见不良反应 (6.1)* 和临床研究 *(14.11)]*。

在 RECOVERY 研究中，接受 ACTEMRA 治疗的 2022 例 COVID-19 患者中，65 岁或以上患者 930 例 (46%) 。在本研究中，65 岁及以上患者和 65 岁以下患者之间没有观察到 ACTEMRA 给药疗效的总体差异*[参见临床研究 (14.11)]*。

8.6 肝功能损伤

尚未在肝功能损伤患者（包括 HBV 和 HCV 血清学阳性患者）中研究 ACTEMRA 的安全性和疗效*[参见警告和注意事项 (5.8)]*。

8.7 肾损伤

轻度或中度肾损伤患者无需调整剂量。尚未在有严重肾损伤患者中进行过 ACTEMRA 研究*[参见临床药理学 (12.3)]*。

9 药物滥用和依赖性

尚未对 ACTEMRA 引起依赖的可能性进行研究。然而，现有数据没有证据表明 ACTEMRA 治疗会导致依赖性。

[1] Ravelli A、Minoia F、Davì S 分别代表儿童风湿病国际试验组织、儿童关节炎和风湿病研究联盟、儿童风湿病合作研究组和组织细胞协会等。2016 年巨噬细胞激活综合征并发全身型幼年特发性关节炎分类标准。2016 年风湿病年鉴；75:481-489。

10 用药过量

关于 ACTEMRA 过量用药的可用数据有限。有报告称，一例多发性骨髓瘤患者接受静脉 ACTEMRA 给药时意外过量，剂量为 40 mg/kg。未观察到药物不良反应。在接受单剂量高达 28 mg/kg 的健康志愿者中，没有观察到严重的药物不良反应，但在 28 mg/kg 最高剂量下，5 例患者均出现了剂量限制性中性粒细胞减少症。

如果过量用药，应检测患者是否出现不良反应的体征和症状。出现不良反应的患者应接受适当的对症治疗。

11 描述

托珠单抗是一种重组人源化抗人白细胞介素 6 (IL-6) 受体单克隆抗体，具有典型的 H_2L_2 多肽结构，属于免疫球蛋白 IgG1κ (gamma 1, kappa) 亚类。每条轻链和重链分别由 214 个和 448 个氨基酸组成。四个多肽链通过二硫键在分子内和分子间连接。ACTEMRA 的分子量约为 148 kDa。该抗体在哺乳动物（中国仓鼠卵巢）细胞中产生。

静脉注射液

ACTEMRA （托珠单抗）注射液是一种无菌、透明、无色至淡黄色、不含防腐剂的溶液，可在静脉输注前进一步稀释，pH 值约为 6.5。每个单剂量药瓶均采用十二水合磷酸二钠/二水合磷酸二氢钠缓冲溶液配制而成，浓度为 20 mg/mL，含有 80 mg/4 mL、200 mg/10 mL 或 400 mg/20 mL 的 ACTEMRA。每毫升溶液含有聚山梨酯 80 （0.5 mg）、蔗糖 （50 mg）和注射溶液 (USP)。

皮下注射液

ACTEMRA （托珠单抗）注射液是一种无菌、透明、无色至微黄色、不含防腐剂的组氨酸缓冲溶液，适合皮下给药，pH 值约为 6.0。

它由带针头安全装置的即用式单剂量 0.9 mL 预充式注射器 (PFS) 或即用式单剂量 0.9 mL 自动注射器提供，该注射器可提供 162 mg 托珠单抗、L -盐酸精氨酸 (19 mg)、L -组氨酸 (1.52 mg)、L -组氨酸盐酸一水 (1.74 mg)、L -蛋氨酸(4.03 mg)、聚山梨醇酯 80 (0.18 mg) 和注射溶液 (USP)。

12 临床药理学

12.1 作用机制

托珠单抗与可溶性和膜结合型 IL-6 受体（sIL-6R 和 mIL-6R）结合，并已被证明可以通过这些受体抑制 IL-6 介导的信号传导。IL-6 是一种多效性促炎细胞因子，由多种细胞类型产生，包括 T 细胞和 B 细胞、淋巴细胞、单核细胞和成纤维细胞。IL-6 已被证明参与多种生理过程，如 T 细胞激活、诱导免疫球蛋白分泌、启动肝脏急性期蛋白合成以及刺激造血前体细胞增殖和分化。IL-6 也由滑膜和内皮细胞产生，导致受类风湿性关节炎等炎症过程影响的关节局部产生 IL-6。

12.2 药效学

在 RA 患者的临床研究中，静脉 ACTEMRA 4 mg/kg 和 8 mg/kg 给药或每周和隔周皮下 162 mg ACTEMRA 给药时，发现 C 反应蛋白 (CRP) 早在第 2 周就可观察到降至正常范围。观察到药效参数随剂量的变化（即类风湿因子、红细胞沉降率 (ESR)、血清淀粉样蛋白 A、纤维蛋白原的降低和血红蛋白的增加），但在 ACTEMRA 8 mg/kg 给药组中观察到的改善最大。在 GCA、SSc-ILD、PJIA 和 SJIA 患者中观察到 ACTEMRA 给药后发生药效学变化（CRP、ESR 降低和血红蛋白增加）。这些药效学结果与临床疗效之间的关系尚不清楚。

在健康受试者中，ACTEMRA 静脉给药剂量为 2 ~ 28 mg/kg，皮下给药剂量为 81 ~ 162 mg，中性粒细胞绝对计数在 ACTEMRA 给药后 3 ~ 5 天降至最低点。此后，中性粒细胞以剂量依赖性方式恢复至基线水平。类风湿性关节炎和 GCA 患者在 ACTEMRA 给药后表现出相似的绝对嗜中性粒细胞计数模式*[*参见警告和注意事项 *(5.4)]*。

12.3 药代动力学

托珠单抗 PK 的特点是线性清除和 Michaelis-Menten 消除相结合的非线性消除。托珠单抗消除过程中的非线性部分导致暴露增加，增加幅度超过了剂量比例。托珠单抗的药代动力学参数不随时间变化。由于总清除率依赖于托珠单抗血清浓度，托珠单抗的半衰期也具有浓度依赖性，并且根据血清浓度水平而变化。迄今为止，在所有接受测试的患者群体中进行的群体药代动力学分析表明，表观清除率与是否存在抗药抗体之间没有关系。

类风湿性关节炎 - 静脉和皮下给药

健康受试者和 RA 患者的药代动力学结果表明，两种人群的药代动力学相似。

群体 PK 模型来自一个分析数据集，该数据集包括研究 I、研究 III、研究 IV 和研究 V 的 1793 例患者，以及来自研究 SC-I 和 SC- II 的 IV 和 SC 数据集的 1759 例患者。使用 C_{mean} 代替 AUC_{tau} 是因为对于给药间隔不同的给药方案，给药期间的平均浓度可以比 AUC_{tau} 更好地表征比较暴露量的特征。

在高血清浓度下，当托珠单抗的总清除率以线性清除率为主时，根据群体参数估计得出约 21.5 天的终末半衰期。

每 4 周一次 4 mg/kg 托珠单抗静脉给药，稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 的估计中位数（范围）分别为 86.1 (44.8 ~ 202) mcg/mL、0.1 (0.0 ~ 14.6) mcg/mL 和 18.0 (8.9 ~ 50.7) mcg/mL。每 4 周一次 8 mg/kg 托珠单抗静脉给药时，C_{max}、C_{trough} 和 C_{mean} 估计中位数（范围）分别为 176 (75.4–557) mcg/mL、13.4 (0.1–154) mcg/mL 和 54.0 (17–260) mcg/mL。每 4 周一次 4-8 mg/kg 静脉注射给药时，C_{max} 的增加与剂量成正比，而 C_{mean} 和 C_{trough} 的增加幅度大于剂量比例。稳态时，8 mg/kg 的 C_{mean} 和 C_{trough} 分别是 4 mg/kg 时的 3.0 倍和 134 倍。

4 mg/kg 和 8 mg/kg 每 4 周一次静脉多次给药后，AUC 和 C_{max} 的累积率较低，而 C_{trough} 的累积率较高（分别为 2.62 和 2.47）。C_{max} 在第 1 次静脉输注后达到稳态值的 90% 以上。AUC_{tau} 和 C_{mean} 在 4 mg/kg 和 8 mg/kg 静脉输注后，在第 1 次和第 3 次输注后可达到稳态值的 90%，而 C_{trough} 在第 4 次静脉输注后可达到稳态值的 90% 左右。

162 mg SC Q2W 给药时，稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 估计中位数（范围）分别为 12.1 (0.4–49.3) mcg/mL、4.1 (0.0–34.2) mcg/mL 和 9.2 (0.2–43.6) mcg/mL。

162 mg SC QW 给药时，稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 估计中位数（范围）分别为 49.8 (3–150) mcg/mL、42.9 (1.3–144) mcg/mL 和 47.3 (2.4–147) mcg/mL 与 162 mg SC Q2W 给药方案相比，162 mg SC QW 给药后的暴露量增加了 5.1 (C_{mean}) 至 10.5 (C_{trough})。

任一 SC 方案多次给药后的累积率均高于 IV 方案后的累积率，其中 C_{trough} 比率最高（162 mg SC Q2W 和 162 mg SC QW 分别为 6.02 和 6.30）。根据低浓度时的非线性清除作用，预计 C_{trough} 的累积量较高。Q2W 和 QW 给药方案中，C_{max} 分别在第 5 次 SC 和第 12 次 SC 注射后达到稳态值的 90% 以上。162 mg SC Q2W 和 QW 给药方案中，AUC_{tau} 和 C_{mean} 在第 6 次和第 12 次注射后分别达到稳态值的 90%。162 mg SC Q2W 和 QW 给药方案中，C_{trough} 分别在第 6 次和第 12 次注射后达到稳态值的约 90%。

群体 PK 分析确定体重是影响托珠单抗药代动力学的重要协变量。当以 mg/kg 为基础进行静脉给药时，预计体重 ≥ 100 kg 的个体的平均稳态暴露量将高于患者群体的平均值。因此，不建议 RA 患者每次输注托珠单抗剂量超过 800 mg*[参见剂量与给药 (2.2)]*。由于托珠单抗 SC 给药采用统一剂量，因此无需对该给药途径进行任何修改。

巨细胞动脉炎 – 皮下和静脉给药

托珠单抗 SC 在 GCA 患者中的药代动力学是通过对每周一次皮下注射 162 mg 或隔周一次皮下注射 162 mg 治疗的 149 例 GCA 患者组成的数据集进行群体药代动力学分析来确定的。

162 mg 每周一次皮下给药时，稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 估计中位数分别为 72.1 (12.2–151) mcg/mL、67.2 (10.7–145) mcg/mL 和 70.6 (11.7–149) mcg/mL。C_{mean} 或 AUC_{tau}、C_{trough} 和 C_{max} 的累积率分别为 10.9、9.6 和 8.9。17 周后达到稳定状态。162 mg 隔周一次给药时，稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 估计中位数分别为 17.2 (1.1–56.2) mcg/mL、7.7 (0.1–37.3) mcg/mL 和 13.7 (0.5–49) mcg/mL。C_{mean} 或 AUC_{tau}、C_{trough} 和 C_{max} 的累积率分别为 2.8、5.6 和 2.3。14 周后达到稳定状态。

通过非房室药代动力学分析对 GCA 患者中托珠单抗 IV 的药代动力学进行了表征，该分析包括 22 例患者，每 4 周以 6 mg/kg 静脉给药，持续 20 周。稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 的中位数（范围）平均值分别为 178 (115-320) mcg/mL、22.7 (3.38-54.5) mcg/mL 和 57.5 (32.9-110) mcg/mL 。GCA 患者接受 162 mg TCZ SC 每周或隔周给药后，其稳态谷浓度均在观察到的范围内。

根据药代动力学暴露以及 RA 和 GCA 患者之间的外推法，以 mg/kg 为基础进行静脉注射时，不建议 GCA 患者每次输注托珠单抗的剂量超过 600 mg*[参见剂量与用法 (2.3)]*。

系统性硬化症相关间质性肺疾病 - 皮下给药

托珠单抗在 SSc-ILD 患者中的药代动力学是通过对每周接受 162 mg 托珠单抗 SC 治疗的 66 例 SSc-ILD 患者组成的数据集进行群体药代动力学分析来确定的。

稳态时托珠单抗的 C_{max}、C_{trough} 和 C_{mean} 的中位数（范围）平均值分别为 52.5 (14.8-121) mcg/mL、47.2 (10.8-114) mcg/mL 和 50.4 (13.4-119) mcg/mL。C_{mean} 或 AUC_{tau}、C_{trough} 和 C_{max} 的累积率分别为 7.11、6.56 和 5.89。13 周后达到稳定状态。

多关节型幼年特发性关节炎–静脉和皮下给药

托珠单抗 (TCZ) 在 PJIA 患者中的药代动力学通过群体药代动力学分析进行表征，该分析包括 188 例接受 TCZ IV 治疗的患者或 52 例接受 TCZ SC 治疗的患者。

每 4 周一次 8 mg/kg 托珠单抗静脉给药时（体重 ≥ 30 kg 的患者），稳态时托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 181 (114–331) mcg/mL、3.28 (0.02–35.4) mcg/mL 和 38.6 (22.2–83.8) mcg/mL。体重 ≥ 30 kg 的患者，每 4 周一次 10 mg/kg 托珠单抗静脉给药时，稳态时托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 167 (125–220) mcg/mL、0.35 (0–11.8) mcg/mL 和 30.8 (16.0–48.0) mcg/mL。

10 mg/kg（体重 < 30 kg）和 8 mg/kg（体重 ≥ 30 kg）静脉给药时， AUC_{4weeks} 的累积率分别为 1.05 和 1.16，C_{trough} 的累积率分别为 1.43 和 2.22。没有观察到 C_{max} 的积累率。2 ~ 17 岁 PJIA 患者每 4 周一次 TCZ IV 10 mg/kg 和 8 mg/kg 给药后，稳态浓度（谷值和平均值)）均在 4 mg/kg 和 8 mg/kg 给药后的成人 RA 患者的暴露范围内，PJIA 患者稳态峰值浓度与成人 RA 患者每 4 周一次 8 mg/kg 给药后的峰值浓度相当。

体重 ≥ 30 kg 的患者，每 2 周一次 162mg 托珠单抗皮下给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 29.7 (7.56–50.3) mcg/mL、12.7 (0.19–23.8) mcg/mL 和 23.0 (3.86–36.9) mcg/mL。体重 < 30 kg 的患者，每 3 周一次 162mg 托珠单抗皮下给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 62.4 (39.4–121) mcg/mL、13.4 (0.21–52.3) mcg/mL 和 35.7 (17.4–91.8) mcg/mL。

每 3 周 162 mg（体重 < 30 kg）和每 2 周 162 mg（体重 ≥ 30 kg）皮下给药时，AUC_{4weeks} 累积比分别为 1.46 和 2.04，C_{trough} 分别为 2.08 和 3.58，C_{max} 分别为 1.32 和 1.72。皮下给药后，两个体重组患者的稳态 C_{trough} 相当，而体重 < 30 kg 组的患者的稳态 C_{max} 和 C_{mean} 高于 ≥ 30 kg 组的患者。所有接受 TCZ SC 治疗的患者在整个体重范围内的稳态 C_{trough} 均等于或高于 TCZ IV 的水平。皮下给药后患者的平均浓度和谷浓度在成人 RA 患者皮下给药推荐方案后达到的浓度范围内。

全身型幼年特发性关节炎—静脉和皮下给药

托珠单抗 (TCZ) 在 SJIA 患者中的药代动力学通过群体药代动力学分析进行表征，其中包括 89 例接受 TCZ IV 治疗的患者或 51 例接受 TCZ SC 治疗的患者。

体重 ≥ 30 kg 的患者，每 2 周一次 8 mg/kg 托珠单抗静脉给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 253 (120–404) mcg/mL、70.7 (5.26–127) mcg/mL 和 117 (37.6–199) mcg/mL。体重 < 30 kg 的患者，每 2 周一次 12 mg/kg 托珠单抗静脉给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 274 (149-444) mcg/mL、65.9 (19.0–135) mcg/mL 和 124 (60-194) mcg/mL。

12 mg/kg（体重 < 30 kg）和 8 mg/kg（体重 ≥ 30 kg）静脉给药时， AUC_{4weeks} 的累积率分别为 1.95 和 2.01，C_{trough} 的累积率分别为 3.41 和 3.20。12 mg/kg（体重 < 30 kg）和 8 mg/kg（体重 ≥ 30 kg）静脉给药时， C_{max} 累积数据分别为 1.37 和 1.42。隔周使用托珠单抗 IV 给药后，两个体重组均在 8 周内达到稳定状态。由体重定义的两个剂量组之间的平均估计托珠单抗暴露参数相似。

体重 ≥ 30 kg 的患者，每周一次 162 mg 托珠单抗皮下给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 89.8 (26.4–190) mcg/mL、72.4 (19.5–158) mcg/mL 和 82.4 (23.9–169) mcg/mL。体重 < 30 kg 的患者，每 2 周一次 162mg 托珠单抗皮下给药时，托珠单抗的 C_{max}、 C_{trough} 和 C_{mean} 的估计中位数范围分别为 127 (51.7–266) mcg/mL、64.2 (16.6–136) mcg/mL 和 92.7 (38.5–199) mcg/mL。

每 2 周 162 mg（体重 < 30 kg）和每周 162 mg（体重 ≥ 30 kg）皮下给药时，AUC_{4weeks} 累积比分别为 2.27 和 4.28，C_{trough} 分别为 3.21 和 4.39，C_{max} 分别为 1.88 和 3.66。皮下给药后，两个体重组均在 12 周内达到稳定状态。所有接受托珠单抗 SC 治疗的患者在整个体重范围内的稳态 C_{max} 均低于托珠单抗 IV 的水平 。皮下给药后患者的谷浓度和平均浓度与托珠单抗 IV 在体重上所达到的浓度相似。

***COVID-19* - 静脉给药**

COVID-19 患者托珠单抗的药代动力学特征是对 COVACTA 研究*[*参见临床研究*(14.11)]*和另一项研究中 380 例接受 8mg/kg 托珠单抗静脉给药 (IV) 的成人患者数据集进行的群体药代动力学分析得出的。

单剂量 8 mg/kg 托珠单抗 IV 给药时，托珠单抗的估计中位数（范围）C_{max} 和 C_{day28} 分别为 151 (77.5-319) mcg/mL 和 0.229 (0.00119-19.4) mcg/mL。间隔至少 8 小时的两次 8 mg/kg 托珠单抗 IV 给药时，托珠单抗的估计中位（范围）C_{max} 和 C_{day28} 分别为 290 (152-604) mcg/mL 和 7.04 (0.00474-54.8) mcg/mL 。RECOVERY 研究中采用的体重分级剂量：体重 >90kg 的患者为 800mg，体重 >65 且 ≤90kg 的患者为 600mg，体重 >40 且 ≤65kg 的患者为 400mg，体重 ≤40kg 的患者为 8mg/kg，预计与 8 mg/kg 剂量具有相似的暴露量。

<u>吸收</u>

RA 和 GCA 患者皮下给药后，吸收半衰期约为 4 天，SSc-ILD 患者的吸收半衰期约为 3 天。皮下制剂的生物利用度为 80%。

PJIA 患者皮下给药后，吸收半衰期约为 2 天，PJIA 患者皮下制剂的生物利用度为 96%。

SJIA 患者皮下给药后，吸收半衰期约为 2 天，SC 制剂在 SJIA 患者中的生物利用度为 95%。

RA 患者每周托珠单抗给药和隔周托珠单抗给药后的 T_{max} 中位值分别为 2.8 天和 4.7 天。

GCA 患者每周托珠单抗给药和隔周托珠单抗给药后的 T_{max} 中位值分别为 3 天和 4.5 天。

SSc-ILD 患者每周托珠单抗给药后的 T_{max} 的中位值为 2.8 天。

分布

静脉给药后，托珠单抗从循环中进行双相消除。类风湿性关节炎患者的中心分布体积为 3.5 L，外周分布体积为 2.9 L，稳态分布体积为 6.4 L。

GCA 患者的中心分布体积为 4.09 L，外周分布体积为 3.37 L，导致稳态分布体积为 7.46 L。

SSc-ILD 患者的中心分布体积为 4.16 L，外周分布体积为 2.58 L，导致稳态分布体积为 6.74 L。

PJIA 儿童患者的中心分布体积为 1.98 L，外周分布体积为 2.1 L，稳态分布体积为 4.08 L。

SJIA 儿童患者的中心分布体积为 1.87 L，外周分布体积为 2.14 L，稳态分布体积容积为 4.01 L。

COVID-19 患者间隔 8 小时静脉输注一或两次托珠单抗 8 mg/kg，估计中心分布体积为 4.52 L，估计外周分布体积为 4.23 L，估计稳态分布体积为 8.75 L。

消除

ACTEMRA 是通过线性间隙和非线性消除相结合的方式来消除的。浓度依赖性非线性消除在低托珠单抗浓度下起主要作用。一旦非线性途径饱和，在较高托珠单抗浓度下，清除率主要由线性清除率决定。非线性消除的饱和导致暴露的增加超过剂量比例。ACTEMRA 的药代动力学参数不随时间变化。

迄今为止，在所有接受测试的患者群体中进行的群体药代动力学分析表明，表观清除率与是否存在抗药抗体之间没有关系。

群体药代动力学分析中的线性清除率估计为：RA 患者为 12.5 mL/h，GCA 患者为 6.7 mL/h，SSc-ILD 患者为 8.8 mL/h，PJIA 儿童患者为 5.8 mL/h，PJIA 儿童为 5.7 mL/h。COVID-19 患者静脉输注 8 mg/kg 托珠单抗 1 次后，平均 35 天后血清浓度低于定量限。群体药代动力学分析中的平均线性清除率估计如下：基线等级量表 3 级患者（OS 3，需要辅助供氧的患者）为 17.6 mL/h，基线 OS 4 级患者（需要高流量氧疗或无创通气的患者）为 22.5 mL/h，基线 OS 5 级患者（需要机械通气的患者）为 29 mL/h。基线 OS 6 的患者（需要体外膜肺氧合或机械通气和其他器官支持的患者）为 35.4 mL/h。

由于总清除率依赖于 ACTEMRA 血清浓度，ACTEMRA 的半衰期也具有浓度依赖性，并且根据血清浓度水平而变化。

RA 患者每 4 周 4mg/kg 和 8mg/kg 静脉给药时，稳态时的浓度依赖性表观 t1/2 分别长达 11 天和 13 天。RA 患者每周和隔周 162 mg 皮下给药时，稳态时的浓度依赖性表观 $t_{1/2}$ 分别为长达 13 天和 5 天。

GCA 患者每周和隔周 162 mg 皮下给药方案中，托珠单抗有效 $t_{1/2}$ 的范围分别为 18.3 ~ 18.9 天以及 4.2 ~ 7.9 天。GCA 患者每 4 周 6 mg/kg 静脉给药后，TCZ 浓度依赖性表观 $t_{1/2}$ 为 13.2 天。

SSc-ILD 患者每周 162 mg 皮下给药方案中，稳态时托珠单抗有效 $t_{1/2}$ 在 12.1 至 13.0 天之间变化。

两个体重组（体重 ≥ 30 kg 的患者为 8 mg/kg，体重 < 30 kg 的患者为 10 mg/kg）稳态时给药间歇期，托珠单抗在 PJIA 儿童中的 $t_{1/2}$ 最长为 17 天。两个体重组（体重 ≥ 30 kg 的患者隔周给药，体重 < 30 kg 的患者每 3 周给药一次）稳态时给药间歇期，托珠单抗静脉给药时，PJIA 患者的 $t_{1/2}$ 最长为 10 天。

两个体重组（体重 ≥ 30 kg 的患者为 8 mg/kg，体重 < 30 kg 的患者为隔周 12 mg/kg）稳态时给药间歇期，托珠单抗静脉给药时，SJIA 儿童患者的 $t_{1/2}$ 最长为 16 天。两个体重组（体重 ≥ 30 kg 的患者每周 162，体重 < 30 kg 的患者为每 2 周 162 mg/）稳态给药间歇期，托珠单抗皮下给药时，SJIA 患者的有效 $t_{1/2}$ 最长为 14 天。

特殊人群

成人类风湿性关节炎患者和 GCA 患者的群体药代动力学分析表明，年龄、性别和种族不影响托珠单抗的药代动力学。发现线性间隙随着体重的增加而增加。在 RA 患者中，按体重计算的给药剂量 (8 mg/kg) 使体重 > 100 kg 的患者的暴露量比体重 < 60 kg 的患者高出约 86%。固定剂量皮下给药方案中，托珠单抗暴露与体重之间呈负相关。

在接受 ACTEMRA-SC 治疗的 GCA 患者中，体重较低的患者观察到较高的暴露量。每周 162 mg 皮下给药方案中，体重 < 60 kg 的患者的稳态 C_{mean} 值比体重在 60 至 100 kg 之间的患者高 51%。隔周 162 mg 皮下给药方案中，体重 < 60 kg 的患者的稳态 C_{mean} 值比体重在 60 至 100 kg 之间的患者高 129%。体重超过 100 公斤的患者的数据有限 (n=7)。

在 COVID-19 患者中，按体重静脉给药 （8 mg/kg 托珠单抗，最大剂量为 800 mg，体重不超过 100 kg）后的暴露情况取决于体重和通过等级量表 (OS) 评估的疾病严重程度。在 OS 类别中，与平均体重为 80 kg 的患者相比，体重 < 60 kg 的患者的暴露量低 20%。体重超过 100 kg 的患者的暴露范围与平均体重为 80 kg 的患者的暴露范围相同。对于体重 80 kg 的患者，暴露量随着 OS 类别的增加而减少；每增加一个类别，曝光度就会减少 13%。

肝功能损伤患者

尚未进行肝功能损伤对托珠单抗药代动力学影响的正式研究。

肾损伤患者

尚未进行肾损伤对托珠单抗药代动力学影响的正式研究。

群体药代动力学分析中大多数 RA、GCA 和 SSc-ILD 患者肾功能正常或轻度肾损伤。轻度肾损伤（根据 Cockcroft-Gault 公式估计肌酐清除率低于 80 mL/min 且等于或高于 50 mL/min）不会影响托珠单抗的药代动力学。

ACTEMRA-SC GCA 临床试验中大约三分之一的患者在基线时有中度肾损伤（估计肌酐清除率为 30-59 mL/min）。这些患者中没有发现对托珠单抗暴露的影响。

轻度或中度肾损伤患者无需调整剂量。

药物相互作用研究

体外数据表明，IL-6 降低了几种 CYP450 同工酶的 mRNA 表达，包括 CYP1A2、CYP2B6、CYP2C9、CYP2C19、CYP2D6 和 CYP3A4，并且通过与临床相关浓度的托珠单抗共孵育可逆转这种降低的表达。因此，用托珠单抗治疗的 RA 患者中 IL-6 信号传导的抑制可能会将 CYP450 活性恢复到比没有托珠单抗时更高的水平，从而导致作为 CYP450 底物的药物代谢增加。它对 CYP2C8 或转运蛋白 （例如 P-gp）的影响尚不清楚。这在临床上与治疗指数较窄的 CYP450 底物相关，其中剂量需单独调整。开始使用 ACTEMRA 后，对于正在接受这些类型药品治疗的患者，应进行疗效（例如华法林）或药物浓度（例如环孢素或茶碱）的治疗监测，并根据需要调整药品的个体剂量。当 ACTEMRA 与药效降低的药物（如口服避孕药（CYP3A4 底物））联合用药时应谨慎*[参见药物相互作用 (7.2)]*。

辛伐他汀

辛伐他汀是 CYP3A4 和 OATP1B1 底物。在 12 例未接受 ACTEMRA 治疗，但接受 40 mg 辛伐他汀治疗的 RA 患者中，辛伐他汀及其代谢物辛伐他汀酸的暴露分别比在健康受试者中观察到的暴露高 4-10 倍和 2 倍。单次输注 ACTEMRA (10 mg/kg) 给药一周后，辛伐他汀和辛伐他汀酸的暴露分别减少 57% 和 39%，与健康受试者中观察到的暴露相似或稍高。RA 患者停用 ACTEMRA 后，辛伐他汀和辛伐他汀酸的暴露增加。为 RA 患者选择辛伐他汀的特定剂量时，应考虑到接受 ACTEMRA 给药后可能导致较低的暴露（由于 CYP3A4 正常化）或终止 ACTEMRA 给药后可能导致较高的暴露。

奥美拉唑

奥美拉唑是 CYP2C19 和 CYP3A4 底物。在接受 10 mg 奥美拉唑治疗的 RA 患者中，奥美拉唑的暴露量比健康受试者中观察到的高约 2 倍。在接受 10 mg 奥美拉唑治疗的 RA 患者中，ACTEMRA 输注前和输注后 1 周 (8 mg/kg)，对于低代谢者 (N=5) 和中间代谢者 (N=5) ，奥美拉唑 AUC_{inf} 下降 12%，对于强代谢者 (N=8)，奥美拉唑 AUC_{inf} 下降 28%，略高于健康受试者中观察到的水平。

右美沙芬

右美沙芬是 CYP2D6 和 CYP3A4 的底物。在 13 例接受 30 mg 右美沙芬治疗的 RA 患者中，右美沙芬的暴露量与健康受试者相当。然而，在健康受试者中观察到一小部分其代谢物右啡烷（CYP3A4 底物）的暴露量。单次输注 ACTEMRA (8 mg/kg) 后一周，右美沙芬暴露量减少约 5%。然而，在 ACTEMRA 输注后，右啡烷水平出现较大下降 (29%)。

13 非临床毒理学

13.1 致癌性、致突变性和生育力受损

尚未进行长期动物研究来确定托珠单抗的潜在致癌性。文献表明，IL-6 途径可以通过促进增强免疫细胞对肿瘤微环境的监视来介导抗肿瘤反应。然而，现有已发表的证据也支持通过 IL-6 受体的 IL-6 信号传导可能参与了导致肿瘤发生的途径。目前尚不清楚托珠单抗等破坏 IL-6 受体信号传导的抗体对人类恶性肿瘤的风险。

每三天静脉注射 50 mg/kg 剂量的托珠单对鼠类雄性和雌性小鼠的生育能力和生殖性能未受影响。

14 临床研究

14.1 类风湿性关节炎—静脉给药

五项随机、双盲、多中心研究评估了静脉注射 ACTEMRA 的疗效和安全性，研究对象为根据美国风湿病学会 (ACR) 标准诊断的 18 岁以上活动性类风湿性关节炎患者。基线时患者至少有 8 个关节压痛和 6 个关节肿胀。ACTEMRA 每 4 周一次静脉注射给药，作为单药用药（研究 I），或与甲氨蝶呤 (MTX)（研究 II 和 III） 或其他疾病缓解抗风湿药物 (DMARDs)（研究 IV） 联合用药治疗对此类药物应答不足的患者，或与 MTX 联合用药治疗对 TNF 拮抗剂应答不足的患者 （研究 V）。

研究 *I* (NCT00109408) 评估了在随机分组前 24 周内未接受过 MTX 治疗，或者既往甲氨蝶呤治疗未因有临床意义的毒性作用或无应答而停止的中度至重度活动性类风湿性关节炎患者。在这项研究中，67% 的患者未接受过 MTX 给药，超过 40% 的患者患有类风湿性关节炎不到 2 年。患者接受 ACTEMRA 8 mg/kg 单药给药或 MTX 单药给药（剂量在 8 周内从每周 7.5 mg 滴定至最大 20 mg）。主要终点是在第 24 周达到 ACR 20 应答的 ACTEMRA 患者比例。

研究 *II* (NCT00106535) 是一项为期 104 周的研究，其中包括可选的 156 周延长期，评估对 MTX 临床应答不足的中度至重度活动性类风湿性关节炎患者。患者接受 ACTEMRA 8 mg/kg、ACTEMRA 4 mg/kg 或安慰剂与 MTX （每周 10 至 25 mg）联合用药治疗，每 4 周一次。52 周结束后，患者接受 ACTEMRA 8 mg/kg 的开放标签治疗直至 104 周，或者如果肿胀/压痛关节计数保持超过 70% 的改善，他们可以选择继续双盲治疗。在第 24 周和第 52 周进行了两次预先指定的中期分析。第 24 周的主要终点是达到 ACR 20 应答的患者比例。在第 52 周和第 104 周，主要终点是改良 Sharp-Genant 总评分相与基线相比的变化以及 HAQ-DI 评分相对于基线变化的曲线下面积 (AUC)。

研究 *III* (NCT00106548) 评估了对 MTX 临床应答不足的中度至重度活动性类风湿性关节炎患者。患者接受 ACTEMRA 8 mg/kg、ACTEMRA 4 mg/kg 或安慰剂与 MTX （每周 10 至 25 mg）联合用药治疗，每 4 周一次。主要终点是在第 24 周达到 ACR 20 应答的患者比例。

研究 *IV* (NCT00106574) 评估了对其现有疗法（包括一种或多种 DMARDs）应答不足的患者。患者每四周接受 ACTEMRA 8 mg/kg 或安慰剂，并与稳定的 DMARDs 联合治疗。主要终点是在第 24 周达到 ACR 20 应答的患者比例。

研究 *V* (NCT00106522) 评估了对一种或多种 TNF 拮抗剂疗法临床应答不足或不耐受的中重度活动性类风湿性关节炎患者。TNF 拮抗剂治疗在随机分组前停止。患者接受 ACTEMRA 8 mg/kg、ACTEMRA 4 mg/kg 或安慰剂与 MTX （每周 10 至 25 mg）联合用药治疗，每 4 周一次。主要终点是在第 24 周达到 ACR 20 应答的患者比例。

临床应答

静脉 ACTEMRA 给药的患者达到 ACR 20、50 和 70 反应的百分比见**表 4**。在所有静脉研究中，第 24 周时，与 MTX 或安慰剂治疗的患者相比，用 8 mg/kg ACTEMRA 治疗的患者具有更高的 ACR 20、ACR 50 和 ACR 70 反应率。

在研究 I 至研究 V 的 24 周对照部分期间，对 DMARDs 或 TNF 拮抗剂治疗反应不足的患者中用 ACTEMRA 剂量 4 mg/kg 治疗的患者与用 ACTEMRA 8 mg/kg 治疗的患者相比有较低的反应率。

表 4　　静脉 ACTEMRA 给药的主动对照试验和安慰剂对照试验中第 24 周和第 52 周的临床应答（患者百分比）

患者百分比													
	研究 I		研究 II			研究 III			研究 IV		研究 V		
	MTX	ACTEMRA 8 mg/kg	安慰剂 + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX	安慰剂 + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX	安慰剂 + DMARDs	ACTEMRA 8 mg/kg + DMARDs	安慰剂 + MTX	ACTEMRA 4 mg/kg + MTX	ACTEMRA 8 mg/kg + MTX
应答率	N=284	N=286 (95% CI)[a]	N=393	N=399 (95% CI)[a]	N=398 (95% CI)[a]	N=204	N=213 (95% CI)[a]	N=205 (95% CI)[a]	N=413	N=803 (95% CI)[a]	N=158	N=161 (95% CI)[a]	N=170 (95% CI)[a]
ACR 20													
第 24 周	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
第 52 周	不适用	不适用	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	不适用	不适用	不适用	不适用	不适用	不适用	不适用	不适用
ACR 50													
第 24 周	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
第 52 周	不适用	不适用	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	不适用	不适用	不适用	不适用	不适用	不适用	不适用	不适用
ACR 70													
第 24 周	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
第 52 周	不适用	不适用	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	不适用	不适用	不适用	不适用	不适用	不适用	不适用	不适用
主要临床应答[b]													
第 52 周	不适用	不适用	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	不适用	不适用	不适用	不适用	不适用	不适用	不适用	不适用

[a] CI:针对研究中心（仅研究 I 的病程）调整后与安慰剂的加权差异的 95% 置信区间

[b] 主要临床应答的定义为连续 24 周达到 ACR 70 应答

在研究 II 中，与接受安慰剂 + MTX 治疗的患者相比，接受 4 mg/kg 和 8 mg/kg ACTEMRA + MTX 治疗的患者中，有更大比例的患者在第 52 周时疾病活动度达到较低水平 （以 DAS 28-ESR 小于 2.6 来衡量）研究 II 中，接受 ACTEMRA 治疗后实现 DAS 28-ESR 小于 2.6 的患者比例以及这些应答者的剩余活动关节数量见 **表 5**。

表 5　　静脉 ACTEMRA 给药试验中，DAS 28-ESR 小于 2.6 的患者比例及剩余活动关节数量

研究 II			
	安慰剂 + MTX **N = 393**	**ACTEMRA 4 mg/kg + MTX** **N = 399**	**ACTEMRA 8 mg/kg + MTX** **N = 398**
DAS28-ESR 小于 2.6			
第 52 周时应答者的比例 (n) 95%置信区间	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
应答者中，关节活动度为 0 的比例 (n)	33% (4)	27% (19)	21% (27)
应答者中，关节活动度为 1 的比例 (n)	8% (1)	19% (13)	13% (16)
应答者中，关节活动度为 2 的比例 (n)	25% (3)	13% (9)	20% (25)
应答者中，关节活动度为 3 或以上的比例 (n)	33% (4)	41% (29)	47% (59)

*n 表示所有百分比的分子。分母是意向治疗人群。并非所有患者在第 52 周时都接受了 DAS28 评估。

表 6 列出了研究 III 和研究 V 的 ACR 应答标准组成部分的结果。研究 I、II 和 IV 中观察到与研究 III 类似的结果。

表 6　　静脉 ACTEMRA 给药试验中，第 24 周时 ACR 应答的组成部分

	研究 III						**研究 V**					
	ACTEMRA 4 mg/kg + MTX N=213		**ACTEMRA 8 mg/kg + MTX N=205**		**安慰剂 + MTX N=204**		**ACTEMRA 4 mg/kg + MTX N=161**		**ACTEMRA 8 mg/kg + MTX N=170**		**安慰剂 + MTX N=158**	
组成部分（平均值）	**基线**	**第 24 周 [a]**	**基线**	**第 24 周 [a]**	**基线**	**第 24 周**	**基线**	**第 24 周 [a]**	**基线**	**第 24 周 [a]**	**基线**	**第 24 周**
压痛关节数量 (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
肿胀关节数量 (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
疼痛 [b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
患者整体评估 [b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
医师整体评估 [b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
残疾指数 (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg/dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

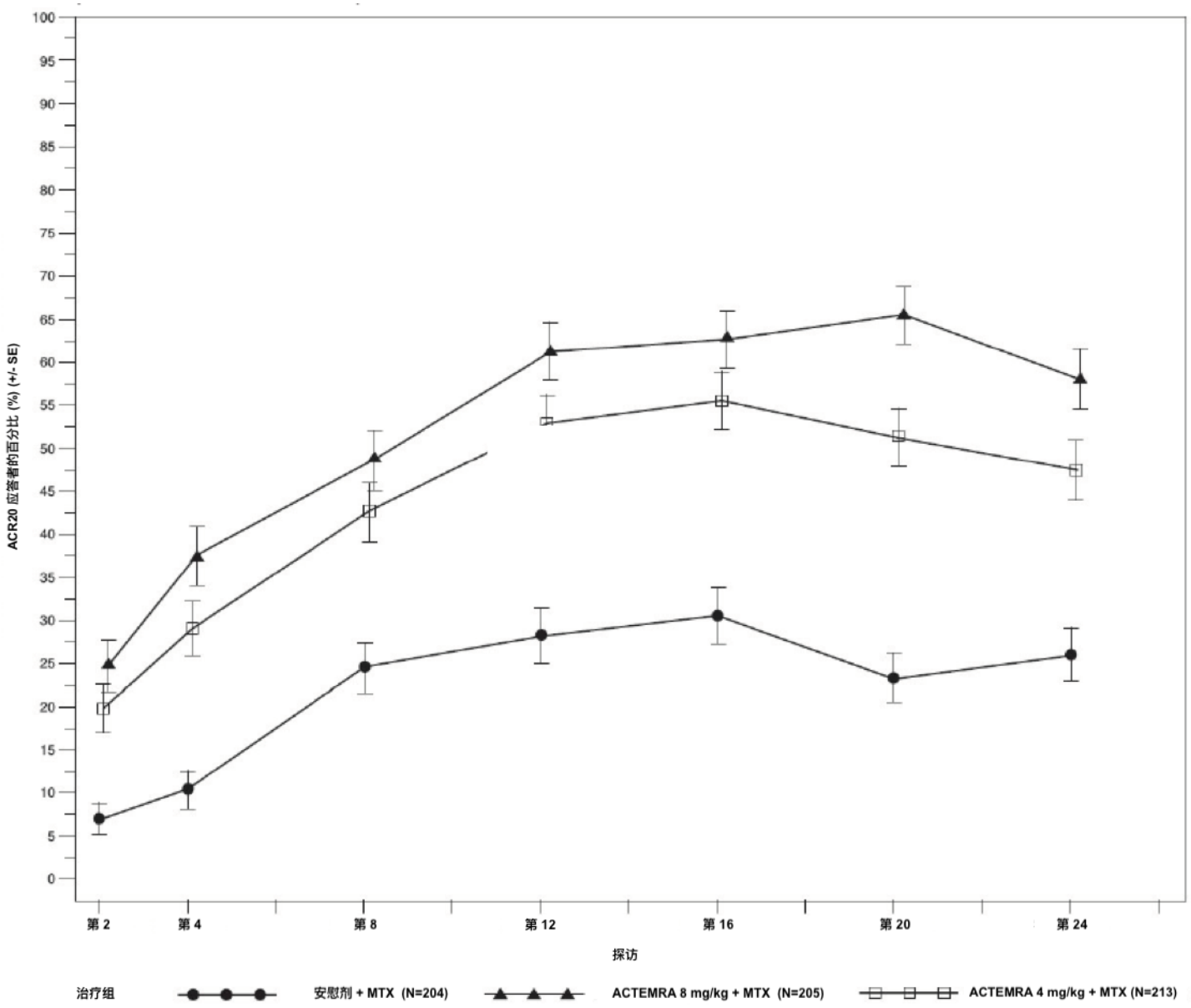
[a] 所示数据为第 24 周时的平均值、第 24 周与安慰剂 + MTX 相比，相对于基线的校正后平均变化的差异，以及该差异的 95% 置信区间

[b] 视觉模拟量表：0 = 最好，100 = 最差

[c] 健康评估问卷：0 = 最好，3 = 最差； 20 个问题； 8 个类别：着装与仪表、起身、饮食、行走、卫生、触及范围、握力和活动

根据研究 III 的访视结果，ACR 20 应答者的百分比如**图 1** 所示。研究 I、II、IV 和 V 中观察到类似的应答曲线。

图 1　　根据研究 III 的访视结果，ACR 20 应答者的百分比 （对 MTX 应答不足）*



* 同一患者可能在每个时间点都无应答。

放射反应

在研究 II 中，对关节结构性损伤进行了放射学评估，并用 Sharp-Genant 总评分及其组成部分、侵蚀评分和关节间隙狭窄评分的变化来表示。分别在基线、24 周、52 周和 104 周拍摄手部/腕部和前足的 X 光片，并由不了解治疗组别和就诊编号的读者进行评分。从基线到第 52 周的结果如**表 7** 所示。第 52 周时，与安慰剂 + MTX 相比，ACTEMRA 4 mg/kg 可减缓（与对照组相比，抑制率低于 75%）结构损伤的进展，而 ACTEMRA 8 mg/kg 可抑制（与对照组相比，抑制率至少达到 75%）结构损伤的进展。

表 7　研究 II 中从基线至第 52 周的平均影像学变化

	安慰剂 + MTX N=294	**ACTEMRA 4 mg/kg + MTX N=343**	**ACTEMRA 8 mg/kg + MTX N=353**
第 52 周*			
Sharp-Genant 总评分，平均值 (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
调整后的平均差 (95%CI)**		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
侵蚀分数，平均值 (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
调整后的平均差 (95%CI)**		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
关节空间狭窄分数，平均值 (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
调整后的平均差 (95%CI)**		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* 第 52 周时分析采用逃避、退出或失访后患者的线性外推数据。
** 调整后平均值之间的差异（ACTEMRA + MTX - 安慰剂 + MTX）
SD = 标准差

在 ACTEMRA 4 mg/kg 剂量组和 8 mg/kg 剂量组中，Sharp-Genant 总评分从基线至第 104 周的平均变化分别为 0.47 (SD = 1.47) 和 0.34 (SD = 1.24)。到第 104 周时，对照组（安慰剂 + MTX）组中的大多数患者已转为积极治疗，因此未将结果纳入比较。活性药物组的患者可能交叉至其他活性药物剂量组，结果按照最初的随机剂量组报告。

在安慰剂组中，第 52 周时 66% 的患者未出现影像学进展（Sharp-Genant 评分总变化 ≤ 0），而在 ACTEMRA 4 mg/kg 剂量组和 8 mg/kg 剂量组中的这一比例分别为 78% 和 83%。治疗 104 周后，最初随机接受 ACTEMRA 4 mg/kg 和 8 mg/kg 治疗的患者分别有 75% 和 83% 未出现结构损伤进展，而接受安慰剂治疗组中的这一比例为 66%。

健康相关结果

研究 II 采用健康评估问卷残疾指数 (HAQ-DI) 评估身体功能和残疾。截至第 52 周，在 HAQ-DI 相对于基线变化的 AUC 方面，ACTEMRA 的两个剂量组均比安慰剂组有较大改善。在 HAQ-DI 中，从基线至第 52 周的平均变化在 ACTEMRA 8 mg/kg 组、ACTEMRA 4 mg/kg 组和安慰剂组中分别为 0.6、0.5 和 0.4。在第 52 周时，ACTEMRA 8 mg/kg 和 ACTEMRA 4 mg/kg 治疗组分别有百分之六十三 (63%) 和百分之六十 (60%) 的患者 HAQ-DI 达到了具有临床意义的改善（相对于基线的变化 ≥0.3 个单位），而安慰剂治疗组为 53%。

其他健康相关成果

研究 I – V 采用简短健康调查 (SF-36) 评估一般健康状况。与安慰剂相比，接受 ACTEMRA 治疗的患者在身体成分总结 (PCS)、精神成分总结 (MCS) 和 SF-36 全部 8 个领域的基线改善幅度更大。

心血管结果

研究 WA25204 (NCT01331837) 是一项随机、开放标签（申办者盲法）、双臂平行组、多中心、非劣效性心血管 (CV) 结局试验，受试者为确诊的中度至重度 RA 患者。这项 CV 安全性研究旨在研究与 TNF 抑制剂标准治疗（依那西普）相比，排除使用 ACTEMRA 治疗的患者增加 CV 中度风险的可能性。

本研究纳入了 3,080 例血清阳性的活动性 RA 患者，这些患者对疾病缓解抗风湿药物应答不足，年龄 ≥ 50 岁，且除 RA 外至少有一个附加的 CV 风险因素。患者按 1:1 随机分配至 ACTEMRA IV 8 mg/kg Q4W 组或依那西普 SC 50 mg QW 组治疗，平均随访 3.2 年。主要终点是比较重大 CV 不良事件（MACE；非致命性心肌梗塞、非致死性卒中或 CV 死亡）复合因素中任何一个因素的首次发生时间，最终的意向治疗分析是基于由独立盲法评审委员会评审的总共 161 例确诊 CV 事件（ACTEMRA 为 83/1538 [5.4%]；依那西普为 78/1542 [5.1%]）。

在心血管风险方面，ACTEMRA 与依那西普相比的非劣效性是通过排除 MACE 风险相对增加 >80% 来确定的。ACTEMRA 与依那西普相比，MACE 风险的估计风险比 (HR) 为 1.05；95% CI (0.77, 1.43)。

14.2 类风湿性关节炎—皮下给药

在两项针对活动性 RA 患者的双盲、对照、多中心研究中，评估了皮下 ACTEMRA 给药的疗效和安全性。SC-I (NCT01194414) 研究是一项非劣效性研究，比较了每周皮下 ACTEMRA 162 mg 给药与每四周静脉 8 mg/kg 给药的疗效和安全性。SC-II (NCT01232569) 研究是一项安慰剂对照优效性研究，评估了隔周皮下 ACTEMRA 162 mg 给药与安慰剂相比的疗效和安全性。SC-I 和 SC-II 研究均要求患者年龄 >18 岁，患有根据 ACR 标准诊断的中度至重度活动性类风湿性关节炎，基线时至少有 4 个关节压痛和 4 个关节肿胀 (SC-I) 或基线时至少有 8 个关节压痛和 6 个关节肿胀 (SC-II)，并且对现有 DMARD 治疗应答不足，其中约 20% 的患者同时对至少一种 TNF 抑制剂应答不足。两项 SC 研究中的患者均接受了背景非生物制剂 DMARD 治疗。

SC-I 研究中，1262 例患者以 1:1 的比例随机接受每周一次 ACTEMRA-SC 162 mg 治疗或每四周一次静脉 ACTEMRA 8 mg/kg 联合 DMARD 治疗。SC-II 研究中，656 例患者以 2:1 的比例随机接受隔周一次 ACTEMRA-SC 162 mg 或安慰剂联合 DMARD 治疗。两项研究的主要终点均为第 24 周时达到 ACR20 应答的患者比例。

表 8 显示了 24 周 ACTEMRA-SC 治疗的临床应答情况。SC-I 研究中，主要结局指标是第 24 周时 ACR20。预设的非劣效界值为 12% 的治疗差异。该研究证明 ACTEMRA 在第 24 周时相对于 ACR20 具有非劣效性； ACR50、ACR70 和 DAS28 应答情况也显示在**表 8** 中。在 SC-II 中，与安慰剂治疗的患者相比，隔周皮下注射 ACTEMRA 162 mg 治疗的患者中有更大一部分获得了 ACR20、ACR50 和 ACR70 应答（表 8）。此外，与用安慰剂治疗的患者相比，隔周皮下注射 ACTEMRA 162 mg 治疗的患者中有更大比例的患者达到较低水平的疾病活动性（如第 24 周时 DAS28-ESR 测量小于 2.6）（表 8）。

表 8　　皮下 ACTEMRA 给药试验第 24 周的临床应答（患者百分比）

	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg 每周一次 + DMARD N=558	TCZ IV 8mg/kg + DMARD N=537	TCZ SC 162 mg 隔周一次 + DMARD N=437	安慰剂 + DMARD N=219
ACR20				
第 24 周	69%	73.4%	61%	32%
加权差 (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
第 24 周	47%	49%	40%	12%
加权差 (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
第 24 周	24%	28%	20%	5%
加权差 (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
DAS28 的变化 [调整后的平均值]				
第 24 周	-3.5	-3.5	-3.1	-1.7
调整后的平均差 (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
第 24 周	38.4%	36.9%	32.0%	4.0%
加权差 (95% CI)	0.9 (-5.0, 6.8)		28.6 (22.0, 35.2)	

TCZ = 托珠单抗
[a] 符合方案人群
[b] 意向治疗人群

在 SC-I 和 SC-II 研究中，ACTEMRA-SC 的 ACR 应答标准的组成部分和 ACR20 应答者百分比的结果与 ACTEMRA-IV 中观察到的结果一致。

放射反应

在 SC-II 研究中，对关节结构性损伤的进展情况进行了放射学评估，用 van der Heijde 改良 Sharp 总评分 (mTSS) 与基线相比的变化来表示。第 24 周时，与安慰剂 + DMARD 组相比，隔周一次 ACTEMRA-SC + DMARD 组患者的影像学进展显著较少；mTSS 相对于基线的平均变化分别为 0.62和 1.23，校正后的平均差异为 -0.60 (-1.1, -0.1)。这些结果与在静脉 ACTEMRA 给药治疗的患者中观察到的结果一致。

健康相关结果

在 SC-I 和 SC-II 研究中，HAQ-DI 从基线到第 24 周的平均降幅分别为 0.6、0.6、0.4 和 0.3，HAQ-DI 达到临床相关改善（与基线变化 ≥ 0.3 单位）的患者比例在每周皮下给药、静脉给药 8 mg/kg、隔周皮下给药和安慰剂给药组中分别为 65%、67%、58% 和 47%。

其他健康相关成果

在 SC-I 和 SC-II 研究中，一般健康状况由 SF-36 进行评估。在研究 SC-II 中，隔周接受 ACTEMRA 的患者与安慰剂相比，在 PCS、MCS 和 SF-36 的全部 8 个领域的基线改善幅度更大。在 SC-I 研究中，ACTEMRA-SC 每周组和 ACTEMRA-IV 8 mg/kg 组的这些评分改善情况相似。

14.3 巨细胞动脉炎—皮下给药

一项针对活动性 GCA 患者的单一、随机、双盲、多中心研究评估了皮下 ACTEMRA 给药的疗效和安全性。在研究 WA28119 (NCT01791153) 中，251 例经过筛选的新发或复发 GCA 患者被随机分配到四个治疗组之一。将两个 ACTEMRA 皮下剂量组（每周 162 mg 和隔周 162 mg）与两个不同剂量的安慰剂对照组（预先设定的 26 周和 52 周泼尼松减量方案）进行比较，随机比例为 2:1:1:1。该研究包括 52 周的盲期，随后是 104 周的开放标签扩展期。

所有患者均接受糖皮质激素（泼尼松）背景治疗。每个 ACTEMRA 治疗组和一个安慰剂治疗组均遵循预先指定的泼尼松逐渐减量方案，目标是到 26 周达到 0 mg，而第二个安慰剂治疗组则遵循预先指定的泼尼松逐渐减量方案，目标是在 52 周内达到 0 mg，旨在更符合标准实践情况。

主要疗效终点是从第 12 周到第 52 周实现持续缓解的患者比例。持续缓解的定义是患者从第 12 周到第 52 周持续达到：(1) 无 GCA 体征和症状；(2) 红细胞沉降率 (ESR) 恢复正常（降至 < 30 mm/hr，且 GCA 引起的红细胞沉降率没有升高至 ≥ 30 mm/hr）、 (3) C 反应蛋白 (CRP) 恢复正常（降至 < 1 mg/dL，且没有连续升高至 ≥ 1 mg/dL）；以及 (4) 持续泼尼松减量方案，即过量泼尼松不超过 100 mg。与安慰剂 + 26 周泼尼松减量相比，每周 ACTEMRA 162 mg 和隔周 162 mg + 26 周泼尼松减量均显示出在从第 12 ~ 52 周达到持续缓解方面均显示出优效性（表 9）。与安慰剂 + 52 周泼尼松减量相比，两个 ACTEMRA 治疗组也显示出优效性（表 9）。

表 9　WA28119 研究的疗效结果

	PBO + 26 周泼尼松减量 **N=50**	**PBO + 52 周泼尼松减量** **N=51**	**TCZ 162mg SC QW + 26 周泼尼松减量** **N=100**	**TCZTCZ 162 mg SC Q2W + 26 周泼尼松减量** **N=49**
持续缓解 [a]				
应答者, n (%)	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
未调整的比例差异 vs PBO + 26 周减量 (99.5% CI)	不适用	不适用	42.0% (18.0, 66.0)	39.1% (12.5, 65.7)
未调整的比例差异 vs PBO + 52 周减量 (99.5% CI)	不适用	不适用	38.4% (14.4, 62.3)	35.4% (8.6, 62.2)
持续缓解的组成部分				
持续缺乏 GCA 体征和症状 [b], n (%)	20 (40.0%)	23 (45.1%)	69 (69.0%)	28 (57.1%)
持续 ESR<30 mm/hr[c], n (%)				
持续 CRP 正常化 [d], n (%)	20 (40.0%)	22 (43.1%)	83 (83.0%)	37 (75.5%)
泼尼松减量成功 [e], n (%)	17 (34.0%)	13 (25.5%)	72 (72.0%)	34 (69.4%)
	10 (20.0%)	20 (39.2%)	60 (60.0%)	28 (57.1%)

[a] 持续缓解是指患者满足以下所有条件：无 GCA 体征和症状 [b]、ESR 正常化 [c]、CRP 正常化 [d] 以及持续泼尼松减量方案 [e]。
[b] 从第 12 周到第 52 周未出现任何 GCA 体征或症状的患者。
[c] 从第 12 周至第 52 周，未出现归类为 GCA 的红细胞沉降率升高 ≥30 mm/h 的患者。
[d] 从第 12 周到第 52 周没有两次或两次以上连续 CRP ≥ 1mg/dL 的患者。
[e] 在第 12 周至第 52 周期间，未出现接受逃逸治疗且同时接受 ≤ 100 mg 额外泼尼松治疗的患者。
在第 52 周之前未完成研究的患者在主要分析和关键次要分析中被归类为无应答者：PBO+26：6 (12.0%), PBO+52：5 (9.8%), TCZ QW：15 (15.0%), TCZ Q2W：9 (18.4%)。
CRP = C 反应蛋白
ESR = 红细胞沉降率
PBO = 安慰剂
Q2W = 每两周剂量
QW = 每周剂量
TCZ = 托珠单抗

与安慰剂组相比，（安慰剂 + 26 周泼尼松，安慰剂 + 52 周泼尼松减量的中位数分别为 3804 mg 和 3902 mg），两个 ACTEMRA 剂量组（ACTEMRA QW 和 Q2W 的中位数分别为 1887 mg 和 2207 mg）的估计泼尼松年累积量较低。

14.4 巨细胞动脉炎 – 静脉给药

WP41152 (NCT03923738) 是一项开放标签 PK-PD 和安全性研究，对 GCA 患者静脉 ACTEMRA 给药进行了评估，以确定 ACTEMRA 的合适静脉剂量，以实现与 ACTEMRA-SC 方案相当的 PK-PD 曲线。

入组时，所有患者 (n=24) 均在 ACTEMRA-IV 治疗后得到缓解。在第 1 阶段，所有患者每 4 周接受开放标签 ACTEMRA-IV 7 mg/kg 治疗，持续 20 周。完成第 1 期并持续缓解的患者 (n=22) 有资格进入第 2 期，同时每 4 周接受开放标签 ACTEMRA-IV 6 mg/kg 治疗，持续 20 周。

静脉 ACTEMRA 6 mg/kg 给药对 GCA 成人患者的疗效是基于药代动力学暴露和对 GCA 患者皮下 ACTEMRA 给药疗效的推断*[参见临床药理 (12.3)* 和临床研究 *(14.3)]*。

14.5 系统性硬化症相关间质性肺病 – 皮下给药

ACTEMRA 的临床疗效在一项针对 SSc 患者的 3 期多中心、随机、双盲、安慰剂对照研究（研究 WA29767）中进行了评估。一项针对 SSc 患者的 2/3 期多中心、随机、双盲、安慰剂对照研究（研究 WA27788）提供了支持性信息。研究 WA29767 (NCT02453256) 纳入了 2013 年美国风湿病学会/欧洲抗风湿病联盟 SSc 分类标准定义的 SSc 成人患者，发病时间（首次非雷诺症状）≤ 5 年，改良 Rodnan 皮肤评分 (mRSS) 筛选时 ≥ 10 且 ≤ 35、炎症标记物（或血小板）升高、且至少符合以下一项的活动性疾病：疾病持续时间 ≤ 18 个月、mRSS 在 6 个月内增加 ≥ 3 个单位、涉及一例新患者身体面积和 mRSS 在 6 个月内增加 ≥ 2，或在前 6 个月内涉及两个新的身体区域，或存在至少一个肌腱摩擦音。研究 WA27788 (NCT01532869) 纳入了发病时间 ≤ 5 年、筛查时 mRSS ≥ 15 且 ≤40、疾病处于活动期、炎症指标或血小板升高的成人 Ssc 患者。两项研究中的患者均不允许使用生物制剂（如 TNF 拮抗剂）、烷化剂或环磷酰胺。

在研究 WA29767 中，212 例患者以 1:1 的比例随机分配，在 48 周双盲安慰剂对照期间每周接受皮下注射 ACTEMRA 162 mg 或安慰剂。16 周后，预计 FVC (ppFVC) 下降超过 10%，或 24 周后，皮肤纤维化恶化，允许在治疗期间进行挽救治疗。主要疗效终点是第 48 周 mRSS 相对于基线的变化。第 48 周时 FVC 相对于基线的变化是关键的次要终点。

在研究 WA29767 的总体人群中，与安慰剂相比，接受 ACTEMRA 给药的患者的 mRSS（主要终点）从基线到第 48 周的平均变化没有统计学上的显着差异（差异：-1.73；95% CI：-3.78，0.32）。在 WA27788 研究中，对 mRSS 主要终点的影响也没有统计学意义。

在研究 WA29767 的总体人群中，与安慰剂治疗患者相比，接受 ACTEMRA 治疗的患者观察到 ppFVC 较基线下降较少，并在 48 周时观察到 FVC。研究 WA27788 的 FVC 结果相似。

在研究 WA29767 中随机分配的 212 例患者中，ACTEMRA 组中的 68 例患者(65%) 和安慰剂组中的 68 例患者 (64%) 在基线时患有 SSc-ILD，经高分辨率计算机断层扫描的视觉读取证实(HRCT) 由盲法胸部放射科医生进行。通过 HRCT 确定的 SSc-ILD 患者的基线平均 ppFVC 为 79.6%（中位数 80.5%）。进行了事后分析以评估患有和不患有 SSc-ILD 患者亚组的结果。

表 10 显示了 WA29767 研究在总体人群和基于基线 SSc-ILD 的亚组中，观察到的 FVC 和 mRSS 从基线到第 48 周的变化。总体人群中的 ppFVC 和观察到的 FVC 结果主要由 SSc-ILD 亚组的结果驱动。在 SSc-ILD 亚组中，与安慰剂相比，ACTEMRA 的 ppFVC 和观察到的 FVC 从基线到第 48 周的平均变化差异分别为 6.47% 和 241 mL。图 2 显示了 SSc-ILD 患者观察到的 FVC 从基线到第 48 周的平均变化。

研究 WA29767 的关键 FVC 次要终点结果支持 ACTEMRA 在降低研究人群肺功能进行性丧失率方面的有效性结论。然而，在试验没有提供对主要终点有影响的证据的情况下，对其他终点的估计影响程度应谨慎解释，与其他产品和研究的结果进行比较可能会产生误导。

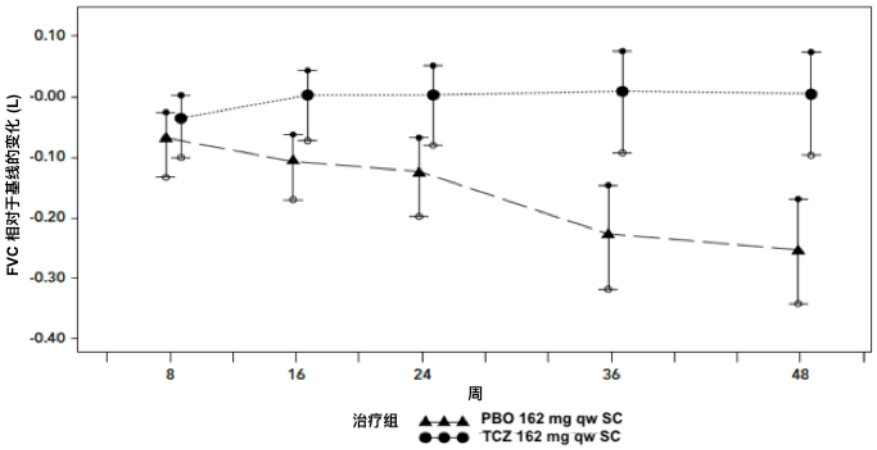
表 10 WA29767 研究的疗效结果

	总体人群		无 SSc-ILD 的亚组*		SSc-ILD 亚组*	
	PBO QW	**TCZ 162 mg QW**	**PBO QW**	**TCZ 162 mg QW**	**PBO QW**	**TCZ 162 mg QW**
患者数量	**106**	**104**	**36**	**34**	**68**	**68**
第 48 周 mRSS 相对于基线的变化						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
LSM、TCZ-安慰剂的差异 (95% CI)	-1.73 (-3.78, 0.32)		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
第 48 周时 ppFVC 相对于基线的变化						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
LSM、TCZ-安慰剂的差异 (95% CI)	4.20 (2.00, 6.40)		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
第 48 周观察到的 FVC (mL) 相对于基线的变化						
LSM	-190	-24	-53	-11	-255	-14
LSM、TCZ-安慰剂的差异 (95% CI)	167 (83, 250)		43 (-60, 145)		241 (124, 358)	

PBO=安慰剂； TCZ = 托珠单抗；ppFVC = 预测用力肺活量百分比；LSM=最小二乘均值；mRSS = 修改后的 Rodnan 皮肤评分；CI=置信区间

*显示了这些亚组的事后结果。4 例患者在基线时 ILD 状态缺失。

图 2 WA29767 研究中 SSc-ILD 患者观察到的用力肺活量从基线到第 48 周的平均变化



PBO = 安慰剂； TCZ = 托珠单抗； QW = 每周剂量

14.6 多关节型幼年特发性关节炎 — 静脉给药

一项名为 WA19977 (NCT00988221) 的研究对 ACTEMRA 的疗效进行了评估，该研究由三个部分组成，其中包括一项开放标签扩展研究，研究对象是对甲氨蝶呤应答不足或不耐受的 2 至 17 岁活动性多关节型幼年特发性关节炎 （PJIA） 患儿。患者患有至少 6 个月的活动性疾病（平均病程为 4.2 ± 3.7 年），至少 5 个关节有活动性关节炎（肿胀或活动受限，伴有疼痛和/或压痛）和/或至少 3 个活动关节活动受限（平均活动关节为 20 ± 14 个）。接受治疗的患者患有 JIA 亚型，发病时包括类风湿因子阳性或阴性多关节型 JIA，或扩展性少关节型 JIA。本研究允许使用稳定剂量的甲氨蝶呤进行治疗，但非必需。研究中不允许同时使用除甲氨蝶呤以外的疾病缓解抗风湿药物 (DMARDs) 或其他生物制剂（例如 TNF 拮抗剂或 T 细胞共刺激调节剂）。

第一部分包括为期 16 周的主动 ACTEMRA 治疗导入期 (n=188)，第二部分是为期 24 周的随机双盲安慰剂对照停药期，第三部分是为期 64 周的开放标签期。体重 ≥ 30 kg 的符合条件的患者每 4 周静脉注射一次 ACTEMRA 8 mg/kg。体重 < 30 kg 的患者按 1:1 随机分配，每 4 周静脉注射一次 ACTEMRA 8 mg/kg 或 10 mg/kg。在开放标签第 I 部分结束时，与基线相比，91% 接受托珠单抗+MTX 背景治疗的患者和 83% 接受托珠单抗单药治疗的患者在第 16 周时达到 ACR 30 应答，并进入了研究盲法停药期（第 II 部分）。在第一部分中，在接受托珠单抗+MTX 背景治疗的患者中，JIA ACR 50/70 应答的患者比例分别为 84.0% 和 64%，在接受托珠单抗单药治疗的患者中，上述比例分别为 80% 和 55%。

在第二部分中，患者 (ITT, n=163) 按 1:1 的比例随机接受 ACTEMRA（与第一部分接受的剂量相同）或安慰剂治疗，并根据是否同时使用甲氨蝶呤和是否同时使用皮质类固醇进行分层。所有患者继续参与研究第二部分，直到第 40 周或直到患者满足 JIA ACR 30 flare 标准（相对于第 16 周）并符合逃脱条件。

主要终点是第 40 周相对于第 16 周出现 JIA ACR 30 flare 的患者比例。JIA ACR 30 flare 被定义为 6 项核心结果变量中至少有 3 项恶化大于 30%，与第 16 周相比，其余变量中至多有 1 项改善超过 30%。

与安慰剂治疗患者相比，接受 ACTEMRA 治疗患者的疾病发作明显减少（26% [21/82] 对比 48% [39/81]；调整后的比例差异 -21%、95% CI：-35%、-8% ）。

在停药阶段（第二部分），与停药接受安慰剂的患者相比，接受 ACTEMRA 治疗的患者在第 40 周时达到 JIA ACR 30/50/70 应答的数量更多。

14.7 多关节型幼年特发性关节炎— 皮下给药

WA28117 (NCT01904279) 是一项为期 52 周、开放标签、多中心、PK-PD 和安全性研究，旨在确定 ACTEMRA 皮下注射的合适剂量，以获得与 ACTEMRA-IV 方案相当的 PK/PD 曲线。年龄为 1 至 17 岁、对 MTX 应答不足或不耐受的 PJIA 患者，包括接受 ACTEMRA-IV 治疗后疾病控制良好的患者和患有活动性疾病的 ACTEMRA-naïve 患者，根据体重接受皮下注射 ACTEMRA 治疗。

体重 ≥ 30 kg 的患者 (n = 25) 每 2 周接受 162 mg ACTEMRA-SC 治疗，体重 < 30 kg 的患者 (n = 27) 每 3 周接受 162 mg ACTEMRA-SC，持续 52 周。在这 52 例患者中，37 例 (71%) 从未接受过 ACTEMRA 治疗，15 例 (29%) 已接受 ACTEMRA-IV 治疗，并在基线时转为 ACTEMRA-SC 治疗。

皮下注射 ACTEMRA 对 2 至 17 岁儿童的疗效是基于药代动力学暴露以及静脉注射 ACTEMRA 对多关节 JIA 患者的既定疗效和皮下注射 ACTEMRA 对 RA 患者的既定疗效推断得出的*[参见临床药理 (12.3)* 和临床研究 *(14.2* 和 *14.6)]*。

14.8 全身型幼年特发性关节炎—静脉给药

一项名为 WA18221 (NCT00642460)，为期 12 周的随机、双盲、安慰剂对照、平行组、双臂研究评估了 ACTEMRA 治疗活动性 SJIA 患者的疗效。联用或不联用 MTX 治疗的患者被随机分配（ACTEMRA:安慰剂 = 2:1）至两个治疗组之一：75 例患者每两周接受 ACTEMRA 输注治疗，体重 ≥ 30 kg 的患者，剂量为 8 mg/kg；体重 < 30 kg 的患者，剂量为 12 mg/kg；37 例患者随机接受每两周一次安慰剂输注。对于达到 JIA ACR 70 应答的患者，皮质类固醇可能会从第六周开始逐渐减少。12 周后或在疾病恶化时，患者以体重合适的剂量在开放标签扩展期接受 ACTEMRA 治疗。

主要终点是在第 12 周时，JIA ACR 核心指标（JIA ACR 30 应答）改善至少 30%，且无发热（前 7 天体温不高于或等于 37.5°C）的患者。JIA ACR（美国风湿病学会）应答的定义是：与基线相比，6 项核心结果变量中至少 3 项有百分比有改善（如 30%、50%、70%），且其余变量中的至多 1 项恶化大于 30%。核心结果变量包括医生总体评估、患者家长的总体评估、活动性关节炎的关节数量、活动受限的关节数量、红细胞沉降率 (ESR) 和功能能力（儿童健康评估问卷-CHAQ）。

主要终点结果和第 12 周的 JIA ACR 应答率如**表 11** 所示。

表 11 第 12 周的疗效结果

	ACTEMRA N=75	**安慰剂 N=37**
主要终点：JIA ACR 30 应答 + 不发烧		
应答者	**85%**	**24%**
加权差 (95% CI)	**62 (45, 78)**	**-**
第 12 周的 JIA ACR 应答率		
JIA ACR 30		
应答者 加权差 [a] (95% CI)[b]	91% 67 (51, 83)	24% -
ACR de 50 para la AIJ		
应答者 加权差 [a] (95% CI)[b]	85% 74 (58, 90)	11% -
ACR de 70 para la AIJ		
应答者 加权差 [a] (95% CI)[b]	71% 63 (46, 80)	8% -

[a] 加权差异是指根据分层因素（体重、病程、口服皮质类固醇和甲氨蝶呤给药情况）调整后，ACTEMRA 和安慰剂应答率之间的差异。

[b] CI：加权差的置信区间。

ACTEMRA 的疗效在 JIA ACR 反应核心变量的所有组成部分中都一致。开放标签扩展研究中的 JIA ACR 评分和无发热反应与对照研究部分（44 周前的数据）一致。

<u>全身症状</u>

在基线时出现发烧或皮疹的患者中，接受 ACTEMRA 治疗的患者的全身症状较少；41 例接受 ACTEMRA 治疗的患者中有 35 例 (85%) 不再发烧（过去 14 天内没有记录到 37.5°C 或以上的体温），而接受安慰剂治疗的 24 例患者中有 5 例 (21%) 出现发烧症状，22 例接受 ACTEMRA 治疗的患者中有 14 例 (64 %) 无皮疹，安慰剂治疗的 18 例患者中的 2 例 (11%) 无皮疹。开放标签扩展中的反应是一致的（数据可提供至 44 周）。

皮质类固醇逐渐减少

在基线接受口服皮质类固醇的患者中，31 例安慰剂患者中的 8 例 (26%) 和 70 例安慰剂中的 48 例 (69%)，ACTEMRA 患者在第 6 周或第 8 周达到了 JIA ACR 70 应答，因此可减少皮质类固醇剂量。17 例 (24%) ACTEMRA 患者与 1 例(3%) 安慰剂患者相比，在第 12 周之前，皮质类固醇的剂量至少减少了 20%，未出现随后的 JIA ACR 30 flare 或全身症状。在该研究的开放标签部分，到第 44 周时，103 例 ACTEMRA 患者中有 44 例 (43%) 停止口服皮质类固醇。在这 44 例患者中，50% 已停用皮质类固醇 ≥18 周。

健康相关结果

使用儿童健康评估问卷残疾指数 (CHAQ-DI) 评估了身体功能和残疾。ACTEMRA 治疗组有 77% (58/75) 的患者在第 12 周时 CHAQ-DI（与基线相比变化 ≥ 0.13 个单位）达到了最小临床意义改善，而安慰剂治疗组只有 19% (7/37) 的患者达到了最小临床意义改善。

14.9 全身型幼年特发性关节炎—皮下给药

WA28118 (NCT01904292) 是一项为期 52 周、开放标签、多中心、PK-PD 和安全性研究，旨在确定 ACTEMRA 皮下注射的合适剂量，以获得与 ACTEMRA-IV 方案相当的 PK/PD 曲线。

符合条件的患者根据体重接受 ACTEMRA 皮下给药，其中体重 ≥30 kg 的患者 (n= 26) 每周给予 162 mg ACTEMRA，体重 < 30 kg 的患者 (n=25) 每 10 天 (n=8) 或每 2 周 (n=17) 给予 162 mg ACTEMRA，持续 52 周。在这 51 例患者中，26 例 (51%) 从未接受过皮下 ACTEMRA 治疗，25 例 (49%) 曾接受静脉 ACTEMRA 治疗，并在基线时转为皮下 ACTEMRA 治疗。

皮下 ACTEMRA 给药对 2 至 17 岁儿童的疗效根据药代动力学暴露和静脉 ACTEMRA 给药对全身性 JIA 患者的既定疗效推断得出*[参见临床药理 (12.3) 和临床研究 (14.8)]*。

14.10 细胞因子释放综合征 — 静脉给药

通过对 CAR T 细胞疗法治疗血液恶性肿瘤临床试验的汇总结果数据进行回顾性分析，评估了 ACTEMRA 治疗 CRS 的疗效。接受过托珠单抗 8 mg/kg（体重小于 30 kg 的患者为 12 mg/kg）治疗的可评估患者曾因严重或危及生命的 CRS 而接受或未接受额外的大剂量皮质类固醇治疗；分析中仅包括首次发作的 CRS。研究人群包括 24 例男性和 21 例女性（总共 45 例患者），中位年龄 12 岁（范围：3-23 岁）； 82% 是白人。从 CRS 开始到首次服用托珠单抗的中位时间为 4 天（范围：0-18 天）。CRS 的消退定义为至少 24 小时内不再发烧且停用血管加压药。如果患者的 CRS 在服用首剂托珠单抗后 14 天内缓解，不需要服用超过 2 剂托珠单抗，并且在治疗过程中未使用托珠单抗和皮质类固醇以外的药物，则被视为应答者。31 例患者（69%；95% CI：53%–82%）有应答。在第二项研究中，15 例（范围：9-75 岁） CAR - T 细胞诱导的 CRS 患者在 14 天内获得了 CRS 缓解。

14.11 COVID-19 – 静脉给药

ACTEMRA 治疗 COVID-19 的疗效基于 RECOVERY (NCT04381936) 研究，这是一项随机、对照、开放标签的平台研究，并得到了 EMPACTA (NCT04372186) 这一随机、双盲、安慰剂对照研究结果的支持。此外，还总结了另外两项随机、双盲、安慰剂对照研究 COVACTA (NCT04320615) 和 REMDACTA (NCT04409262) 的结果，这两项研究评估了 ACTEMRA 治疗 COVID-19 的疗效。

在确诊为 *COVID-19* 的住院成人患者中开展的 *RECOVERY*（*COVID-19* 治疗的随机评估）协作组研究

RECOVERY 是一项在英国进行的随机、对照、开放标签、多中心研究，旨在评估潜在治疗方法对住院成人重症 COVID-19 肺炎患者的疗效和安全性。本研究 ACTEMRA 部分符合纳入标准的患者患有临床疑似或实验室确诊的 SARS-CoV-2 感染，无任何治疗的医学禁忌证，并有进展性 COVID-19 的临床证据（定义为吸入室内空气或接受氧疗时的氧饱和度为 92%，并且 CRP≥75 mg/L）。随后，患者被随机分配接受标准护理 (SoC) 或静脉 ACTEMRA 给药，剂量按体重分级，与推荐剂量相当*[参见临床药理学 (12.3)]*。

疗效分析在意向治疗 (ITT) 人群中进行，意向治疗人群包括 4116 例成人患者，他们被随机分配到 ACTEMRA + SoC 治疗组（2022 例）或 SoC 治疗组（2094 例）。参与者的平均年龄为 64 岁（范围：20 至 101），患者中 67% 为男性，76% 为白人，11% 为亚洲人，3% 为黑人或非裔美国人，1% 为混血儿。基线时，0.2% 的患者未使用辅助供氧，45% 的患者需要低流量供氧，41% 的患者需要无创通气或高流量供氧，14% 的患者需要有创机械通气；据报告，82% 的患者正在接受全身性皮质类固醇治疗。

主要疗效终点是截至第 28 天的死亡时间。表 12 总结了随机分组时接受或未接受全身性皮质类固醇治疗的总体人群和患者亚组的结果。

表 12 恢复期第 28 天的死亡率

	ACTEMRA + SoC N=2022 n (%)[1]	**SoC N=2094 n (%)[1]**	**危险比率 (95% CI)**	**风险差异 (95% CI)**
死亡	621 (30.7%)	729 (34.9%)	0.85 (0.76, 0.94) p= 0.0028[1]	-4.1% (-7.0, -1.3)
根据皮质类固醇使用的基线情况				
随机分组时接受全身性皮质类固醇治疗的患者的死亡率 [2]	482/1664 (29.0%)	600/1721 (34.9%)	0.79 (0.70, 0.89)	-5.9% (-9.1, -2.8)
随机分组时未接受全身性皮质类固醇治疗的患者的死亡率 [2]	139/357 (39.0%)	127/367 (34.6%)	1.16 (0.91, 1.48)	4.4% (-2.6, 11.5)

[1] P 值表示 RECOVERY 试验的主要分析结果在双侧显著性水平 α=0.05 时具有统计学意义。
[2] 通过 Kaplan-Meier 方法估算第 28 天时的死亡概率。

EMPACTA

EMPACTA 是一项随机、双盲、安慰剂对照的多中心研究，旨在评估静脉 ACTEMRA 8 mg/kg 与 SoC 联合给药，非机械通气的 COVID-19 成年住院患者。符合条件的患者年龄至少为 18 岁，通过逆转录酶聚合酶链反应 (RT-PCR) 结果确诊为 SARS-CoV-2 感染，通过放射线照相证实患有肺炎，并且环境空气中 SpO2 < 94%。

在 389 例随机分配的患者中，在改良意向治疗 (mITT) 人群中进行了疗效分析，其中包括 377 例随机分配并接受研究药物的患者（ACTEMRA 组 249 例；安慰剂组 128 例）。参与者的平均年龄为 56 岁（范围：20 至 95）； 59% 的患者为男性，56% 为西班牙裔或拉丁裔，53% 为白人，20% 为美洲印第安人/阿拉斯加原住民，15% 为黑人/非裔美国人，2% 为亚洲人。基线时，9% 的患者无需辅助供氧，64% 的患者需要低流量吸氧，27% 的患者需要高流量吸氧，73% 的患者使用皮质类固醇。

主要疗效终点评估了第 28 天进展为机械通气或死亡的时间。ACTEMRA 与安慰剂的风险比为 0.56（95% CI，0.33 至 0.97），具有统计学显着性结果（对数秩，p 值 = 0.036）。ACTEMRA 组中第 28 天需要机械通气或死亡的患者累计比例为 12.0%（95% CI，8.5% 至 16.9%），安慰剂组为 19.3%（95% CI，13.3% 至 27.4%）。

ACTEMRA 组第 28 天的死亡率为 10.4%，安慰剂组为 8.6%（加权差异（ACTEMRA 组 - 安慰剂组）：2.0% [95% CI，-5.2% 至 7.8%]）。

COVACTA

COVACTA 是一项随机、双盲、安慰剂对照、多中心研究，旨在评估静脉注射 ACTEMRA 8 mg/kg 与 SoC 联合治疗因严重 COVID-19 肺炎住院的成人患者。该研究将 452 例患者随机分组，这些患者年龄至少 18 岁，RT-PCR 结果呈阳性，确诊为 SARS-CoV-2 感染，经 X 线检查确诊为肺炎，环境空气中的氧饱和度为 93% 或更低。动脉氧分压至吸入氧分数 300 mmHg 或更低。基线时，3% 的患者未辅助供氧，28% 接受低流量吸氧，30% 接受无创通气或高流量吸氧，38% 接受有创机械通气，22% 接受皮质类固醇。主要疗效终点是第 28 天的临床状态，按照从“出院”到“死亡”的 7 类顺序量表进行评估。当比较 ACTEMRA 组与安慰剂组时，第 28 天时 7 类序数量表的临床状态分布没有观察到统计学上的显着差异。

ACTEMRA 组第 28 天的死亡率为 19.7%，安慰剂组为 19.4%（加权差异（ACTEMRA 组 - 安慰剂组）：0.3% [95% CI, -7.6 to 8.2])。

REMDACTA

REMDACTA 是一项随机、双盲、安慰剂对照、多中心研究，旨在评估静脉注射 ACTEMRA 8 mg/kg 联合静脉注射瑞德西韦 (RDV) 200 mg（第一天），然后每天一次 100 mg，共 10 天住院治疗重症 COVID-19 肺炎患者。该研究将 649 例成人患者随机分组，这些患者经聚合酶链式反应 (PCR) 结果确诊为 SARS-CoV-2 感染，经 X 线检查确诊为肺炎，并且需要 > 6 L/min 辅助供氧以维持 SpO2 > 93%。基线时，7% 的患者接受低流量吸氧，80% 的患者接受无创通气或高流量吸氧，14% 的患者接受有创机械通气，84% 的患者接受皮质类固醇治疗。

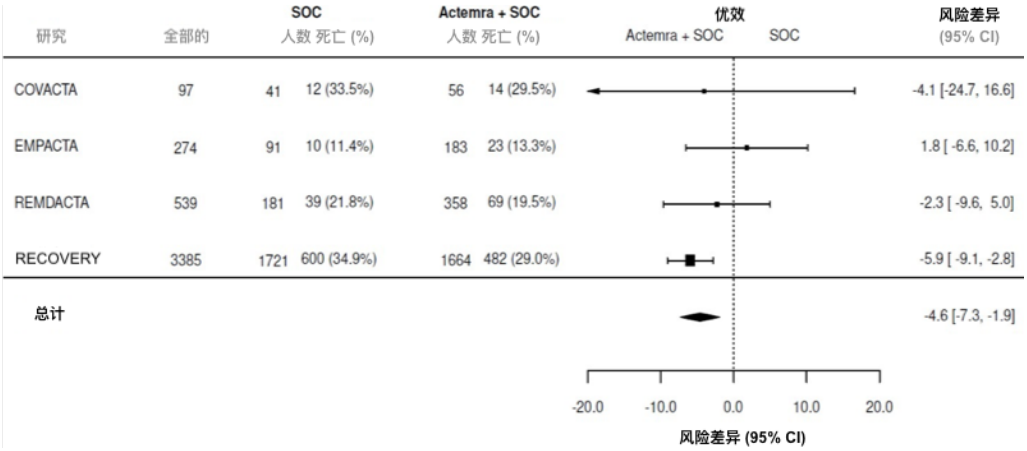
主要疗效终点为从随机分配到出院或“准备出院”的时间，直至第 28 天。在出院或 "准备出院 "至第 28 天的时间方面，各治疗组之间的差异无统计学意义。

ACTEMRA+ RDV 组第 28 天的死亡率为 18.1%，而安慰剂 +RDV 组为 19.5%（加权差异（ACTEMRA 组 - 安慰剂组）：-1.3% [95% CI，-7.8% 至 5.2%]）。

各项研究中接受皮质类固醇治疗患者的死亡率

对 EMPACTA、COVACTA、REMDACTA 和 RECOVERY 研究进行了研究级荟萃分析。在四项研究中，每项研究都采用 Kaplan-Meier 法估算了接受基线皮质类固醇治疗的亚组患者在第 28 天时的风险差异，见图 3。来自 RECOVERY 试验的患者占本次荟萃分析中总样本量的 78.8%。综合风险差异显示，与 SoC (n=2034) 相比，ACTEMRA 治疗 (n=2261) 使第 28 天的死亡风险绝对值降低了 4.61%（风险差异=-4.6%；95% CI：-7.3%至-1.9%）。

图 3　　RECOVERY、EMPACTA、COVACTA 和 REMDACTA 研究中基线使用皮质类固醇亚群在第 28 天的风险差异



16　包装/储存和处理方式

静脉输液

ACTEMRA （托珠单抗）注射液是一种不含防腐剂、无菌、透明、无色至淡黄色溶液。ACTEMRA 以 80 mg/4 mL (NDC 50242-135-01)、200 mg/10 mL (NDC 50242-136-01) 和 400 mg/20 mL (NDC 50242-137-01) 独立包装的 20 mg/mL 单剂量药瓶供应，供静脉注射前进一步稀释。

皮下注射

ACTEMRA（托珠单抗）注射液以不含防腐剂、无菌、透明、无色至微黄色溶液形式提供，用于皮下注射。提供以下封装配置：

- 每个单剂量预充式注射器可输送 162 mg/0.9 mL (NDC 50242-138-01)。
- 每个单剂量 ACTPen®自动注射器可输送 162 mg/0.9 mL (NDC 50242-143-01)。

储存和处理方式：请勿在容器、包装、预充式注射器或自动注射器上的到期日后使用。ACTEMRA 必须 36°F 至 46°F（2°C 至 8°C）冷藏保存。请勿冷冻。使用前将药瓶、注射器和自动注射器存放在原包装中避光，并保持注射器和自动注射器干燥。从冰箱中取出后，预充式注射器和自动注射器可在 86°F (30°C) 或以下的温度下保存长达 2 周。预充式注射器和自动注射器必须始终保存在纸箱中。

17　患者咨询信息

建议患者阅读 FDA 批准的患者标签 （用药指南和使用说明）。

严重感染

告知患者 ACTEMRA 可能降低他们对感染的抵抗力*[*参见警告和注意事项*(5.1)]*。告知患者在出现感染症状时立即联系医生的重要性，以确保快速评估和适当的治疗。

胃肠穿孔

告知患者，一些接受过 ACTEMRA 治疗的患者会出现严重的胃肠副作用*[*参见警告和注意事项 *(5.2)]*。指导患者当出现发烧、严重以及持续性腹痛症状和排便习惯改变等症状时应立即联系医生，以确保快速评估和适当的治疗。

超敏反应和严重过敏反应

告知患者，一些接受过 ACTEMRA 治疗的患者会出现严重过敏反应，包括过敏性反应，以及严重的皮肤反应*[*参见警告和注意事项*(5.6)]*。建议患者如果出现任何严重过敏反应症状（如皮疹、荨麻疹、面部、嘴唇、舌头或咽喉肿胀，导致呼吸或吞咽困难），应立即停用 ACTEMRA 并立即就医。

注射技术指导

评估患者是否适合居家皮下注射。在专业医护人员的指导下进行首次注射。如果患者或照料者要皮下注射 ACTEMRA，应指导其注射技巧并评估其皮下注射能力，以确保皮下注射 ACTEMRA 的正确给药和适合家庭使用*[*参见使用说明*]*。

使用前，从冰箱中取出预充式注射器 (PFS) 或自动注射器，并在纸箱外室温下放置 30 分钟 (PFS) 或 45 分钟（自动注射器），并将其放在儿童接触不到的地方。请勿以任何其他方式加热 ACTEMRA。

如果未收到全部剂量，建议患者咨询医务人员。

应使用防刺穿容器来处理针头、注射器和自动注射器，并放置在儿童接触不到的地方。指导患者照料者使用该技术以及正确处理针头、注射器和自动注射器，并注意不要重复使用这些物品。

妊娠期

告知具有生育能力的女性患者 ACTEMRA 可能会对胎儿造成伤害，并告知其处方医师已知或疑似妊娠*[*参见特定人群中的应用 *(8.1)]*。

ACTEMRA® (托珠单抗)

制造商：
Genentech, Inc.
罗氏集团子公司
1 DNA Way
South San Francisco, CA 94080-4990

美国许可证号：1048

用药指南

ACTEMRA® (AC-TEM-RA)
（托珠单抗）静脉注射用药
ACTEMRA® (AC-TEM-RA)
（托珠单抗）皮下注射用药

关于 ACTEMRA 我应该了解哪些最重要的信息?

ACTEMRA 可能会导致严重的副作用，包括：

1. **严重感染。**ACTEMRA 是一种影响您的免疫系统的药物。ACTEMRA 可能降低免疫系统抵抗感染的能力。有些人在服用 ACTEMRA 期间出现严重感染，包括结核病 (TB) 以及由细菌、真菌或病毒引起的可传播到全身的感染。有人死于这些感染。医务人员应在开始接受 ACTEMRA 治疗之前评估您是否患有结核病（除非您患有 COVID-19）。

如果您患有 COVID-19，医务人员应在 ACTEMRA 治疗期间和治疗后监测您是否出现了新感染的体征和症状。

医务人员应在 ACTEMRA 治疗期间以及治疗后密切监测您是否出现了结核病体征和症状。

- 如果您患有任何类型的感染，则不应接受 ACTEMRA 治疗，除非医务人员表示可以。

在接受 ACTEMRA 治疗之前，如有以下情况，请告知医务人员：

- 认为您已感染或有感染症状，无论是否发烧，例如：
  - 出汗或发冷
  - 气促
  - 身体上的皮肤或溃疡发热、发红或疼痛
  - 异常疲劳
  - 肌肉疼痛
  - 痰中带血
  - 腹泻或胃痛
  - 咳嗽
  - 体重减轻
  - 小便时有烧灼感或小便次数多于正常情况
- 正在接受感染治疗。
- 遭受大量感染或感染不断复发。
- 患有糖尿病、艾滋病毒或免疫系统较弱。患有这些疾病的人感染的机会更高。
- 患有结核病，或与结核病患者有过密切接触。
- 居住或曾经居住或去过该国的某些地区（例如俄亥俄州和密西西比河谷以及西南部），这些地区感染某些类型的真菌感染 （组织胞浆菌病、球孢子菌病或芽生菌病）的机会增加。如果进行 ACTEMRA 给药，这些感染可能会发生或变得更加严重。如果您不知道自己是否居住在这些感染常见的地区，请咨询医务人员。
- 患有或曾经患有乙型肝炎。

接受 ACTEMRA 治疗后，如果您出现任何感染症状，请立即致电医务人员。ACTEMRA 可能会使您更容易受到感染或使您所感染的情况变得更严重。

2. **胃或肠破损（穿孔）。**
   - 如果您患有憩室炎（大肠部分炎症）或胃或肠道溃疡，请告诉医务人员。有些服用 ACTEMRA 的患者会出现胃或肠破损的情况。这种情况最常发生在联用非甾体类抗炎药 (NSAID)、皮质类固醇或甲氨蝶呤的患者中。
   - 如果您出现发烧、胃部疼痛持续不消退且排便习惯发生变化，请立即告知医务人员。
3. **肝脏问题（肝毒性）。**有些人患过严重危及生命的肝脏疾病，曾需要进行肝脏移植否则会导致死亡。如果您在接受 ACTEMRA 治疗期间出现新的或更严重的肝脏问题，医务人员可能会让您停用 ACTEMRA。如果您出现以下任何症状，请立即告诉医务人员：
   - 疲劳（疲倦）
   - 几天或更长时间缺乏食欲（厌食症）
   - 皮肤或眼白发黄（黄疸）
   - 胃部右侧腹部肿胀和疼痛
   - 浅色粪便
   - 虚弱
   - 恶心和呕吐
   - 意识混乱
   - 深色“茶色”尿液
4. **某些实验室测试结果发生变化。**医务人员应在您开始接受 ACTEMRA 治疗之前进行血液检查。如果您患有类风湿性关节炎 (RA)、巨细胞动脉炎 (GCA) 或系统性硬化症-间质性肺病 (SSc-ILD)，医务人员应在您开始接受 ACTEMRA 的前 6 个月后每 4 至 8 周进行一次血液检查，此后每 3 个月一次。如果您患有多关节型幼年特发性关节炎 (PJIA)，您将在治疗期间每 4 至 8 周进行一次血液检查。如果您患有(SJIA)，您将在治疗期间每 2 至 4 全身型幼年特发性关节炎周进行一次血液检查。这些血液测试是为了检查 ACTEMRA 的以下副作用：
   - 中性粒细胞计数低。中性粒细胞是帮助身体抵抗细菌感染的白细胞。
   - 血小板计数低。血小板是有助于血液凝固和止血的血细胞。

- 某些肝功能测试增加。
- 血液胆固醇水平升高。您的其他实验室检查也可能会发生变化，例如血液胆固醇水平。医务人员应在您开始接受 ACTEMRA 治疗后 4 至 8 周进行血液检查，以检查您的胆固醇水平。

医务人员将确定您进行后续血液检查的频率。确保您按照医务人员的要求完成所有后续血液检查。

如果您的中性粒细胞或血小板计数太低或您的肝功能测试太高，您不应接受 ACTEMRA 治疗。

由于这些血液检测结果的变化，医务人员可能会在一段时间内停止 ACTEMRA 给药或酌情调整剂量。

5. **癌症。**ACTEMRA 可能会改变您的免疫系统运作方式，增加您患某些癌症的风险。如果您曾经患有任何类型的癌症，请告诉医务人员。

请参阅**“ACTEMRA 可能有哪些副作用?”**了解有关副作用的更多信息。

ACTEMRA 是什么?

ACTEMRA 是一种称为白细胞介素 6 (IL-6) 受体拮抗剂的处方药。ACTEMRA 适用于：

- 治疗中度至重度活动性类风湿性关节炎 (RA) 成人患者，在此之前，至少已使用过一种名为“疾病缓解抗风湿药物” (DMARD) 的药物，但效果不佳。
- 治疗巨细胞动脉炎 (GCA) 成人患者。
- 减缓患有系统性硬化症相关间质性肺病 (SSc-ILD)（也称为硬皮病相关 ILD）的成人肺功能下降速度。
- 治疗 2 岁及以上活动性 PJIA 患者。
- 治疗 2 岁及以上活动性 SJIA 患者。
- 治疗在嵌合抗原受体 (CAR) T 细胞治疗后出现严重或危及生命的细胞因子释放综合征 (CRS) 的 2 岁及以上患者。
- 治疗患有 2019 冠状病毒病 (COVID-19)、接受全身性皮质类固醇治疗并需要辅助供氧或机械通气的住院成人患者。
- ACTEMRA 未被批准用于 CRS 或 COVID-19 患者皮下给药。

目前尚不清楚 ACTEMRA 对于 2 岁以下患有 PJIA、SJIA 或 CRS 的儿童或患有 PJIA、SJIA 或 CRS 以外疾病的儿童是否安全有效。

请勿接受 ACTEMRA 治疗：如果您对托珠单抗或 ACTEMRA 中的任何成分过敏。有关 ACTEMRA 成分的完整列表，请参阅本药物指南的末尾。

在接受 ACTEMRA 治疗之前，请告诉医务人员您的病史，包括：

- 是否有感染。**请参阅“关于 ACTEMRA 我应该了解的最重要的信息是什么?”**
- 是否有肝脏问题。
- 是否有胃部（腹部）疼痛或被诊断患有憩室炎或胃或肠道溃疡。
- 之前是否对托珠单抗或 ACTEMRA 中的任何成分有过反应。
- 是否患有或曾经患有影响神经系统的疾病，例如多发性硬化症。
- 最近是否已接种或计划接种疫苗：
  - 除非需要紧急治疗，否则在开始接受 ACTEMRA 治疗前已完成所有最新疫苗接种。
  - 接受 ACTEMRA 治疗的人不应接种活疫苗。
  - 接受 ACTEMRA 治疗的人可以接种非活疫苗。
- 是否计划进行手术或医疗程序。
- 是否已怀孕或计划怀孕。ACTEMRA 可能会伤害您未出生的婴儿。如果您在 ACTEMRA 治疗期间怀孕或认为自己可能怀孕，请告诉医务人员。
- 是否正在母乳喂养或计划母乳喂养。目前尚不清楚 ACTEMRA 是否会进入您的母乳。如果您服用 ACTEMRA，请与医务人员讨论喂养婴儿的最佳方式。

告诉医务人员您服用的所有药物，包括处方药、非处方药、维生素和草药补充剂。ACTEMRA 和其他药物可能会相互影响，导致副作用。

如果您服用以下药物，请特别告知医务人员：

- 治疗 RA 的任何其他药物。ACTEMRA 与这些药物联用可能会增加感染的风险。
- 影响某些肝酶发挥作用的药物。如果您不确定您的药物是否属于其中之一，请咨询医务人员。

了解您服用的药物。保留一份清单，以便在您获得新药时向医务人员和药剂师出示。

我如何接受 ACTEMRA 治疗?

静脉注射（IV 或静脉输注）治疗类风湿性关节炎、巨细胞动脉炎、PJIA、SJIA、CRS 或 COVID-19：

- 如果医务人员开具的 ACTEMRA 是静脉输液处方，您将从医务人员处获得 ACTEMRA，该 ACTEMRA 将通过插入您手臂静脉的针头进行注射。大约需要 1 个小时才能输完药量。
- 类风湿性关节炎、巨细胞动脉炎或 PJIA 患者将大约每 4 周接受一剂 ACTEMRA。
- SJIA 患者将大约每 2 周接受一剂 ACTEMRA。
- CRS 患者将接受单剂量的 ACTEMRA，酌情可接受额外剂量。
- COVID-19 患者将接受单剂量的 ACTEMRA，酌情可再接受一剂。
- 在接受 ACTEMRA 治疗的同时，您可以按照医务人员的指示继续联合使用其他有助于治疗类风湿性关节炎、PJIA、SJIA 或 COVID-19 的药物，例如甲氨蝶呤、非甾体类抗炎药 (NSAID) 和处方类固醇。
- 保留所有后续预约并按照医务人员的要求进行血液检查。

皮下注射（SC 或皮下注射）治疗类风湿性关节炎、巨细胞动脉炎、SSc-ILD、PJIA 或 SJIA：

- **请参阅本药物指南末尾的使用说明，了解有关在家准备和注射 ACTEMRA 的正确方法的说明。**
- ACTEMRA 可作为单剂量预充式注射器或单剂量预充式 ACTPen® 自动注射器使用。
- 您还可以接受皮下 ACTEMRA 注射给药。如果医务人员决定您或照料者可以在家注射 ACTEMRA，您或您的照料者应接受有关准备和注射 ACTEMRA 的正确方法的培训。在医务人员向您展示正确的注射方法之前，请勿尝试注射 ACTEMRA。
- PJIA 或 SJIA 患者可以使用预充式注射器或预充式 ACTPen® 自动注射器自行注射，或者如果医务人员和父母/法定监护人都认为合适，您的照料者可以为您注射 ACTEMRA。
- 医务人员会告诉您需要使用的 ACTEMRA 剂量以及使用时间。

ACTEMRA 可能有哪些副作用?

ACTEMRA 可能会导致严重的副作用，包括：

- 请参阅**“关于 ACTEMRA 我应该了解的最重要的信息是什么?”**
- 血液中携带病毒的人感染**乙型肝炎**。如果您是乙型肝炎病毒（一种影响肝脏的病毒）携带者，当您接受 ACTEMRA 治疗时，该病毒可能会变得活跃。医务人员可能会在您开始接受 ACTEMRA 治疗之前和治疗期间进行血液检查。如果您出现以下任何可能感染乙型肝炎的症状，请告诉医务人员：
  - 异常疲劳
  - 呕吐
  - 发冷
  - 深色尿液
  - 皮肤或眼睛看起来发黄
  - 粘土色的大便
  - 胃部不适
  - 皮疹
  - 食欲不振
  - 发烧
  - 肌肉疼痛
- **严重过敏反应。**ACTEMRA 可能会发生严重的过敏反应，包括死亡。任何一次输注或注射 ACTEMRA 都可能出现这些反应，即使之前的输注或注射没有出现这些反应。如果您在注射后出现荨麻疹、皮疹或潮红，请在下次注射前告知医务人员。如果您出现以下任何严重过敏反应的迹象，应立即停用 ACTEMRA 并联系您的医疗服务提供者，同时寻求紧急帮助：
  - 面部、嘴唇、口腔或舌头肿胀
  - 呼吸困难
  - 喘息
  - 严重瘙痒
  - 皮疹、荨麻疹、注射部位以外的皮肤发红或肿胀
  - 感到头晕或昏厥
  - 心跳加快或胸部有心跳剧烈的感觉（心动过速）
  - 出汗
- **神经系统问题。**接受 ACTEMRA 治疗的人被诊断出患有多发性硬化症的情况虽然罕见，但也有发生。目前尚不清楚 ACTEMRA 对某些神经系统疾病可能有什么影响。

ACTEMRA 最常见的副作用包括：

- 上呼吸道感染（普通感冒、鼻窦感染）
- 头痛
- 血压升高（高血压）
- 注射部位反应

请告知医务人员任何让您感到不适或持续存在的副作用。这些并非 ACTEMRA 可能引起的所有副作用。欲了解更多信息，请咨询医务人员或药剂师。

请致电您的医生，征求有关副作用的医疗建议。请致电 1-800-FDA-1088 向 FDA 报告副作用。
您也可以致电 1-888-835-2555 向 Genentech 报告副作用。

有关安全有效使用 ACTEMRA 的一般信息。
除《用药指南》中列出的用途外，有时还会开具其他用途的处方。请勿将 ACTEMRA 给予他人，即使他们有与您相同的症状。这可能会伤害他们。您可以向药剂师或医务人员咨询有关 ACTEMRA 的信息，这些信息是为医疗专业人员编写的。

ACTEMRA 的成分是什么?

活性成分：托珠单抗。
ACTEMRA 静脉用药的非活性成分：十二水磷酸二钠/二水磷酸二氢钠缓冲液、聚山梨醇酯 80、蔗糖和注射溶液。
ACTEMRA 皮下的非活性成分：L-精氨酸盐酸盐、L-组氨酸、L-组氨酸盐酸盐一水合物、L-蛋氨酸、聚山梨酯 80 和注射溶液。

Genentech, Inc.,罗氏集团子公司， 1 DNA Way, South San Francisco, CA 94080-4990
美国许可证号：1048

如需了解更多信息，请访问 www.ACTEMRA.com 或致电 1-800-ACTEMRA。

使用说明

ACTEMRA® (AC-TEM-RA)

（托珠单抗）

注射液，供皮下注射用

单剂量预充式注射器

在开始使用 ACTEMRA 预充式注射器之前以及每次获取处方补充药时，请阅读并遵循 ACTEMRA 预充式注射器附带的使用说明。在您首次使用 ACTEMRA 预充式注射器之前，请确保医务人员向您展示正确的使用方法。

- **在准备好注射 ACTEMRA 之前，请勿取下针头保护帽。**
- **请勿在任何时候尝试拆开注射器。**
- **不得重复使用同一注射器。**

ACTEMRA 预充式注射器组件 **（见图 A）**。

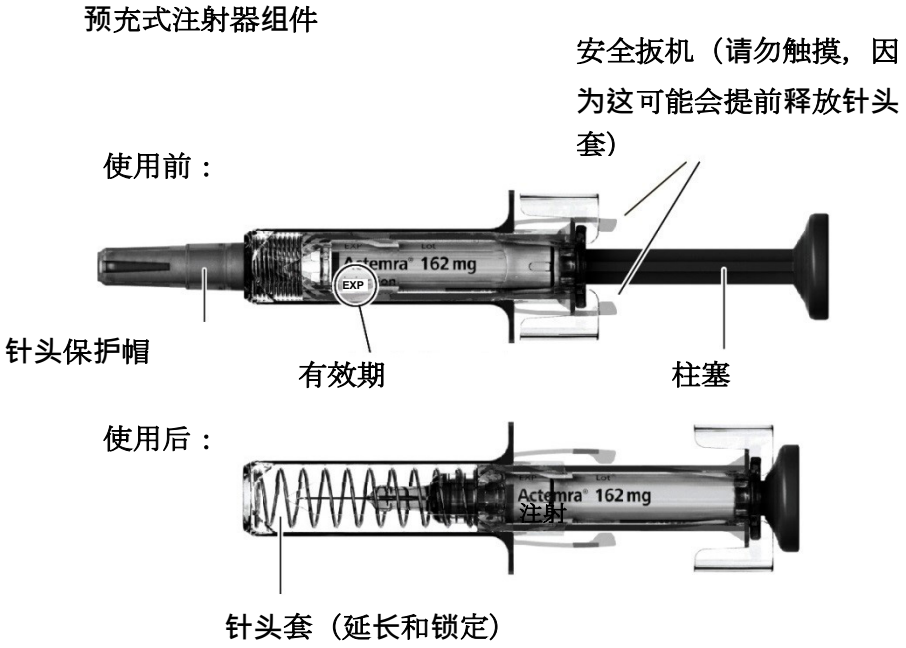


图 A

ACTEMRA 预充式注射器注射时所需的用品（见图 B）：

- ACTEMRA 预充式注射器
- 酒精棉片
- 无菌棉球或纱布
- 耐穿刺容器或锐器容器，用于安全处理针头保护帽和用过的注射器**（请参阅步骤 4 “注射器处理”）**

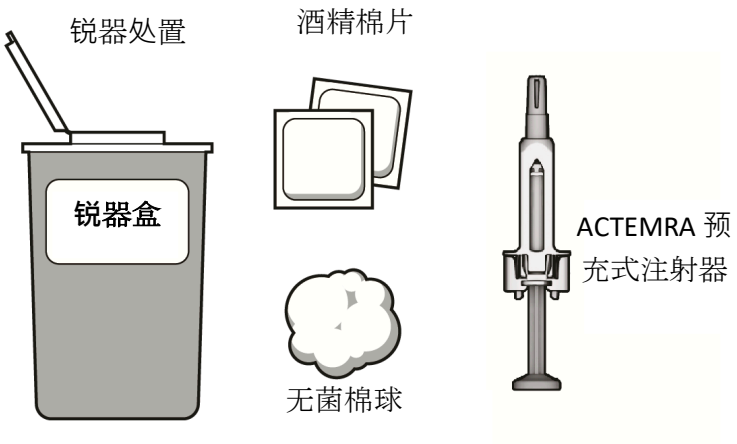


图 B

步骤 1。 ACTEMRA注射液制备

找一个舒适的空间，一个干净、平坦的工作台面。

- 将装有注射器的盒子从冰箱中取出并打开。**请勿**触摸注射器上的安全扳机，否则可能会损坏注射器。
- 从包装盒中取出 1 个一次性 ACTEMRA 预充式注射器，静置 30 分钟以使其达到室温。如果注射器未达到室温，可能会导致注射时不适，并且难以下压柱。
- **不得**以任何方式加快升温过程，例如使用微波炉或将注射器置入温水中。
- 检查 ACTEMRA 预充式注射器上的有效期（**见图A**）。如果超过有效期，**请勿**使用，因为不安全。如果已过有效期，请将注射器安全地弃置在锐器盒中并更换新的注射器。

在 ACTEMRA 预充式注射器恢复至室温的过程中，请勿取下针头保护帽。

- 请将未使用的注射器存放在原包装盒中，并保存在 36°F 至 46°F（2°C 至 8°C）的冰箱中。**请勿**冷冻。
- 从冰箱中取出后，预充式注射器可在 86°F (30°C) 或以下的温度下保存长达 2 周。本预充式注射器必须始终保存在原包装盒中，以避光和防潮。握住 ACTEMRA 预充式注射器，使带盖的针头朝下（**见图 C**）。

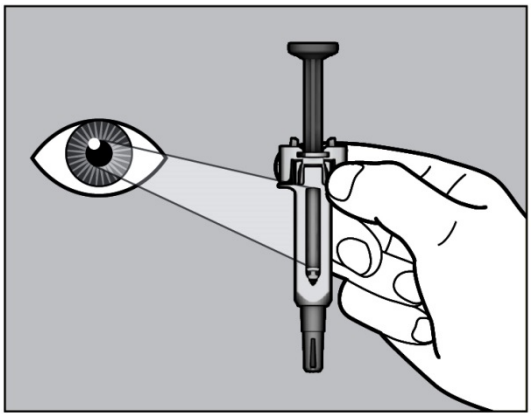


图 C

- 检查 ACTEMRA 预充式注射器中的液体。液体应为澄清的无色至浅黄色。如果液体浑浊、变色或有结块或颗粒，请勿注射 ACTEMRA，因为不安全。将注射器安全地弃置在锐器盒中并更换新的注射器。
- 用肥皂和水彻底洗手。

步骤 2。选择注射部位并进行准备

选择注射部位

- 推荐的注射部位是大腿前部和腹部，肚脐周围 5 厘米左右的区域除外（**见图 D**）。
- 如果是由照料者进行注射，也可使用上臂外侧区域。请勿尝试自行在上臂区域注射（**见图 D**）。

轮换注射部位

- 每次注射都要选择不同的注射部位，距离上次注射部位至少 2.5 厘米。
- 请勿注射到痣、疤痕、瘀伤或皮肤柔软、发红、坚硬或不完整的区域。

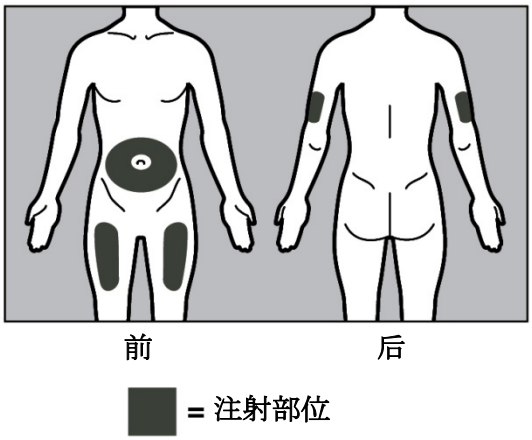


图 D

注射部位的准备工作

- 用酒精棉片打圈擦拭注射部位，然后自然风干以减少感染的风险。注射前**不得**再次触摸注射部位。
- **请勿**对已清洁区域扇干或吹风。

步骤 3。 注射 ACTEMRA

- 用一只手握住 ACTEMRA 预充式注射器，用另一只手直接取下针头保护帽（**见图 E**）。取下针头保护帽时，**请勿**抓握柱塞。如果您无法取下针头保护帽，应该向照料者寻求帮助或联系医务人员。

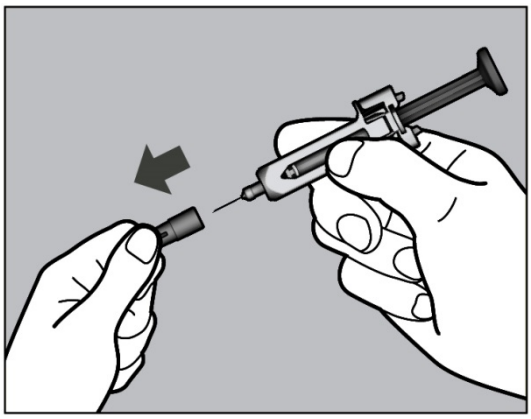


图 E

- 将针头保护帽扔进锐器盒中。
- ACTEMRA 预充式注射器中可能存在小气泡。无需处理。
- 您可能会在针头末端看到一滴液体。这是正常现象，不会对剂量产生影响。
- **请勿**触摸针头或让针头接触任何物体表面。
- 如果预充式注射器掉落，**请勿**继续使用。
- 如果取下针头保护帽后 5 分钟内未使用，则应将注射器丢弃在耐穿刺容器或锐器盒中，并应使用新注射器。
- 取下后切勿重新盖上针头保护帽。
- 用一只手的拇指和食指夹住 ACTEMRA 预充式注射器（**见图 F**）。

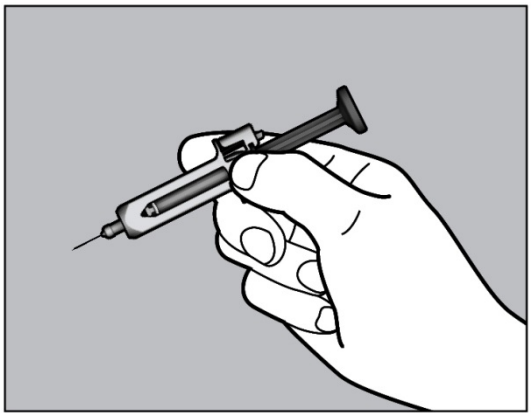


图 F

- **请勿**回拉注射器的柱塞。
- 用另一只手轻轻捏住已清洁的皮肤区域。紧紧握住捏住的皮肤。请务必捏住皮肤，以确保注射到皮下（进入脂肪组织中），而非更深的部位（进入肌肉）中。若注射入肌肉，可能会导致不适。
- 将针头插入皮肤时，**请勿**握住或推动柱塞。
- 迅速有力地将针头以 45° 至 90° 的角度全部刺入捏起的皮肤（**见图 G**）。选取正确的角度以确保药物注射到皮下（进入脂肪组织）非常重要，否则注射可能会疼痛，药物可能不起作用。

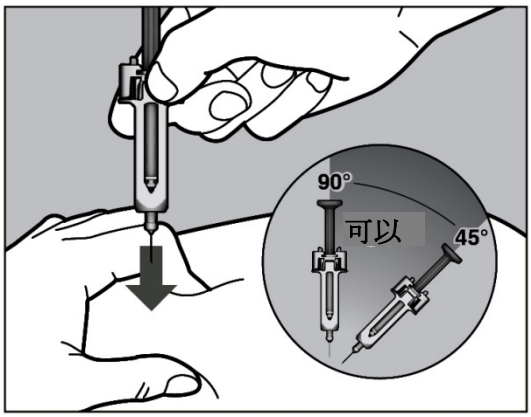


图 G

- 将注射器保持在适当位置并松开捏起的皮肤。
- 轻轻向下推动柱塞，缓慢注射所有药物（**见图 H**）。 您必须一直向下按压柱塞，以确保获得完整剂量，并确保注射装置上的安全扳机被完全推向一侧。如果柱塞未完全压下，针头套在取下时则无法完全覆盖针头。如果没有盖住针头，请小心地将注射器放入耐刺穿容器中，以免针头损坏。

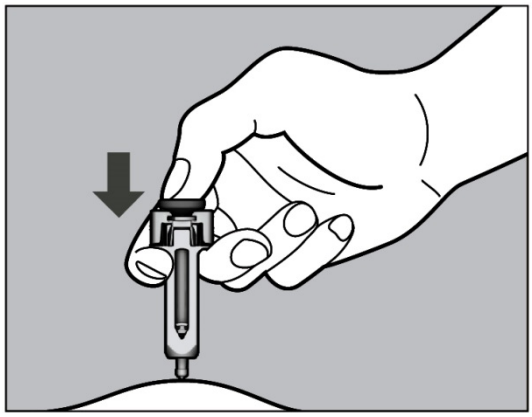


图 H

- 一直向下推动柱塞后，持续向下按压柱塞，确保在将针头从皮肤中取出之前注射完所有药物。
- 继续按下柱塞，同时以与插入时相同的角度将针头从皮肤中取出（**见图 I**）。

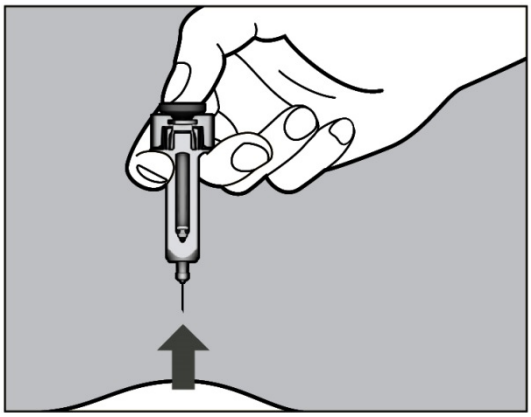


图 I

- 将针头完全从皮肤中取出后，松开柱塞，让针头套护住针头（**见图 J**）。

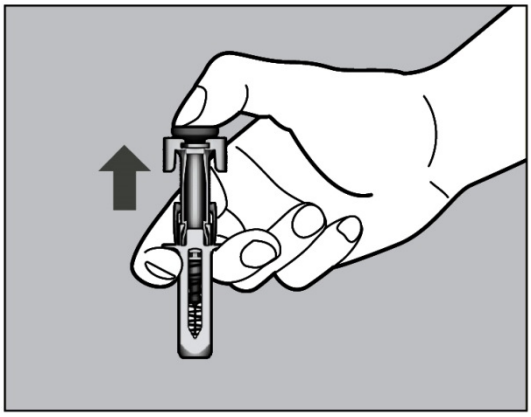


图 J

注射后

- 注射部位可能会有少量出血。可用棉球或纱布压在注射部位。
- **请勿**摩擦注射部位。
- 如有需要，您可以用创可贴覆盖注射部位。

步骤 4。注射器处理

- ACTEMRA 预充式注射器不得重复使用
- 将用过的注射器放入耐刺穿容器中（**请参阅“如何丢弃用过的注射器?”**）

- **请勿**将针头保护帽套回针头上。
- **如果是他人为您注射，则此人在取出注射器和处置注射器时也必须小心，以防止意外针头刺伤和传播感染。**

如何丢弃用过的注射器？

- 使用后立即将用过的针头和注射器（包括 ACTEMRA）放入经 FDA 批准的锐器处置盒中（**见图 K**）。**请勿随意将松动的针头和注射器丢弃在家用垃圾箱。**

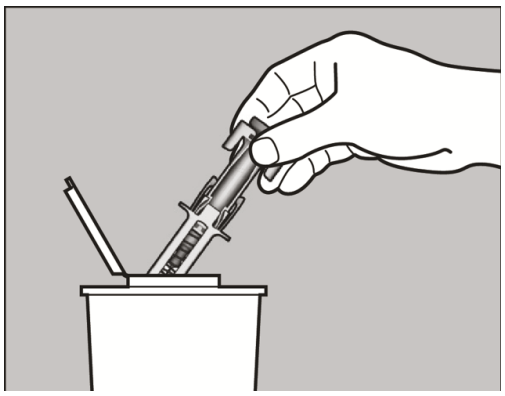


图 K

- 如果您没有 FDA 批准的锐器盒，您可以使用以下家用容器：
  - 重型塑料材质
  - 可用紧密贴合的防刺穿盖子封闭，使得锐器不能透出
  - 使用过程中保持直立稳定
  - 密闭防漏
  - 贴上适当的标签，警告容器内存危险废弃物
    - 当锐器盒快要装满时，您需要遵循社区指南，了解处理锐器盒的正确方法。州或地方法律可能规定了如何丢弃用过的针头和注射器。有关安全锐器处置的更多信息，以及有关您所居住州锐器处置的具体信息，请访问 FDA 网站： http://www.fda.gov/safesharpsdisposal。
    - 除非您的社区指南允许，否则请勿将用过的锐器盒放入家庭垃圾中。请勿回收用过的锐器盒。

- **将 ACTEMRA 预充式注射器和处置盒放在儿童接触不到的地方。**

记录您的注射情况

- 记录自行注射的日期、时间和注射的具体部位。记录下有关注射的任何问题或疑虑，以便向医务人员进行咨询。

如果您对 ACTEMRA 预充式注射器有疑问或疑虑，请联系熟悉 ACTEMRA 的医务人员或致电 1-800-ACTEMRA。

本用药指南和使用说明已获得美国食品药品监督管理局批准。
用药指南修订日期：2024 年 9 月

Genentech, Inc.
罗氏集团子公司
1 DNA Way
South San Francisco, CA 94080-4990

美国许可证号：1048

使用说明

ACTEMRA® (AC-TEM-RA)

（托珠单抗）

注射液，供皮下注射用

单剂量预充式 ACTPen® (AKT-PEN) 自动注射器

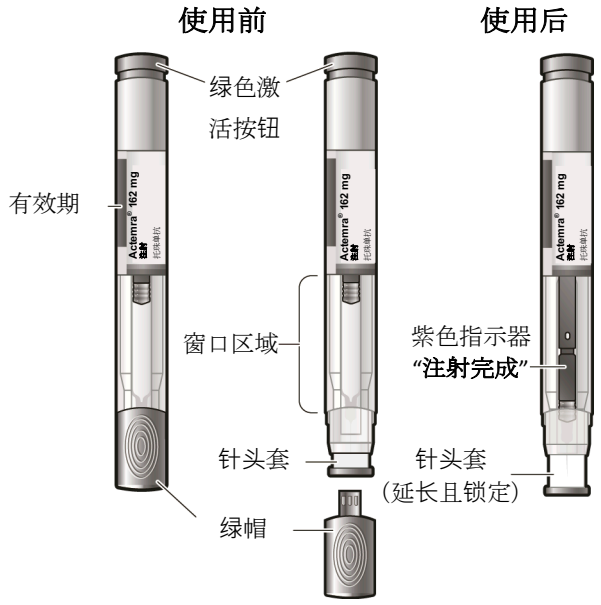
在开始使用 ACTEMRA ACTPen 自动注射器之前以及每次重新配药时，请阅读并遵循 ACTEMRA ACTPen 自动注射器附带的使用说明。在您首次使用 ACTEMRA ACTPen 自动注射器之前，请确保医务人员向您展示正确的使用方法。

重要提示：将未使用的自动注射器放在原包装盒中，并保存在 36°F 至 46°F（2°C 至 8°C）的冰箱中。**请勿**冷冻。从冰箱中取出后，自动注射器可在 86°F (30°C) 或以下的温度下保存长达 2 周。自动注射器必须始终保存在原包装盒中，以避光和防潮。

- 在准备好注射 ACTEMRA 之前，**请勿**取下自动注射器保护帽。
- **请勿**在任何时候尝试拆开自动注射器。
- **请勿**重复使用同一自动注射器。
- **请勿**隔着衣物使用自动注射器。
- **请勿**让自动注射器无人看管
- 如果自动注射器有损坏或不小心掉落，**请勿**使用自动注射器。
- 请放置在儿童接触不到的地方。

ACTEMRA ACTPen 自动注射器组件 **（见图 A）**。

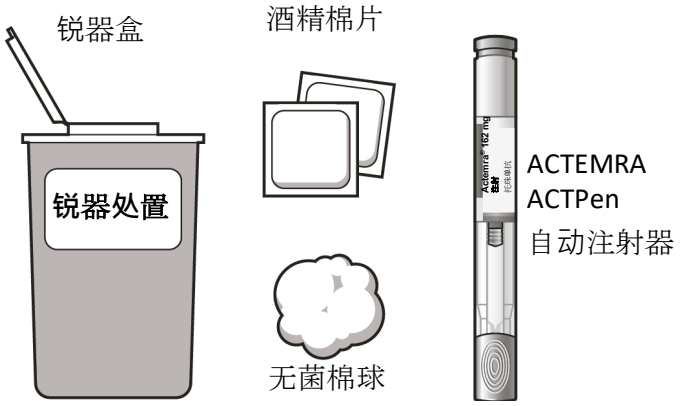
图 A



使用 ACTEMRA ACTPen 自动注射器注射所需的用品（见图 B）：

- 1 个 ACTEMRA ACTPen 自动注射器
- 1 个酒精棉片
- 1 个无菌棉球或纱布
- 1 个耐刺穿容器或锐器盒，用于安全处理自动注射器盖和用过的自动注射器**（请参阅步骤 4 “自动注射器的处理”）**

图 B

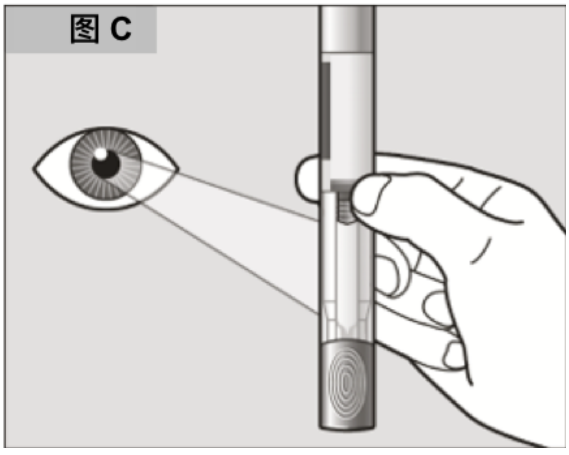


步骤 1。ACTEMRA 注射液制备

找一个舒适的空间，有一个干净、平坦的工作台面。

- 从冰箱中取出装有自动注射器的盒子。
- 如果是第一次打开盒子，请检查以确保其密封完好。如果盒子疑似已经被打开，**请勿**使用自动注射器。
- 检查自动注射器盒是否损坏。如果盒子疑似已损坏，**请勿**使用 ACTEMRA ACTPen 自动注射器。
- **检查自动注射器盒上的有效期。**如果已过有效期，**请勿**使用自动注射器，因为可能不安全。
- 打开包装盒，从包装盒中取出 1 个一次性 ACTEMRA ACTPen 自动注射器。
- 将盒子中剩余的自动注射器放回冰箱。
- **检查 ACTEMRA ACTPen 自动注射器上的有效期（见图 A）**。如果超过有效期，**请勿**使用，因为不安全。如果已过有效期，请将自动注射器安全地弃置在锐器盒中并更换新的注射器。
- **检查自动注射器以确保其未损坏。**如果自动注射器有损坏或不小心掉落，**请勿**使用自动注射器。
- 将自动注射器放在干净、平坦的表面上，让自动注射器静置 45 分钟，使其达到室温。如果自动注射器未达到室温，可能会导致注射时不适，并且注射时间可能会更长。
  - **不得**以任何方式加速加热过程，例如使用微波炉或将自动注射器放入温水中。
  - **请勿**让自动注射器在阳光直射下预热。
  - 当 ACTEMRA ACTPen 自动注射器达到室温时，**请勿**取下绿帽。
- 握住 ACTEMRA ACTPen 自动注射器，使绿帽朝下**（参见图 C）**。
- 查看透明窗口区域。检查 ACTEMRA ACTPen 自动注射器中的液体**（见图 C）**。液体应为澄清的无色至浅黄色。如果液体浑浊、变色或有结块或颗粒，**请勿**注射 ACTEMRA，因为不安全。将自动注射器安全地弃置在锐器盒中并更换一个新的注射器。

图 C



- 用肥皂和水彻底洗手。

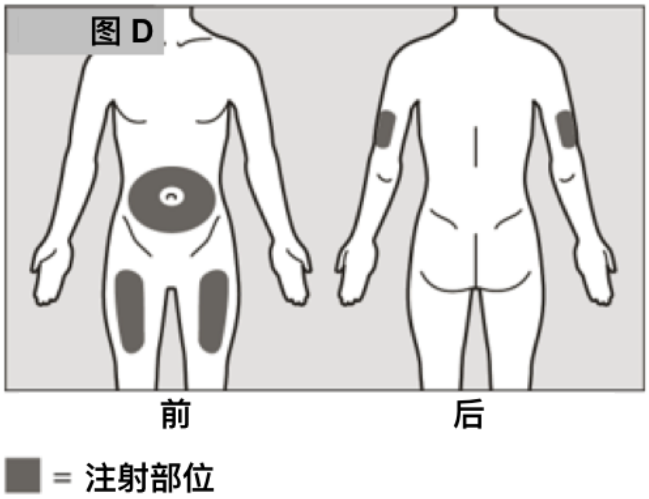
步骤 2。选择注射部位并进行准备

选择注射部位

- 推荐的注射部位是大腿前部和腹部，但肚脐周围约 5 厘米内区域除外（**见图 D**）。
- 如果是由照料者进行注射，也可使用上臂外侧区域。**请勿**尝试自行在上臂区域注射（**见图 D**）。

轮换注射部位

- 每次注射时都要选择不同的注射部位，距离上次注射的部位至少 2.5 厘米。
- **请勿**注射到痣、疤痕、瘀伤或皮肤柔软、发红、坚硬或不完整的区域。

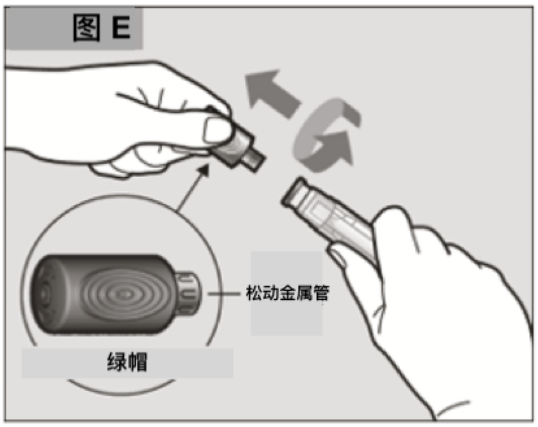


注射部位的准备工作

- 用酒精棉片打圈擦拭注射部位，然后自然风干以减少感染的风险。注射前**不得**再次触摸注射部位。
- **请勿**对已清洁区域扇干或吹风。

步骤 3。注射 ACTEMRA

- 用一只手握住 ACTEMRA ACTPen 自动注射器。用另一只手扭转并拉下绿帽（**见图 E**）。 绿帽包含一根宽松的金属管。
- 如果您无法取下绿帽，应向照料者寻求帮助或联系医务人员。

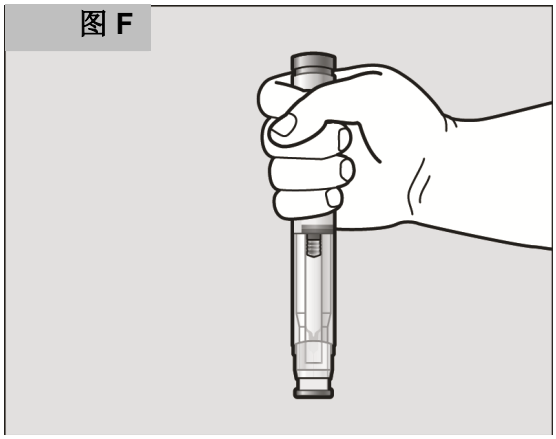


重要提示：请勿触摸位于窗口区域下方的自动注射器尖端的针护罩（见图 A），以避免意外的针刺伤。

- 将绿帽扔进锐器盒中。

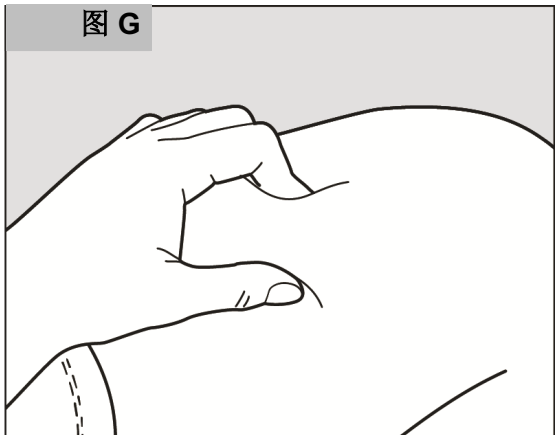
- 取下绿帽后，便可使用自动注射器。**如果在取下绿帽后 3 分钟内未使用自动注射器，则应将自动注射器丢弃在锐器盒中，并应使用新的自动注射器。**
- 取下绿帽后切勿重新装上。
- 用一只手轻轻握住自动注射器的上部，以便您可以看到自动注射器的窗口区域（**见图 F**）。

图 F



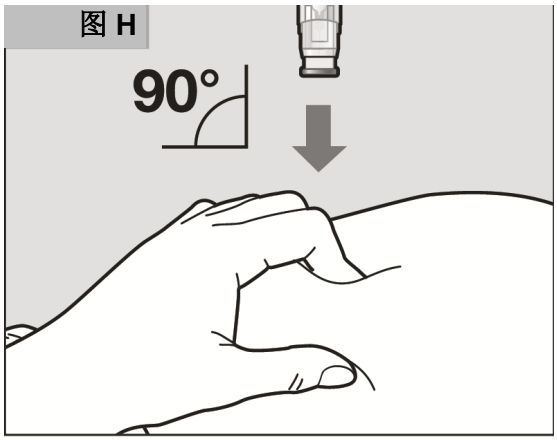
- 用另一只手轻轻捏住已清洁的皮肤区域，准备好牢固的注射部位（**见图 G**）。自动注射器需要牢固的注射部位才能正确激活。请务必捏住皮肤，以确保注射到皮下（进入脂肪组织中），而非更深的部位（进入肌肉）中。若注射入肌肉，可能会导致不适。

图 G

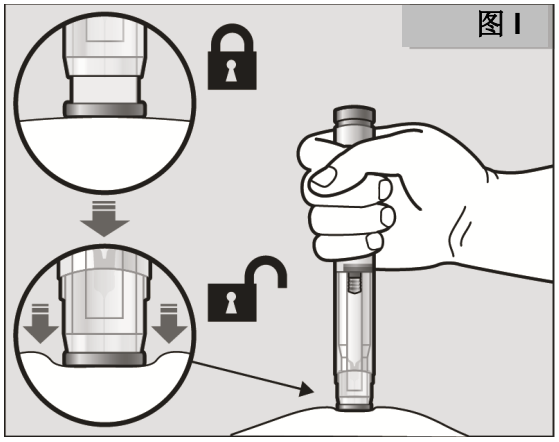


- **请勿**按绿色激活按钮。

  将自动注射器的针头套以 90° 角靠在捏紧的皮肤上（**见图 H**）。
- 重要的是选取正确的角度，以确保药物注射到皮肤下（进入脂肪组织），否则注射可能会疼痛，药物可能不起作用。
- **在整个注射过程中继续轻捏。**



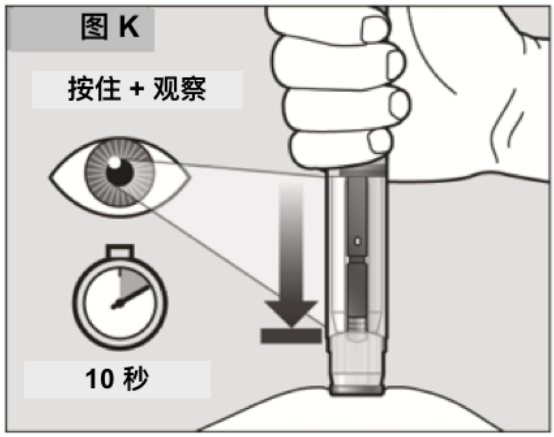
- 您必须解锁绿色激活按钮方能使用自动注射器。如需绿色激活按钮，请将自动注射器用力压在捏紧的皮肤上，直到针头套完全推入（**见图 I**）。



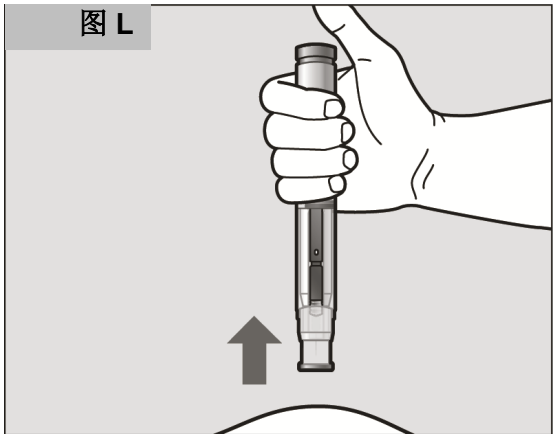
- 继续将针头套推入。如果没有将针头套完全推向皮肤，绿色激活按钮将不起作用。继续捏住皮肤，同时将自动注射器保持在适当的位置。

- 按绿色激活按钮开始注射。“咔哒”声表示注射**开始**。按住绿色按钮并继续将自动注射器紧紧地压在皮肤上（**见图 J**）。如果无法开始注射，应向照料者寻求帮助或联系医务人员。

- 注射期间紫色指示器将沿着窗口区域移动（**见图 K**）。
- **观察紫色指示器直至其停止移动，**以确保注射了全部剂量的药物。这可能需要长达 **10 秒的时间。**



- 注射过程中您可能会听到第二次“咔哒”声，但应该继续将自动注射器紧贴皮肤，直到紫色指示器停止移动。
- 当紫色指示器停止移动时，松开绿色按钮。将自动注射器以 90° 角直接从注射部位提起，将针头从皮肤上取下。然后，针头套将移出并锁定到位，覆盖针头（**见图 L**）。



- 检查窗口区域，查看其是否充满紫色指示器（**见图 L**）。
- 如果窗口区域没有被紫色指示器填充，则：
  - 针头套可能未锁定。**请勿**触摸自动注射器的针头套，因为您可能会被针头刺伤。如果未覆盖针头，请小心地将自动注射器放入锐器盒中，以避免针头造成任何伤害。
  - 您可能尚未获取全部剂量的 ACTEMRA。**请勿**尝试重复使用自动注射器。**请勿**用另一个自动注射器重复注射。致电医务人员寻求帮助。

注射后

- 注射部位可能会有少量出血。可用棉球或纱布压在注射部位。
- **请勿**摩擦注射部位。
- 如有需要，您可以用创可贴覆盖注射部位。

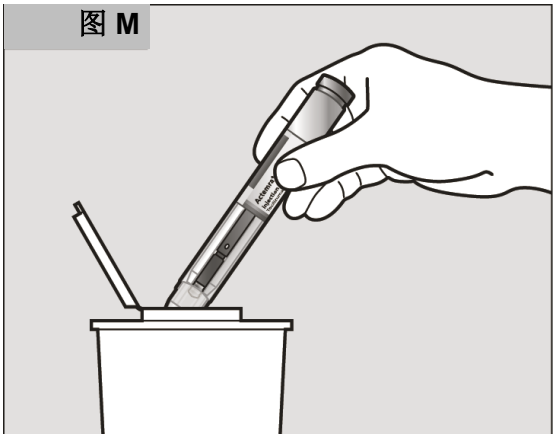
步骤 4。自动注射器处理

- ACTEMRA ACTPen 自动注射器不应重复使用。
- 将用过的自动注射器放入锐器盒中（**请参阅“如何处理用过的自动注射器?”**）。
- **请勿**将保护帽盖回自动注射器。
- **如果是他人为您注射，则此人在取出注射器和处置注射器时也必须小心，以防意外针头刺伤和感染。**

如何处理用过的自动注射器?

- 使用后立即将用过的 ACTEMRA ACTPen 自动注射器和绿帽放入经 FDA 批准的锐器盒中（**见图 M**）。
- **请勿**将自动注射器和绿帽丢弃（放置）在家用垃圾箱中。

图 M



- 如果您没有 FDA 批准的锐器盒，您可以使用以下家用容器：
    - 重型塑料材质
    - 可用紧密贴合的防刺穿盖子封闭，使得锐器不能透出
    - 使用过程中保持直立稳定
    - 密闭防漏
    - 贴上适当的标签，警告容器内存危险废弃物
        - 当锐器盒快要装满时，您需要遵循社区指南，了解处理锐器盒的正确方法。州或地方法律可能对如何处理用过的自动注射器进行了规定。有关安全锐器处置的更多信息，以及有关您所居住州锐器处置的具体信息，请访问 FDA 网站： http://www.fda.gov/safesharpsdisposal。
        - **除非您的社区指南允许，**否则请勿将用过的锐器盒放入家庭垃圾中。**请勿**回收用过的锐器盒。

将 ACTEMRA ACTPen 自动注射器和处置容器放在儿童接触不到的地方。

记录您的注射情况

- 记录自行注射的日期、时间和注射的具体部位。记录下有关注射的任何问题或疑虑，以便向医务人员进行咨询。

如果您对 ACTEMRA ACTPen 自动注射器有任何疑问或疑虑，请咨询熟悉 ACTEMRA 的医务人员或致电 1-800-ACTEMRA。

本用药指南和使用说明已获得美国食品药品监督管理局批准。
用药指南修订日期：2024 年 9 月
ACTEMRA 是罗氏集团成员中外制药株式会社的注册商标。
ACTPen 是罗氏集团成员中外制药株式会社的注册商标。

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1 DNA Way
South San Francisco, CA 94080-4990

美国许可证号：1048

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ACTEMRA safely and effectively. See full prescribing information for ACTEMRA.

ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use
Initial U.S. Approval: 2010

WARNING: RISK OF SERIOUS INFECTIONS
See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including tuberculosis (TB), bacterial, invasive fungal, viral, and other opportunistic infections have occurred in patients receiving ACTEMRA. (5.1)**
- **If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)**
- **Perform test for latent TB (except patients with COVID-19); if positive, start treatment for TB prior to starting ACTEMRA. (5.1)**
- **Monitor all patients for active TB during treatment, even if initial latent TB test is negative. (5.1)**

----------RECENT MAJOR CHANGES----------
Warnings and Precautions (5.2, 5.6) 09/2024
----------INDICATIONS AND USAGE----------
ACTEMRA® (tocilizumab) is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of:

Rheumatoid Arthritis (RA) (1.1)
- Adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

Giant Cell Arteritis (GCA) (1.2)
- Adult patients with giant cell arteritis.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) (1.3)
- Slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease (SSc-ILD)

Polyarticular Juvenile Idiopathic Arthritis (PJIA) (1.4)
- Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis.

Systemic Juvenile Idiopathic Arthritis (SJIA) (1.5)
- Patients 2 years of age and older with active systemic juvenile idiopathic arthritis.

Cytokine Release Syndrome (CRS) (1.6)
- Adults and pediatric patients 2 years of age and older with chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome.

Coronavirus Disease 2019 (COVID-19) (1.7)
- Hospitalized adult patients with coronavirus disease 2019 (COVID-19) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

----------DOSAGE AND ADMINISTRATION----------
For RA, pJIA and sJIA, ACTEMRA may be used alone or in combination with methotrexate: and in RA, other non-biologic DMARDs may be used. (2)

General Administration and Dosing Information (2.1)
- *RA, GCA, SSc-ILD, PJIA and SJIA* – It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or ALT or AST above 1.5 times the upper limit of normal (ULN)*(5.3, 5.4)*.
- *COVID-19* – It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 1000 per mm^3, platelet count below 50,000 mm^3, or ALT or AST above 10 times ULN *(5.3, 5.4)*.
- In *RA, CRS or COVID-19* patients, ACTEMRA doses exceeding 800 mg per infusion are not recommended. (2.2, 2.7, 12.3)
- In *GCA* patients, ACTEMRA doses exceeding 600 mg per infusion are not recommended. (2.3, 12.3)

Rheumatoid Arthritis (2.2)
Recommended Adult Intravenous Dosage:
When used in combination with non-biologic DMARDs or as monotherapy the recommended starting dose is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

Recommended Adult Subcutaneous Dosage:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

Giant Cell Arteritis (2.3)
Recommended Adult Intravenous Dosage:
The recommended dose is 6 mg per kg every 4 weeks in combination with a tapering course of glucocorticoids. ACTEMRA can be used alone following discontinuation of glucocorticoids.

Recommended Adult Subcutaneous Dosage:
The recommended dose is 162 mg given once every week as a subcutaneous injection, in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection, in combination with a tapering course of glucocorticoids, may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD) (2.4)
Recommended Adult Subcutaneous Dosage:
The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

Polyarticular Juvenile Idiopathic Arthritis (2.5)

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every three weeks
Patients at or above 30 kg weight	162 mg once every two weeks

Systemic Juvenile Idiopathic Arthritis (2.6)

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg every two weeks
Patients at or above 30 kg weight	162 mg every week

Cytokine Release Syndrome (2.7)

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids.	

Coronavirus Disease 2019 (2.8)
The recommended dosage of ACTEMRA for adult patients with COVID-19 is 8 mg per kg administered by a 60-minute intravenous infusion.

Administration of Intravenous formulation (2.9)
- For patients with RA, GCA, COVID-19, CRS, PJIA, and SJIA patients at or above 30 kg, dilute to 100 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.
- For PJIA, SJIA and CRS patients less than 30 kg, dilute to 50 mL in 0.9% or 0.45% Sodium Chloride Injection, USP for intravenous infusion using aseptic technique.

- Administer as a single intravenous drip infusion over 1 hour; do not administer as bolus or push.

Administration of Subcutaneous formulation (2.10)
- Follow the Instructions for Use for prefilled syringe and prefilled ACTPen® autoinjector

Dose Modifications (2.11)
- Recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia.

----------DOSAGE FORMS AND STRENGTHS----------

Intravenous Infusion
Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion (3)
Subcutaneous Injection
Injection: 162 mg/0.9 mL in a single-dose prefilled syringe or single-dose prefilled ACTPen® autoinjector (3)

----------CONTRAINDICATIONS----------

Known hypersensitivity to ACTEMRA. (4)

----------WARNINGS AND PRECAUTIONS----------
- Serious Infections – do not administer ACTEMRA during an active infection, including localized infections. If a serious infection develops, interrupt ACTEMRA until the infection is controlled. (5.1)
- Gastrointestinal (GI) perforation—use with caution in patients who may be at increased risk. (5.2)
- Hepatotoxicity- Monitor patients for signs and symptoms of hepatic injury. Modify or discontinue ACTEMRA if abnormal liver tests persist or worsen or if clinical signs and symptoms of liver disease develop. (2.10, 5.3)
- Laboratory monitoring—recommended due to potential consequences of treatment-related changes in neutrophils, platelets, lipids, and liver function tests. (2.10, 5.4)
- Hypersensitivity reactions, including anaphylaxis and death, and serious cutaneous reactions including Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) – discontinue ACTEMRA, treat promptly, and monitor until reaction resolves. (5.6)
- Live vaccines—Avoid use with ACTEMRA. (5.9, 7.3)

----------ADVERSE REACTIONS----------

Most common adverse reactions (incidence of at least 5%): upper respiratory tract infections, nasopharyngitis, headache, hypertension, increased ALT, injection site reactions. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------USE IN SPECIFIC POPULATIONS----------
- **Pregnancy:** Based on animal data, may cause fetal harm. (8.1)
- **Lactation:** Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 09/2024

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF SERIOUS INFECTIONS

Patients treated with ACTEMRA are at increased risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions (5.1), Adverse Reactions (6.1)]*. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids.

If a serious infection develops, interrupt ACTEMRA until the infection is controlled.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients, except those with COVID-19, should be tested for latent tuberculosis before ACTEMRA use and during therapy. Treatment for latent infection should be initiated prior to ACTEMRA use.**
- **Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral and other infections due to opportunistic pathogens.**

The risks and benefits of treatment with ACTEMRA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

1.1 Rheumatoid Arthritis (RA)

ACTEMRA® (tocilizumab) is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease-Modifying Anti-Rheumatic Drugs (DMARDs).

1.2 Giant Cell Arteritis (GCA)

ACTEMRA® (tocilizumab) is indicated for the treatment of giant cell arteritis (GCA) in adult patients.

1.3 Systemic Sclerosis-Associated Interstitial Lung Disease (SSc-ILD)

ACTEMRA® (tocilizumab) is indicated for slowing the rate of decline in pulmonary function in adult patients with systemic sclerosis-associated interstitial lung disease.

1.4 Polyarticular Juvenile Idiopathic Arthritis (PJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older.

1.5 Systemic Juvenile Idiopathic Arthritis (SJIA)

ACTEMRA® (tocilizumab) is indicated for the treatment of active systemic juvenile idiopathic arthritis in patients 2 years of age and older.

1.6 Cytokine Release Syndrome (CRS)

ACTEMRA® (tocilizumab) is indicated for the treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients 2 years of age and older.

1.7 Coronavirus Disease 2019 (COVID-19)

ACTEMRA® (tocilizumab) is indicated for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adult patients who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

2 DOSAGE AND ADMINISTRATION

2.1 General Considerations for Administration

Not Recommended for Concomitant Use with Biological DMARDs

ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists, IL-1R antagonists, anti-CD20 monoclonal antibodies and selective co-stimulation modulators because of the possibility of increased immunosuppression and increased risk of infection. Avoid using ACTEMRA with biological DMARDs.

Baseline Laboratory Evaluation Prior to Treatment

Obtain and assess baseline complete blood count (CBC) and liver function tests prior to treatment.

- *RA, GCA, SSc-ILD, PJIA and SJIA* – It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 2000 per mm^3, platelet count below 100,000 per mm^3, or ALT or AST above 1.5 times the upper limit of normal (ULN) *[see Warnings and Precautions (5.3, 5.4)]*.
- *CRS* – Patients with severe or life-threatening CRS frequently have cytopenias or elevated ALT or AST due to the lymphodepleting chemotherapy or the CRS. The decision to administer ACTEMRA should take into account the potential benefit of treating the CRS versus the risks of short-term treatment with ACTEMRA.
- *COVID-19* – It is recommended that ACTEMRA not be initiated in patients with an absolute neutrophil count (ANC) below 1000 per mm^3, platelet count below 50,000 mm^3, or ALT or AST above 10 times ULN *[see Warnings and Precautions (5.3, 5.4)]*.

2.2 Recommended Dosage for Rheumatoid Arthritis

ACTEMRA may be used as monotherapy or concomitantly with methotrexate or other non-biologic DMARDs as an intravenous infusion or as a subcutaneous injection.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 4 mg per kg every 4 weeks followed by an increase to 8 mg per kg every 4 weeks based on clinical response.

- Reduction of dose from 8 mg per kg to 4 mg per kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11), Warnings and Precautions (5.3, 5.4), and Adverse Reactions (6.1)]*.
- Doses exceeding 800 mg per infusion are not recommended in RA patients *[see Clinical Pharmacology (12.3)]*.

Recommended Subcutaneous Dosage Regimen:

Patients less than 100 kg weight	162 mg administered subcutaneously every other week, followed by an increase to every week based on clinical response
Patients at or above 100 kg weight	162 mg administered subcutaneously every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose or reduction in frequency of administration of subcutaneous dose from every week to every other week dosing is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11), Warnings and Precautions (5.3, 5.4), and Adverse Reactions (6.2)]*.

2.3 Recommended Dosage for Giant Cell Arteritis

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for adult patients given as a 60-minute single intravenous drip infusion is 6 mg per kg every 4 weeks in combination with tapering course of glucocorticoids.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11)]*.
- Doses exceeding 600 mg per infusion are not recommended in GCA patients *[see Clinical Pharmacology (12.3)]*.

Recommended Subcutaneous Dosage Regimen:

The recommended dose of ACTEMRA for adult patients with GCA is 162 mg given once every week as a subcutaneous injection in combination with a tapering course of glucocorticoids.

A dose of 162 mg given once every other week as a subcutaneous injection in combination with a tapering course of glucocorticoids may be prescribed based on clinical considerations.

ACTEMRA can be used alone following discontinuation of glucocorticoids.

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dose or reduction in frequency of administration of subcutaneous dose from every week to every other week dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11)]*.

2.4 Recommended Dosage for Systemic Sclerosis-Associated Interstitial Lung Disease

The recommended dose of ACTEMRA for adult patients with SSc-ILD is 162 mg given once every week as a subcutaneous injection.

- Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11)]*.
- Subcutaneous administration with the prefilled ACTPen® autoinjector has not been studied in SSc-ILD.
- Intravenous administration is not approved for SSc-ILD.

2.5 Recommended Dosage for Polyarticular Juvenile Idiopathic Arthritis

ACTEMRA may be used as an intravenous infusion or as a subcutaneous injection alone or in combination with methotrexate. Do not change dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dosage of ACTEMRA for PJIA patients given once every 4 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous PJIA Dosage Every 4 Weeks	
Patients less than 30 kg weight	10 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous PJIA Dosage	
Patients less than 30 kg weight	162 mg once every 3 weeks
Patients at or above 30 kg weight	162 mg once every 2 weeks

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose instead of the next scheduled intravenous dose.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11]*.

2.6 Recommended Dosage for Systemic Juvenile Idiopathic Arthritis

ACTEMRA may be used as an intravenous infusion or as a subcutaneous injection alone or in combination with methotrexate. Do not change a dose based solely on a single visit body weight measurement, as weight may fluctuate.

Recommended Intravenous Dosage Regimen:

The recommended dose of ACTEMRA for SJIA patients given once every 2 weeks as a 60-minute single intravenous drip infusion is:

Recommended Intravenous SJIA Dosage Every 2 Weeks	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg

Recommended Subcutaneous Dosage Regimen:

Recommended Subcutaneous SJIA Dosage	
Patients less than 30 kg weight	162 mg once every two weeks
Patients at or above 30 kg weight	162 mg once every week

When transitioning from ACTEMRA intravenous therapy to subcutaneous administration, administer the first subcutaneous dose when the next scheduled intravenous dose is due.

Interruption of dosing may be needed for management of dose-related laboratory abnormalities including elevated liver enzymes, neutropenia, and thrombocytopenia *[see Dosage and Administration (2.11)]*.

2.7 Recommended Dosage for Cytokine Release Syndrome (CRS)

Use only the intravenous route for treatment of CRS. The recommended dose of ACTEMRA for treatment of CRS given as a 60-minute intravenous infusion is:

Recommended Intravenous CRS Dosage	
Patients less than 30 kg weight	12 mg per kg
Patients at or above 30 kg weight	8 mg per kg
Alone or in combination with corticosteroids	

- If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of ACTEMRA may be administered. The interval between consecutive doses should be at least 8 hours.
- Doses exceeding 800 mg per infusion are not recommended in CRS patients.
- Subcutaneous administration is not approved for CRS.

2.8 Coronavirus Disease 2019 (COVID-19)

Administer ACTEMRA by intravenous infusion only.

The recommended dosage of ACTEMRA for treatment of adult patients with COVID-19 is 8 mg per kg administered as a single 60-minute intravenous infusion. If clinical signs or symptoms worsen or do not improve after the first dose, one additional infusion of ACTEMRA may be administered at least 8 hours after the initial infusion.

- Doses exceeding 800 mg per infusion are not recommended in patients with COVID-19.
- Subcutaneous administration is not approved for COVID-19.

2.9 Preparation and Administration Instructions for Intravenous Infusion

ACTEMRA for intravenous infusion should be diluted by a healthcare professional using aseptic technique as follows:

- Use a sterile needle and syringe to prepare ACTEMRA.
- Patients **less than 30 kg**: use a **50 mL** infusion bag or bottle of 0.9% or 0.45% Sodium Chloride Injection, USP, and then follow steps 1 and 2 below.
- Patients **at or above 30 kg weight**: use a **100 mL** infusion bag or bottle, and then follow steps 1 and 2 below.
- Step 1. Withdraw a volume of 0.9% or 0.45% Sodium Chloride Injection, USP, equal to the volume of the ACTEMRA injection required for the patient's dose from the infusion bag or bottle *[see Dosage and Administration (2.2, 2.5, 2.6, 2.7)]*.

For Intravenous Use: Volume of ACTEMRA Injection per kg of Body Weight		
Dosage	**Indication**	**Volume of ACTEMRA injection per kg of body weight**
4 mg/kg	Adult RA	0.2 mL/kg
6 mg/kg	Adult GCA	0.3 mL/kg
8 mg/kg	Adult RA Adult COVID-19 SJIA, PJIA and CRS (greater than or equal to 30 kg of body weight)	0.4 mL/kg
10 mg/kg	PJIA (less than 30 kg of body weight)	0.5 mL/kg
12 mg/kg	SJIA and CRS (less than 30 kg of body weight)	0.6 mL/kg

- Step 2. Withdraw the amount of ACTEMRA for intravenous infusion from the vial(s) and add slowly into the 0.9% or 0.45% Sodium Chloride Injection, USP infusion bag or bottle. To mix the solution, gently invert the bag to avoid foaming.
- The fully diluted ACTEMRA solutions for infusion using 0.9% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) or room temperature for up to 24 hours and should be protected from light.
- The fully diluted ACTEMRA solutions for infusion using 0.45% Sodium Chloride Injection, USP may be stored at 36°F to 46°F (2°C to 8°C) for up to 24 hours or room temperature for up to 4 hours and should be protected from light.
- ACTEMRA solutions do not contain preservatives; therefore, unused product remaining in the vials should not be used.
- Allow the fully diluted ACTEMRA solution to reach room temperature prior to infusion.
- The infusion should be administered over 60 minutes, and must be administered with an infusion set. Do not administer as an intravenous push or bolus.
- ACTEMRA should not be infused concomitantly in the same intravenous line with other drugs. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of ACTEMRA with other drugs.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. If particulates and discolorations are noted, the product should not be used.
- Fully diluted ACTEMRA solutions are compatible with polypropylene, polyethylene and polyvinyl chloride infusion bags and polypropylene, polyethylene and glass infusion bottles.

2.10 Preparation and Administration Instructions for Subcutaneous Injection

- ACTEMRA for subcutaneous injection is not intended for intravenous drip infusion.
- Assess suitability of patient for subcutaneous home use and instruct patients to inform a healthcare professional before administering the next dose if they experience any symptoms of allergic reaction. Patients should seek immediate medical attention if they develop symptoms of serious allergic reactions. ACTEMRA subcutaneous injection is intended for use under the guidance of a healthcare practitioner. After proper training in subcutaneous injection technique, a patient may self-inject ACTEMRA or the patient's caregiver may administer ACTEMRA if a healthcare practitioner determines that it is appropriate. PJIA and SJIA patients may self-inject with the ACTEMRA prefilled syringe or ACTPen® autoinjector, or the patient's caregiver may administer ACTEMRA if both the healthcare practitioner and the parent/legal guardian determines it is appropriate *[see Use in Specific Populations (8.4)]*. Patients, or patient caregivers,

should be instructed to follow the directions provided in the Instructions for Use (IFU) for additional details on medication administration.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use ACTEMRA prefilled syringes (PFS) or prefilled ACTPen® autoinjectors exhibiting particulate matter, cloudiness, or discoloration. ACTEMRA for subcutaneous administration should be clear and colorless to pale yellow. Do not use if any part of the PFS or ACTPen® autoinjector appears to be damaged.
- Patients using ACTEMRA for subcutaneous administration should be instructed to inject the full amount in the syringe (0.9 mL) or full amount in the ACTPen® autoinjector (0.9 mL), which provides 162 mg of ACTEMRA, according to the directions provided in the IFU.
- Injection sites should be rotated with each injection and should never be given into moles, scars, or areas where the skin is tender, bruised, red, hard, or not intact.

2.11 Dosage Modifications due to Serious Infections or Laboratory Abnormalities

Serious Infections

Hold ACTEMRA treatment if a patient develops a serious infection until the infection is controlled.

Laboratory Abnormalities

Rheumatoid Arthritis, Giant Cell Arteritis and Systemic Sclerosis-Associated Interstitial Lung Disease

Liver Enzyme Abnormalities *[see Warnings and Precautions (5.3,5.4)]*		
Lab Value	**Recommendation for RA and SSc-ILD**	**Recommendation for GCA**
Greater than 1 to 3x ULN	Dose modify concomitant DMARDs if appropriate For persistent increases in this range: • For patients receiving intravenous ACTEMRA, reduce dose to 4 mg per kg or hold ACTEMRA until ALT or AST have normalized • For patients receiving subcutaneous ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate.	Dose modify immunomodulatory agents if appropriate For persistent increases in this range: • For patients receiving intravenous ACTEMRA, hold ACTEMRA until ALT or AST have normalized • For patients receiving subcutaneous ACTEMRA, reduce injection frequency to every other week or hold dosing until ALT or AST have normalized. Resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
Greater than 3 to 5x ULN (confirmed by repeat testing)	Hold ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue ACTEMRA	Hold ACTEMRA dosing until less than 3x ULN and follow recommendations above for greater than 1 to 3x ULN For persistent increases greater than 3x ULN, discontinue ACTEMRA
Greater than 5x ULN	Discontinue ACTEMRA	Discontinue ACTEMRA

Low Absolute Neutrophil Count (ANC) ***[see Warnings and Precautions (5.4)]***		
Lab Value (cells per mm^3)	**Recommendation for RA and SSc-ILD**	**Recommendation for GCA**
ANC greater than 1000	Maintain dose	Maintain dose
ANC 500 to 1000	Hold ACTEMRA dosing When ANC greater than 1000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate	Hold ACTEMRA dosing When ANC greater than 1000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 6 mg per kg • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
ANC less than 500	Discontinue ACTEMRA	Discontinue ACTEMRA

Low Platelet Count ***[see Warnings and Precautions (5.4)]***		
Lab Value (cells per mm^3)	**Recommendation for RA and SSc-ILD**	**Recommendation for GCA**
50,000 to 100,000	Hold ACTEMRA dosing When platelet count is greater than 100,000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 4 mg per kg and increase to 8 mg per kg as clinically appropriate • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate	Hold ACTEMRA dosing When platelet count is greater than 100,000 cells per mm^3: • For patients receiving intravenous ACTEMRA, resume ACTEMRA at 6 mg per kg • For patients receiving subcutaneous ACTEMRA, resume ACTEMRA at every other week and increase frequency to every week as clinically appropriate
Less than 50,000	Discontinue ACTEMRA	Discontinue ACTEMRA

Polyarticular and Systemic Juvenile Idiopathic Arthritis

Dose reduction of ACTEMRA has not been studied in the PJIA and SJIA populations. Dose interruptions of ACTEMRA are recommended for liver enzyme abnormalities, low neutrophil counts, and low platelet counts in patients with PJIA and SJIA at levels similar to what is outlined above for patients with RA and GCA. If appropriate, dose modify or stop concomitant methotrexate and/or other medications and hold ACTEMRA dosing until the clinical situation has been evaluated. In PJIA and SJIA the decision to discontinue ACTEMRA for a laboratory abnormality should be based upon the medical assessment of the individual patient.

3 DOSAGE FORMS AND STRENGTHS

Intravenous Infusion
Injection: 80 mg/4 mL, 200 mg/10 mL, 400 mg/20 mL as a clear, colorless to pale yellow solution in 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

Subcutaneous Injection
Injection: 162 mg/0.9 mL clear, colorless to slightly yellowish solution in a single-dose prefilled syringe or single-dose prefilled ACTPen® autoinjector.

4 CONTRAINDICATIONS

ACTEMRA is contraindicated in patients with known hypersensitivity to ACTEMRA *[see Warnings and Precautions (5.6)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Infections

Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, protozoal, or other opportunistic pathogens have been reported in patients receiving immunosuppressive agents including ACTEMRA. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis *[see Adverse Reactions (6.1)]*. Among opportunistic infections, tuberculosis, cryptococcus, aspergillosis, candidiasis, and pneumocystosis were reported with ACTEMRA. Other serious infections, not reported in clinical studies, may also occur (e.g., histoplasmosis, coccidioidomycosis, listeriosis). Patients have presented with disseminated rather than localized disease, and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids which in addition to rheumatoid arthritis may predispose them to infections.

Do not administer ACTEMRA in patients with an active infection, including localized infections. The risks and benefits of treatment should be considered prior to initiating ACTEMRA in patients:

- with chronic or recurrent infection;
- who have been exposed to tuberculosis;
- with a history of serious or an opportunistic infection;
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with ACTEMRA, as signs and symptoms of acute inflammation may be lessened due to suppression of the acute phase reactants *[see Dosage and Administration (2.8), Adverse Reactions (6.1), and Patient Counseling Information (17)]*.

Hold ACTEMRA if a patient develops a serious infection, an opportunistic infection, or sepsis. A patient who develops a new infection during treatment with ACTEMRA should undergo a prompt and complete diagnostic workup appropriate for an immunocompromised patient, initiate appropriate antimicrobial therapy, and closely monitor the patient.

COVID-19

In patients with COVID-19, monitor for signs and symptoms of new infections during and after treatment with ACTEMRA. There is limited information regarding the use of ACTEMRA in patients with COVID-19 and concomitant active serious infections. The risks and benefits of treatment with ACTEMRA in COVID-19 patients with other concurrent infections should be considered.

Tuberculosis

Evaluate patients for tuberculosis risk factors and test for latent infection prior to initiating ACTEMRA. In patients with COVID-19, testing for latent infection is not necessary prior to initiating treatment with ACTEMRA.

Consider anti-tuberculosis therapy prior to initiation of ACTEMRA in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent tuberculosis but having risk factors for tuberculosis infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended to aid in the decision whether initiating anti-tuberculosis therapy is appropriate for an individual patient.

Closely monitor patients for the development of signs and symptoms of tuberculosis including patients who tested negative for latent tuberculosis infection prior to initiating therapy.

The incidence of tuberculosis in worldwide clinical development programs is 0.1%. Patients with latent tuberculosis should be treated with standard antimycobacterial therapy before initiating ACTEMRA.

Viral Reactivation

Viral reactivation has been reported with immunosuppressive biologic therapies and cases of herpes zoster exacerbation were observed in clinical studies with ACTEMRA. No cases of Hepatitis B reactivation were observed in the trials; however patients who screened positive for hepatitis were excluded.

5.2 Gastrointestinal Perforations

Events of gastrointestinal perforation have been reported in clinical trials, primarily as complications of diverticulitis in patients treated with ACTEMRA. Use ACTEMRA with caution in patients who may be at increased risk for gastrointestinal perforation. Promptly evaluate patients presenting with fever, new onset abdominal symptoms, and a change in bowel habits for early identification of gastrointestinal perforation *[see Adverse Reactions (6.1)]*.

5.3 Hepatotoxicity

Serious cases of hepatic injury have been observed in patients taking intravenous or subcutaneous ACTEMRA. Some of these cases have resulted in liver transplant or death. Time to onset for cases ranged from months to years after treatment initiation with tocilizumab. While most cases presented with marked elevations of transaminases (> 5 times ULN), some cases presented with signs or symptoms of liver dysfunction and only mildly elevated transaminases.

During randomized controlled studies, treatment with ACTEMRA was associated with a higher incidence of transaminase elevations *[see Adverse Reactions (6.1, 6.2, 6.6, 6.8)]*. Increased frequency and magnitude of these elevations was observed when potentially hepatotoxic drugs (e.g., MTX) were used in combination with ACTEMRA.

For RA, GCA and SSc-ILD patients, obtain a liver test panel (serum alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase, and total bilirubin) before initiating ACTEMRA, every 4 to 8 weeks after start of therapy for the first 6 months of treatment and every 3 months thereafter. It is not recommended to initiate ACTEMRA treatment in RA, GCA or SSc-ILD patients with elevated transaminases ALT or AST greater than 1.5x ULN. In patients who develop elevated ALT or AST greater than 5x ULN, discontinue ACTEMRA. For recommended modifications based upon increase in transaminases *see Dosage and Administration (2.11)*.

Patients hospitalized with COVID-19 may have elevated ALT or AST levels. Multi-organ failure with involvement of the liver is recognized as a complication of severe COVID-19. The decision to administer ACTEMRA should balance the potential benefit of treating COVID-19 against the potential risks of acute treatment with ACTEMRA. It is not recommended to initiate ACTEMRA treatment in COVID-19 patients with elevated ALT or AST above 10 x ULN. Monitor ALT and AST during treatment.

Measure liver tests promptly in patients who report symptoms that may indicate liver injury, such as fatigue, anorexia, right upper abdominal discomfort, dark urine or jaundice. In this clinical context, if the patient is found to have abnormal liver tests (e.g., ALT greater than three times the upper limit of the reference range, serum total bilirubin greater than two times the upper limit of the reference range), ACTEMRA treatment should be interrupted and investigation done to establish the probable cause. ACTEMRA should only be restarted in patients with another explanation for the liver test abnormalities after normalization of the liver tests.

A similar pattern of liver enzyme elevation is noted with ACTEMRA treatment in the PJIA and SJIA populations. Monitor liver test panel at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA.

5.4 Changes in Laboratory Parameters

Patients with Rheumatoid Arthritis, Giant Cell Arteritis, Systemic Sclerosis-Associated Interstitial Lung Disease and Coronavirus Disease 2019

Neutropenia

Treatment with ACTEMRA was associated with a higher incidence of neutropenia. Infections have been uncommonly reported in association with treatment-related neutropenia in long-term extension studies and postmarketing clinical experience.

- It is not recommended to initiate ACTEMRA treatment in RA, GCA and SSc-ILD patients with a low neutrophil count, i.e., absolute neutrophil count (ANC) less than 2000 per mm^3. In patients who develop an absolute neutrophil count less than 500 per mm^3 treatment is not recommended.
- Monitor neutrophils 4 to 8 weeks after start of therapy and every 3 months thereafter *[see Clinical Pharmacology (12.2)]*. For recommended modifications based on ANC results *see Dosage and Administration (2.11)*.
- It is not recommended to initiate ACTEMRA treatment in COVID-19 patients with an ANC less than 1000 per mm^3. Neutrophils should be monitored.

Thrombocytopenia

Treatment with ACTEMRA was associated with a reduction in platelet counts. Treatment-related reduction in platelets was not associated with serious bleeding events in clinical trials *[see Adverse Reactions (6.1, 6.2)]*.

- It is not recommended to initiate ACTEMRA treatment in RA, GCA and SSc-ILD patients with a platelet count below 100,000 per mm^3. In patients who develop a platelet count less than 50,000 per mm^3 treatment is not recommended.
- Monitor platelets 4 to 8 weeks after start of therapy and every 3 months thereafter. For recommended modifications based on platelet counts *see Dosage and Administration (2.11)*.
- In COVID-19 patients with a platelet count less than 50,000 per mm^3, treatment is not recommended. Platelets should be monitored.

Elevated Liver Enzymes

Refer to 5.3 Hepatotoxicity. For recommended modifications *[see Dosage and Administration (2.11)]*

Lipid Abnormalities

Treatment with ACTEMRA was associated with increases in lipid parameters such as total cholesterol, triglycerides, LDL cholesterol, and/or HDL cholesterol *[see Adverse Reactions (6.1, 6.2)]*.

- Assess lipid parameters approximately 4 to 8 weeks following initiation of ACTEMRA therapy.
- Subsequently, manage patients according to clinical guidelines [e.g., National Cholesterol Educational Program (NCEP)] for the management of hyperlipidemia.

Patients with Polyarticular and Systemic Juvenile Idiopathic Arthritis

A similar pattern of liver enzyme elevation, low neutrophil count, low platelet count and lipid elevations is noted with ACTEMRA treatment in the PJIA and SJIA populations. Monitor neutrophils, platelets, ALT and AST at the time of the second administration and thereafter every 4 to 8 weeks for PJIA and every 2 to 4 weeks for SJIA. Monitor lipids as above for approved adult indications *[see Dosage and Administration (2.11)]*.

5.5 Immunosuppression

The impact of treatment with ACTEMRA on the development of malignancies is not known but malignancies were observed in clinical studies *[see Adverse Reactions (6.1)]*. ACTEMRA is an immunosuppressant, and treatment with immunosuppressants may result in an increased risk of malignancies.

5.6 Hypersensitivity Reactions, Including Anaphylaxis

Hypersensitivity reactions, including anaphylaxis, have been reported in association with ACTEMRA and anaphylactic events with a fatal outcome have been reported with intravenous infusion of ACTEMRA. Anaphylaxis and other hypersensitivity reactions that required treatment discontinuation were reported in 0.1% (3 out of 2644) of patients in the 6-month controlled trials of intravenous ACTEMRA, 0.2% (8 out of 4009) of patients in the intravenous all-exposure RA population, 0.7% (8 out of 1068) in the subcutaneous 6-month controlled RA trials, and in 0.7% (10 out of 1465) of patients in the subcutaneous all-exposure population. In the SJIA controlled trial with intravenous ACTEMRA, 1 out of 112 patients (0.9%) experienced hypersensitivity reactions that required treatment discontinuation. In the PJIA controlled trial with intravenous ACTEMRA, 0 out of 188 patients (0%) in the ACTEMRA all-exposure population experienced hypersensitivity reactions that required treatment discontinuation. Reactions that required treatment discontinuation included generalized erythema, rash, and urticaria. Injection site reactions were categorized separately *[see Adverse Reactions (6)]*.

In the postmarketing setting, events of hypersensitivity reactions, including anaphylaxis and death have occurred in patients treated with a range of doses of intravenous ACTEMRA, with or without concomitant therapies. Events have occurred in patients who received premedication. Hypersensitivity, including anaphylaxis events, have occurred both with and without previous hypersensitivity reactions and as early as the first infusion of ACTEMRA *[see Adverse Reactions (6.12)]*. In addition, serious cutaneous reactions, including

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported in patients with autoinflammatory conditions treated with ACTEMRA.

ACTEMRA for intravenous use should only be infused by a healthcare professional with appropriate medical support to manage anaphylaxis. For ACTEMRA subcutaneous injection, advise patients to seek immediate medical attention if they experience any symptoms of a hypersensitivity reaction. If a hypersensitivity reaction occurs, immediately discontinue ACTEMRA, treat promptly and monitor until signs and symptoms resolve.

5.7 Demyelinating Disorders

The impact of treatment with ACTEMRA on demyelinating disorders is not known, but multiple sclerosis and chronic inflammatory demyelinating polyneuropathy were reported rarely in RA clinical studies. Monitor patients for signs and symptoms potentially indicative of demyelinating disorders. Prescribers should exercise caution in considering the use of ACTEMRA in patients with preexisting or recent onset demyelinating disorders.

5.8 Active Hepatic Disease and Hepatic Impairment

Treatment with ACTEMRA is not recommended in patients with active hepatic disease or hepatic impairment *[see Adverse Reactions (6.1), Use in Specific Populations (8.6)]*.

5.9 Vaccinations

Avoid use of live vaccines concurrently with ACTEMRA as clinical safety has not been established. No data are available on the secondary transmission of infection from persons receiving live vaccines to patients receiving ACTEMRA.

No data are available on the effectiveness of vaccination in patients receiving ACTEMRA. Because IL-6 inhibition may interfere with the normal immune response to new antigens, it is recommended that all patients, particularly pediatric or elderly patients, if possible, be brought up to date with all immunizations in agreement with current immunization guidelines prior to initiating ACTEMRA therapy. The interval between live vaccinations and initiation of ACTEMRA therapy should be in accordance with current vaccination guidelines regarding immunosuppressive agents.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in labeling:

- Serious Infections *[see Warnings and Precautions (5.1)]*
- Gastrointestinal Perforations *[see Warnings and Precautions (5.2)]*
- Laboratory Parameters *[see Warnings and Precautions (5.4)]*
- Immunosuppression *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions, Including Anaphylaxis *[see Warnings and Precautions (5.6)]*
- Demyelinating Disorders *[see Warnings and Precautions (5.7)]*
- Active Hepatic Disease and Hepatic Impairment *[see Warnings and Precautions (5.8)]*

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not predict the rates observed in a broader patient population in clinical practice.

6.1 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The ACTEMRA-IV data in rheumatoid arthritis (RA) includes 5 double-blind, controlled, multicenter studies. In these studies, patients received doses of ACTEMRA-IV 8 mg per kg monotherapy (288 patients), ACTEMRA-IV 8 mg per kg in combination with DMARDs (including methotrexate) (1582 patients), or ACTEMRA-IV 4 mg per kg in combination with methotrexate (774 patients).

The all exposure population includes all patients in registration studies who received at least one dose of ACTEMRA-IV. Of the 4009 patients in this population, 3577 received treatment for at least 6 months, 3309 for at least one year; 2954 received treatment for at least 2 years and 2189 for 3 years.

All patients in these studies had moderately to severely active rheumatoid arthritis. The study population had a mean age of 52 years, 82% were female and 74% were Caucasian.

The most common serious adverse reactions were serious infections *[see Warnings and Precautions (5.1)]*. The most commonly reported adverse reactions in controlled studies up to 24 weeks (occurring in at least 5% of patients treated with ACTEMRA-IV monotherapy or in combination with DMARDs) were upper respiratory tract infections, nasopharyngitis, headache, hypertension and increased ALT.

The proportion of patients who discontinued treatment due to any adverse reactions during the double-blind, placebo-controlled studies was 5% for patients taking ACTEMRA-IV and 3% for placebo-treated patients. The most common adverse reactions that required discontinuation of ACTEMRA-IV were increased hepatic transaminase values (per protocol requirement) and serious infections.

Overall Infections

In the 24 week, controlled clinical studies, the rate of infections in the ACTEMRA-IV monotherapy group was 119 events per 100 patient-years and was similar in the methotrexate monotherapy group. The rate of infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 133 and 127 events per 100 patient-years, respectively, compared to 112 events per 100 patient-years in the placebo plus DMARD group. The most commonly reported infections (5% to 8% of patients) were upper respiratory tract infections and nasopharyngitis.

The overall rate of infections with ACTEMRA-IV in the all exposure population remained consistent with rates in the controlled periods of the studies.

Serious Infections

In the 24 week, controlled clinical studies, the rate of serious infections in the ACTEMRA-IV monotherapy group was 3.6 per 100 patient-years compared to 1.5 per 100 patient-years in the methotrexate group. The rate of serious infections in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group was 4.4 and 5.3 events per 100 patient-years, respectively, compared to 3.9 events per 100 patient-years in the placebo plus DMARD group.

In the all-exposure population, the overall rate of serious infections remained consistent with rates in the controlled periods of the studies. The most common serious infections included pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis and bacterial arthritis. Cases of opportunistic infections have been reported *[see Warnings and Precautions (5.1)]*.

In the cardiovascular outcomes Study WA25204, the rate of serious infections in the ACTEMRA 8 mg/kg IV every 4 weeks group, with or without DMARD, was 4.5 per 100 patient-years, and the rate in the etanercept 50 mg weekly SC group, with or without DMARD, was 3.2 per 100 patient-years *[see Clinical Studies (14.1)]*.

Gastrointestinal Perforations

During the 24 week, controlled clinical trials, the overall rate of gastrointestinal perforation was 0.26 events per 100 patient-years with ACTEMRA-IV therapy.

In the all-exposure population, the overall rate of gastrointestinal perforation remained consistent with rates in the controlled periods of the studies. Reports of gastrointestinal perforation were primarily reported as complications of diverticulitis including generalized purulent peritonitis, lower GI perforation, fistula and abscess. Most patients who developed gastrointestinal perforations were taking concomitant nonsteroidal anti-inflammatory medications (NSAIDs), corticosteroids, or methotrexate *[see Warnings and Precautions (5.2)]*. The relative contribution of these concomitant medications versus ACTEMRA-IV to the development of GI perforations is not known.

Infusion Reactions

In the 24 week, controlled clinical studies, adverse events associated with the infusion (occurring during or within 24 hours of the start of infusion) were reported in 8% and 7% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 5% of patients in the placebo plus DMARD group. The most frequently reported event on the 4 mg per kg and 8 mg per kg dose during the infusion was hypertension (1% for both doses), while the most frequently reported event occurring within 24 hours of finishing an infusion were headache (1% for both doses) and skin reactions (1% for both doses), including rash, pruritus and urticaria. These events were not treatment limiting.

Anaphylaxis

Hypersensitivity reactions requiring treatment discontinuation, including anaphylaxis, associated with ACTEMRA-IV were reported in 0.1% (3 out of 2644) in the 24 week, controlled trials and in 0.2% (8 out of 4009) in the all-exposure population. These reactions were generally observed during the second to fourth infusion of ACTEMRA-IV. Appropriate medical treatment should be available for immediate use in the event of a serious hypersensitivity reaction *[see Warnings and Precautions (5.6)]*.

Laboratory Abnormalities

Neutropenia

In the 24 week, controlled clinical studies, decreases in neutrophil counts below 1000 per mm^3 occurred in 1.8% and 3.4% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD group, respectively, compared to 0.1% of patients in the placebo plus DMARD group. Approximately half of the instances of ANC below 1000 per mm^3 occurred within 8 weeks of starting therapy. Decreases in neutrophil counts below 500 per mm^3 occurred in 0.4% and 0.3% of patients in the 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.1% of patients in the placebo plus DMARD group. There was no clear relationship between decreases in neutrophils below 1000 per mm^3 and the occurrence of serious infections.

In the all-exposure population, the pattern and incidence of decreases in neutrophil counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.4)]*.

Thrombocytopenia

In the 24 week, controlled clinical studies, decreases in platelet counts below 100,000 per mm^3 occurred in 1.3% and 1.7% of patients on 4 mg per kg and 8 mg per kg ACTEMRA-IV plus DMARD, respectively, compared to 0.5% of patients on placebo plus DMARD, without associated bleeding events.

In the all-exposure population, the pattern and incidence of decreases in platelet counts remained consistent with what was seen in the 24 week controlled clinical studies *[see Warnings and Precautions (5.4)]*.

Elevated Liver Enzymes

Liver enzyme abnormalities are summarized in **Table 1**. In patients experiencing liver enzyme elevation, modification of treatment regimen, such as reduction in the dose of concomitant DMARD, interruption of ACTEMRA-IV, or reduction in ACTEMRA-IV dose, resulted in decrease or normalization of liver enzymes *[see Dosage and Administration (2.11)]*. These elevations were not associated with clinically relevant increases in direct bilirubin, nor were they associated with clinical evidence of hepatitis or hepatic insufficiency *[see Warnings and Precautions (5.3, 5.4)]*.

Table 1 Incidence of Liver Enzyme Abnormalities in the 24 Week Controlled Period of Studies I to V*

	ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)	**Methotrexate N = 284 (%)**	**ACTEMRA 4 mg per kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)**	**Placebo + DMARDs N = 1170 (%)**
AST (U/L)					
> ULN to 3x ULN	22	26	34	41	17
> 3x ULN to 5x ULN	0.3	2	1	2	0.3
> 5x ULN	0.7	0.4	0.1	0.2	< 0.1
ALT (U/L)					
> ULN to 3x ULN	36	33	45	48	23
> 3x ULN to 5x ULN	1	4	5	5	1
> 5x ULN	0.7	1	1.3	1.5	0.3

ULN = Upper Limit of Normal
*For a description of these studies, see Section 14, Clinical Studies.

In the all-exposure population, the elevations in ALT and AST remained consistent with what was seen in the 24 week, controlled clinical trials.

In Study WA25204, of the 1538 patients with moderate to severe RA *[see Clinical Studies (14.1)]* and treated with tocilizumab, elevations in ALT or AST >3 x ULN occurred in 5.3% and 2.2% patients, respectively. One serious event of drug induced hepatitis with hyperbilirubinemia was reported in association with tocilizumab.

Lipids

Elevations in lipid parameters (total cholesterol, LDL, HDL, triglycerides) were first assessed at 6 weeks following initiation of ACTEMRA-IV in the controlled 24 week clinical trials. Increases were observed at this time point and remained stable thereafter. Increases in triglycerides to levels above 500 mg per dL were rarely observed. Changes in other lipid parameters from baseline to week 24 were evaluated and are summarized below:

- Mean LDL increased by 13 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 20 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 25 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean HDL increased by 3 mg per dL in the ACTEMRA 4 mg per kg+DMARD arm, 5 mg per dL in the ACTEMRA 8 mg per kg+DMARD, and 4 mg per dL in ACTEMRA 8 mg per kg monotherapy.
- Mean LDL/HDL ratio increased by an average of 0.14 in the ACTEMRA 4 mg per kg+DMARD arm, 0.15 in the ACTEMRA 8 mg per kg+DMARD, and 0.26 in ACTEMRA 8 mg per kg monotherapy.
- ApoB/ApoA1 ratios were essentially unchanged in ACTEMRA-treated patients.

Elevated lipids responded to lipid lowering agents.

In the all-exposure population, the elevations in lipid parameters remained consistent with what was seen in the 24 week, controlled clinical trials.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to tocilizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In the 24 week, controlled clinical studies, a total of 2876 patients have been tested for anti-tocilizumab antibodies. Forty-six patients (2%) developed positive anti-tocilizumab antibodies, of whom 5 had an associated, medically significant, hypersensitivity reaction leading to withdrawal. Thirty patients (1%) developed neutralizing antibodies.

Malignancies

During the 24 week, controlled period of the studies, 15 malignancies were diagnosed in patients receiving ACTEMRA-IV, compared to 8 malignancies in patients in the control groups. Exposure-adjusted incidence was similar in the ACTEMRA-IV groups (1.32 events per 100 patient-years) and in the placebo plus DMARD group (1.37 events per 100 patient-years).

In the all-exposure population, the rate of malignancies remained consistent with the rate observed in the 24 week, controlled period *[see Warnings and Precautions (5.5)]*.

Other Adverse Reactions

Adverse reactions occurring in 2% or more of patients on 4 or 8 mg per kg ACTEMRA-IV plus DMARD and at least 1% greater than that observed in patients on placebo plus DMARD are summarized in **Table 2.**

Table 2 Adverse Reactions Occurring in at Least 2% or More of Patients on 4 or 8 mg per kg ACTEMRA plus DMARD and at Least 1% Greater Than That Observed in Patients on Placebo plus DMARD

24 Week Phase 3 Controlled Study Population					
Preferred Term	**ACTEMRA 8 mg per kg MONOTHERAPY N = 288 (%)**	**Methotrexate N = 284 (%)**	**ACTEMRA 4 mg per kg + DMARDs N = 774 (%)**	**ACTEMRA 8 mg per kg + DMARDs N = 1582 (%)**	**Placebo + DMARDs N = 1170 (%)**
Upper Respiratory Tract Infection	7	5	6	8	6
Nasopharyngitis	7	6	4	6	4
Headache	7	2	6	5	3
Hypertension	6	2	4	4	3
ALT increased	6	4	3	3	1
Dizziness	3	1	2	3	2
Bronchitis	3	2	4	3	3
Rash	2	1	4	3	1
Mouth Ulceration	2	2	1	2	1
Abdominal Pain Upper	2	2	3	3	2

Gastritis	1	2	1	2	1
Transaminase increased	1	5	2	2	1

Other infrequent and medically relevant adverse reactions occurring at an incidence less than 2% in rheumatoid arthritis patients treated with ACTEMRA-IV in controlled trials were:

Infections and Infestations: oral herpes simplex
Gastrointestinal disorders: stomatitis, gastric ulcer
Investigations: weight increased, total bilirubin increased
Blood and lymphatic system disorders: leukopenia
General disorders and administration site conditions: edema peripheral
Respiratory, thoracic, and mediastinal disorders: dyspnea, cough
Eye disorders: conjunctivitis
Renal disorders: nephrolithiasis
Endocrine disorders: hypothyroidism

6.2 Clinical Trials Experience in Rheumatoid Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The ACTEMRA-SC data in rheumatoid arthritis (RA) includes 2 double-blind, controlled, multicenter studies. Study SC-I was a non-inferiority study that compared the efficacy and safety of tocilizumab 162 mg administered every week subcutaneously and 8 mg/kg intravenously every four weeks in 1262 adult subjects with rheumatoid arthritis. Study SC-II was a placebo controlled superiority study that evaluated the safety and efficacy of tocilizumab 162 mg administered every other week subcutaneously or placebo in 656 patients. All patients in both studies received background non-biologic DMARDs.

The safety observed for ACTEMRA-SC administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), which were more common with ACTEMRA-SC compared with placebo SC injections (IV arm).

Injection Site Reactions

In the 6-month control period, in SC-I, the frequency of ISRs was 10.1% (64/631) and 2.4% (15/631) for the weekly ACTEMRA-SC and placebo SC (IV-arm) groups, respectively. In SC-II, the frequency of ISRs was 7.1% (31/437) and 4.1% (9/218) for the every other week ACTEMRA-SC and placebo groups, respectively. These ISRs (including erythema, pruritus, pain and hematoma) were mild to moderate in severity. The majority resolved without any treatment and none necessitated drug discontinuation.

Immunogenicity

In the 6-month control period in SC-I, 0.8% (5/625) in the ACTEMRA-SC arm and 0.8% (5/627) in the IV arm developed anti-tocilizumab antibodies; of these, all developed neutralizing antibodies. In SC-II, 1.6% (7/434) in the ACTEMRA-SC arm compared with 1.4 % (3/217) in the placebo arm developed anti- tocilizumab antibodies; of these, 1.4% (6/434) in the ACTEMRA-SC arm and 0.5% (1/217) in the placebo arm also developed neutralizing antibodies.

A total of 1454 (>99%) patients who received ACTEMRA-SC in the all exposure group have been tested for anti-tocilizumab antibodies. Thirteen patients (0.9%) developed anti-tocilizumab antibodies, and, of these, 12 patients (0.8%) developed neutralizing antibodies.

The rate is consistent with previous intravenous experience. No correlation of antibody development to adverse events or loss of clinical response was observed.

Laboratory Abnormalities
Neutropenia

During routine laboratory monitoring in the 6-month controlled clinical trials, a decrease in neutrophil count below 1×10^9/L occurred in 2.9% and 3.7% of patients receiving ACTEMRA-SC weekly and every other week, respectively.

There was no clear relationship between decreases in neutrophils below 1×10^9/L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-SC 6-month controlled clinical trials, none of the patients had a decrease in platelet count to $\leq 50{,}000/mm^3$.

Elevated Liver Enzymes

During routine laboratory monitoring in the 6-month controlled clinical trials, elevation in ALT or AST ≥3 x ULN occurred in 6.5% and 1.4% of patients, respectively, receiving ACTEMRA-SC weekly and 3.4% and 0.7% receiving ACTEMRA-SC every other week.

Lipid Parameters Elevations

During routine laboratory monitoring in the ACTEMRA-SC 6-month clinical trials, 19% of patients dosed weekly and 19.6% of patients dosed every other week and 10.2% of patients on placebo experienced sustained elevations in total cholesterol > 6.2 mmol/l (240 mg/dL), with 9%, 10.4% and 5.1% experiencing a sustained increase in LDL to 4.1 mmol/l (160 mg/dL) receiving ACTEMRA-SC weekly, every other week and placebo, respectively.

6.3 Clinical Trials Experience in Giant Cell Arteritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA (tocilizumab) has been studied in one Phase III study (WA28119) with 251 GCA patients. The total patient years duration in the ACTEMRA-SC GCA all exposure population was 138.5 patient years during the 12-month double blind, placebo-controlled phase of the study. The overall safety profile observed in the ACTEMRA-SC treatment groups was generally consistent with the known safety profile of ACTEMRA. There was an overall higher incidence of infections in GCA patients relative to RA patients. The rate of infection/serious infection events was 200.2/9.7 events per 100 patient years in the ACTEMRA-SC weekly group and 160.2/4.4 events per 100 patient years in the ACTEMRA-SC every other week group as compared to 156.0/4.2 events per 100 patient years in the placebo + 26 week prednisone taper and 210.2/12.5 events per 100 patient years in the placebo + 52 week taper groups.

6.4 Clinical Trials Experience in Giant Cell Arteritis Patients Treated With Intravenous ACTEMRA (ACTEMRA-IV)

The safety of ACTEMRA-IV was studied in an open label PK-PD and safety study in 24 patients with GCA who were in remission on ACTEMRA-IV at time of enrollment. Patients received ACTEMRA 7 mg/kg every 4 weeks for 20 weeks, followed by 6 mg/kg every 4 weeks for 20 weeks. The total patient years exposure to treatment was 17.5 years. The overall safety profile observed for ACTEMRA administered intravenously in GCA patients was consistent with the known safety profile of ACTEMRA.

6.5 Clinical Trials Experience in Systemic Sclerosis-Associated Interstitial Lung Disease Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of subcutaneous ACTEMRA was evaluated in two double-blind, placebo-controlled, multicenter studies (WA29767 and WA27788). In the Phase 3 Study WA29767, 212 patients with SSc were randomized to

tocilizumab 162 mg administered every week subcutaneously or placebo for 48 weeks, followed by open-label tocilizumab 162 mg administered subcutaneously every week for another 48 weeks. In the Phase 2/3 Study WA27788, 87 patients were randomized to tocilizumab 162 mg administered every week subcutaneously or placebo for 48 weeks, followed by open-label tocilizumab 162 mg administered subcutaneously every week for another 48 weeks.

The safety profile for ACTEMRA through week 48 in WA29767 was comparable for SSc-ILD and SSc patients overall, and in both studies was consistent with the known safety profile of ACTEMRA.

Immunogenicity

In the two clinical studies, WA29767 and WA27788, the incidence of treatment-induced anti-TCZ antibodies at week 96 was low (3 out of 169 patients, 1.8%). These anti-drug antibodies were of neutralizing potential, and none of the patients experienced hypersensitivity reactions.

6.6 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Intravenous ACTEMRA (ACTEMRA-IV)

The safety of ACTEMRA-IV was studied in 188 pediatric patients 2 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the ACTEMRA-IV all exposure population (defined as patients who received at least one dose of ACTEMRA-IV) was 184.4 patient years. At baseline, approximately half of the patients were taking oral corticosteroids and almost 80% were taking methotrexate. In general, the types of adverse drug reactions in patients with PJIA were consistent with those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.8)]*.

Infections

The rate of infections in the ACTEMRA-IV all exposure population was 163.7 per 100 patient years. The most common events observed were nasopharyngitis and upper respiratory tract infections. The rate of serious infections was numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (12.2 per 100 patient years) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (4.0 per 100 patient years). The incidence of infections leading to dose interruptions was also numerically higher in patients weighing less than 30 kg treated with 10 mg/kg tocilizumab (21%) compared to patients weighing at or above 30 kg, treated with 8 mg/kg tocilizumab (8%).

Infusion Reactions

In PJIA patients, infusion-related reactions are defined as all events occurring during or within 24 hours of an infusion. In the ACTEMRA-IV all exposure population, 11 patients (6%) experienced an event during the infusion, and 38 patients (20.2%) experienced an event within 24 hours of an infusion. The most common events occurring during infusion were headache, nausea and hypotension, and occurring within 24 hours of infusion were dizziness and hypotension. In general, the adverse drug reactions observed during or within 24 hours of an infusion were similar in nature to those seen in RA and SJIA patients *[see Adverse Reactions (6.1 and 6.8)]*.

No clinically significant hypersensitivity reactions associated with tocilizumab and requiring treatment discontinuation were reported.

Immunogenicity

One patient, in the 10 mg/kg less than 30 kg group, developed positive anti-tocilizumab antibodies without developing a hypersensitivity reaction and subsequently withdrew from the study.

Laboratory Abnormalities

Neutropenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 3.7% of patients.

There was no clear relationship between decreases in neutrophils below 1×10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, 1% of patients had a decrease in platelet count at or less than 50,000 per mm^3 without associated bleeding events.

Elevated Liver Enzymes

During routine laboratory monitoring in the ACTEMRA-IV all exposure population, elevation in ALT or AST at or greater than 3 x ULN occurred in 4% and less than 1% of patients, respectively.

Lipids

During routine laboratory monitoring in the tocilizumab all exposure population, elevation in total cholesterol greater than 1.5-2 x ULN occurred in one patient (0.5%) and elevation in LDL greater than 1.5-2 x ULN occurred in one patient (0.5%).

6.7 Clinical Trials Experience in Polyarticular Juvenile Idiopathic Arthritis Patients Treated With Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety of ACTEMRA-SC was studied in 52 pediatric patients 1 to 17 years of age with PJIA who had an inadequate clinical response or were intolerant to methotrexate. The total patient exposure in the PJIA ACTEMRA-SC population (defined as patients who received at least one dose of ACTEMRA-SC and accounting for treatment discontinuation) was 49.5 patient years. In general, the safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of injection site reactions (ISRs), and neutropenia.

Injection Site Reactions

During the 1-year study, a frequency of 28.8% (15/52) ISRs was observed in ACTEMRA-SC treated PJIA patients. These ISRs occurred in a greater proportion of patients at or above 30 kg (44.0%) compared with patients below 30 kg (14.8%). All ISRs were mild in severity and none of the ISRs required patient withdrawal from treatment or dose interruption. A higher frequency of ISRs was observed in ACTEMRA-SC treated PJIA patients compared to what was seen in adult RA or GCA patients *[see Adverse Reactions (6.2 and 6.3)]*.

Immunogenicity

Three patients, 1 patient below 30 kg and 2 patients at or above 30 kg, developed positive anti-tocilizumab antibodies with neutralizing potential without developing a serious or clinically significant hypersensitivity reaction. One patient subsequently withdrew from the study.

Neutropenia

During routine laboratory monitoring in the ACTEMRA-SC all exposure population, a decrease in neutrophil counts below 1×10^9 per L occurred in 15.4% of patients, and was more frequently observed in the patients less than 30 kg (25.9%) compared to patients at or above 30 kg (4.0%). There was no clear relationship between decreases in neutrophils below 1×10^9 per L and the occurrence of serious infections.

6.8 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The data described below reflect exposure to ACTEMRA-IV in one randomized, double-blind, placebo-controlled trial of 112 pediatric patients with SJIA 2 to 17 years of age who had an inadequate clinical response to nonsteroidal anti-inflammatory drugs (NSAIDs) or corticosteroids due to toxicity or lack of efficacy. At baseline, approximately half of the patients were taking 0.3 mg/kg/day corticosteroids or more, and almost 70% were taking methotrexate. The trial included a 12 week controlled phase followed by an open-label extension. In the 12 week double-blind, controlled portion of the clinical study 75 patients received treatment with ACTEMRA-IV (8 or 12 mg per kg based upon body weight). After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA-IV in the open-label extension phase.

The most common adverse events (at least 5%) seen in ACTEMRA-IV treated patients in the 12 week controlled portion of the study were: upper respiratory tract infection, headache, nasopharyngitis and diarrhea.

Infections

In the 12 week controlled phase, the rate of all infections in the ACTEMRA-IV group was 345 per 100 patient-years and 287 per 100 patient-years in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of infections was 304 per 100 patient-years.

In the 12 week controlled phase, the rate of serious infections in the ACTEMRA-IV group was 11.5 per 100 patient years. In the open label extension over an average duration of 73 weeks of treatment, the overall rate of serious infections was 11.4 per 100 patient years. The most commonly reported serious infections included pneumonia, gastroenteritis, varicella, and otitis media.

Macrophage Activation Syndrome

In the 12 week controlled study, no patient in any treatment group experienced macrophage activation syndrome (MAS) while on assigned treatment; 3 per 112 (3%) developed MAS during open-label treatment with ACTEMRA-IV. One patient in the placebo group escaped to ACTEMRA-IV 12 mg per kg at Week 2 due to severe disease activity, and ultimately developed MAS at Day 70. Two additional patients developed MAS during the long-term extension. All 3 patients had ACTEMRA-IV dose interrupted (2 patients) or discontinued (1 patient) for the MAS event, received treatment, and the MAS resolved without sequelae. Based on a limited number of cases, the incidence of MAS does not appear to be elevated in the ACTEMRA-IV SJIA clinical development experience; however no definitive conclusions can be made.

Infusion Reactions

Patients were not premedicated, however most patients were on concomitant corticosteroids as part of their background treatment for SJIA. Infusion related reactions were defined as all events occurring during or within 24 hours after an infusion. In the 12 week controlled phase, 4% of ACTEMRA-IV and 0% of placebo treated patients experienced events occurring during infusion. One event (angioedema) was considered serious and life-threatening, and the patient was discontinued from study treatment.

Within 24 hours after infusion, 16% of patients in the ACTEMRA-IV treatment group and 5% of patients in the placebo group experienced an event. In the ACTEMRA-IV group the events included rash, urticaria, diarrhea, epigastric discomfort, arthralgia and headache. One of these events, urticaria, was considered serious.

Anaphylaxis

Anaphylaxis was reported in 1 out of 112 patients (less than 1%) treated with ACTEMRA-IV during the controlled and open label extension study *[see Warnings and Precautions (5.6)]*.

Immunogenicity

All 112 patients were tested for anti-tocilizumab antibodies at baseline. Two patients developed positive anti-tocilizumab antibodies: one of these patients experienced serious adverse events of urticaria and angioedema consistent with an anaphylactic reaction which led to withdrawal; the other patient developed macrophage activation syndrome while on escape therapy and was discontinued from the study.

Laboratory Abnormalities

Neutropenia

During routine monitoring in the 12 week controlled phase, a decrease in neutrophil below 1×10^9 per L occurred in 7% of patients in the ACTEMRA-IV group, and in no patients in the placebo group. In the open label extension over an average duration of 73 weeks of treatment, a decreased neutrophil count occurred in 17% of the ACTEMRA-IV group. There was no clear relationship between decrease in neutrophils below 1 x 10^9 per L and the occurrence of serious infections.

Thrombocytopenia

During routine monitoring in the 12 week controlled phase, 1% of patients in the ACTEMRA-IV group and 3% in the placebo group had a decrease in platelet count to no more than 100,000 per mm^3.

In the open label extension over an average duration of 73 weeks of treatment, decreased platelet count occurred in 4% of patients in the ACTEMRA-IV group, with no associated bleeding.

Elevated Liver Enzymes

During routine laboratory monitoring in the 12 week controlled phase, elevation in ALT or AST at or above 3x ULN occurred in 5% and 3% of patients, respectively in the ACTEMRA-IV group and in 0% of placebo patients.

In the open label extension over an average duration of 73 weeks of treatment, the elevation in ALT or AST at or above 3x ULN occurred in 13% and 5% of ACTEMRA-IV treated patients, respectively.

Lipids

During routine laboratory monitoring in the 12 week controlled phase, elevation in total cholesterol greater than 1.5x ULN – 2x ULN occurred in 1.5% of the ACTEMRA-IV group and in 0% of placebo patients. Elevation in LDL greater than 1.5x ULN – 2x ULN occurred in 1.9% of patients in the ACTEMRA-IV group and 0% of the placebo group.

In the open label extension study over an average duration of 73 weeks of treatment, the pattern and incidence of elevations in lipid parameters remained consistent with the 12 week controlled study data.

6.9 Clinical Trials Experience in Systemic Juvenile Idiopathic Arthritis Patients Treated with Subcutaneous ACTEMRA (ACTEMRA-SC)

The safety profile of ACTEMRA-SC was studied in 51 pediatric patients 1 to 17 years of age with SJIA who had an inadequate clinical response to NSAIDs and corticosteroids. In general, the safety observed for ACTEMRA administered subcutaneously was consistent with the known safety profile of intravenous ACTEMRA, with the exception of ISRs where a higher frequency was observed in ACTEMRA-SC treated SJIA patients compared to PJIA patients and adult RA or GCA patients *[see Adverse Reactions (6.2, 6.3 and 6.7)]*.

Injection Site Reactions (ISRs)

A total of 41.2% (21/51) SJIA patients experienced ISRs to ACTEMRA-SC. The most common ISRs were erythema, pruritus, pain, and swelling at the injection site. The majority of ISRs reported were Grade 1 events and all ISRs reported were non-serious and none required patient withdrawal from treatment or dose interruption.

Immunogenicity

Forty-six of the 51 (90.2%) patients who were tested for anti-tocilizumab antibodies at baseline had at least one post-baseline screening assay result. No patient developed positive anti-tocilizumab antibodies post-baseline.

6.10 Clinical Trials Experience in Patients with Cytokine Release Syndrome Treated with Intravenous ACTEMRA (ACTEMRA-IV)

In a retrospective analysis of pooled outcome data from multiple clinical trials 45 patients were treated with tocilizumab 8 mg/kg (12 mg/kg for patients less than 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CAR T-cell-induced CRS. A median of 1 dose of tocilizumab (range, 1-4 doses) was administered. No adverse reactions related to tocilizumab were reported *[see Clinical Studies (14.10)]*.

6.11 Clinical Trials Experience in COVID-19 Patients Treated with Intravenous ACTEMRA (ACTEMRA-IV)

The safety of ACTEMRA in hospitalized COVID-19 patients was evaluated in a pooled safety population that includes patients enrolled in EMPACTA, COVACTA, AND REMDACTA. The analysis of adverse reactions included a total of 974 patients exposed to ACTEMRA. Patients received a single, 60-minute infusion of intravenous ACTEMRA 8 mg/kg (maximum dose of 800 mg). If clinical signs or symptoms worsened or did not improve, one additional dose of ACTEMRA 8 mg/kg could be administered between 8- 24 hours after the initial dose.

Adverse reactions summarized in **Table 3** occurred in at least 3% of ACTEMRA-treated patients and more commonly than in patients on placebo in the pooled safety population.

Table 3 Adverse Reactions[1] Identified From the Pooled COVID-19 Safety Population

Adverse Reaction	**ACTEMRA 8 mg per kg N = 974 (%)**	**Placebo N = 483 (%)**
Hepatic Transaminases increased	10%	8%
Constipation	9 %	8%
Urinary tract infection	5%	4%
Hypertension	4%	1%
Hypokalaemia	4%	3%
Anxiety	4%	2%
Diarrhea	4%	2%
Insomnia	4%	3%
Nausea	3%	2%

[1] Patients are counted once for each category regardless of the number of reactions

In the pooled safety population, the rates of infection/serious infection events were 30%/19% in patients receiving ACTEMRA versus 32%/23% receiving placebo.

Laboratory Abnormalities

In the pooled safety population of EMPACTA, COVACTA, and REMDACTA, neutrophil counts <1000 cells/mcl occurred in 3.4% of patients who received ACTEMRA and 0.5% of patients who received placebo. Platelet counts <50,000 cells/mcl occurred in 3.2% of patients who received ACTEMRA and 1.5% of patients who received placebo. ALT or AST at or above 5x ULN occurred in 11.7% of patients who received ACTEMRA and 9.9% of patients who received placebo.

6.12 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ACTEMRA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Hypersensitivity Reactions: Fatal anaphylaxis, Stevens-Johnson Syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) [*see Warnings and Precautions (5.6)*]
- Pancreatitis
- Drug-induced liver injury, Hepatitis, Hepatic failure, Jaundice *[see Warnings and* Precautions *(5.3)]*

7 DRUG INTERACTIONS

7.1 Concomitant Drugs for Treatment of Adult Indications

In RA patients, population pharmacokinetic analyses did not detect any effect of methotrexate (MTX), non-steroidal anti-inflammatory drugs or corticosteroids on tocilizumab clearance. Concomitant administration of a single intravenous dose of 10 mg/kg ACTEMRA with 10-25 mg MTX once weekly had no clinically significant effect on MTX exposure. ACTEMRA has not been studied in combination with biological DMARDs such as TNF antagonists *[see Dosage and Administration (2.2)]*.

In GCA patients, no effect of concomitant corticosteroid on tocilizumab exposure was observed.

7.2 Interactions with CYP450 Substrates

Cytochrome P450s in the liver are down-regulated by infection and inflammation stimuli including cytokines such as IL-6. Inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. In vitro studies showed that tocilizumab has the potential to affect expression of multiple CYP enzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4. Its effect on CYP2C8 or transporters is unknown. In vivo studies with omeprazole, metabolized by CYP2C19 and CYP3A4, and simvastatin, metabolized by CYP3A4, showed up to a 28% and 57% decrease in exposure one week following a single dose of ACTEMRA, respectively. The effect of tocilizumab on CYP enzymes may be clinically relevant for CYP450 substrates with narrow therapeutic index, where the dose is individually adjusted. Upon initiation or discontinuation of ACTEMRA, in patients being treated with these types of medicinal products, perform therapeutic monitoring of effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) and the individual dose of the medicinal product adjusted as needed. Exercise caution when coadministering ACTEMRA with CYP3A4 substrate drugs where decrease in effectiveness is

undesirable, e.g., oral contraceptives, lovastatin, atorvastatin, etc. The effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy *[see Clinical Pharmacology (12.3)]*.

7.3 Live Vaccines

Avoid use of live vaccines concurrently with ACTEMRA *[see Warnings and Precautions (5.9)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The available data with ACTEMRA from a pregnancy exposure registry, retrospective cohort study, pharmacovigilance, and published literature are insufficient to draw conclusions about a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. These studies had methodological limitations, including small sample size of tocilizumab exposed groups, missing exposure and outcomes information, and lack of adjustment for confounders. Monoclonal antibodies, such as tocilizumab, are actively transported across the placenta during the third trimester of pregnancy and may affect immune response in the *in utero* exposed infant *[see Clinical Considerations]*. In animal reproduction studies, intravenous administration of tocilizumab to Cynomolgus monkeys during organogenesis caused abortion/embryo-fetal death at doses 1.25 times and higher than the maximum recommended human dose by the intravenous route of 8 mg per kg every 2 to 4 weeks. The literature in animals suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition *[see Data]*. Based on the animal data, there may be a potential risk to the fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal adverse reactions

Monoclonal antibodies are increasingly transported across the placenta as pregnancy progresses, with the largest amount transferred during the third trimester. Risks and benefits should be considered prior to administering live or live-attenuated vaccines to infants exposed to ACTEMRA *in utero [see Warnings and Precautions 5.9)]*.

Disease-associated Maternal Risk

Published data suggest that the risk of adverse pregnancy outcomes in women with rheumatoid arthritis is associated with increased disease activity. Adverse pregnancy outcomes include preterm delivery (before 37 weeks of gestation), low birth weight (less than 2500 g) infants, and small for gestational age at birth.

Data

Animal Data

An embryo-fetal developmental toxicity study was performed in which pregnant Cynomolgus monkeys were treated intravenously with tocilizumab at daily doses of 2, 10, or 50 mg/ kg during organogenesis from gestation day (GD) 20-50. Although there was no evidence for a teratogenic/dysmorphogenic effect at any dose, tocilizumab produced an increase in the incidence of abortion/embryo-fetal death at doses 1.25 times and higher the MRHD by the intravenous route at maternal intravenous doses of 10 and 50 mg/ kg. Testing of a murine analogue of tocilizumab in mice did not yield any evidence of harm to offspring during the pre- and postnatal development phase when dosed at 50 mg/kg intravenously with treatment every three days from implantation

(GD 6) until post-partum day 21 (weaning). There was no evidence for any functional impairment of the development and behavior, learning ability, immune competence and fertility of the offspring.

Parturition is associated with significant increases of IL-6 in the cervix and myometrium. The literature suggests that inhibition of IL-6 signaling may interfere with cervical ripening and dilatation and myometrial contractile activity leading to potential delays of parturition. For mice deficient in IL-6 ($Il6^{-/-}$ null mice), parturition was delayed relative to wild-type ($Il6^{+/+}$) mice. Administration of recombinant IL-6 to $Il6^{-/-}$ null mice restored the normal timing of delivery.

8.2 Lactation

Risk Summary

No information is available on the presence of tocilizumab in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Maternal immunoglobulin G (IgG) is present in human milk. If tocilizumab is transferred into human milk, the effects of local exposure in the gastrointestinal tract and potential limited systemic exposure in the infant to tocilizumab are unknown. The lack of clinical data during lactation precludes clear determination of the risk of ACTEMRA to an infant during lactation; therefore the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ACTEMRA and the potential adverse effects on the breastfed child from tocilizumab or from the underlying maternal condition.

8.4 Pediatric Use

ACTEMRA by intravenous use is indicated for the treatment of pediatric patients with:

- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older
- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Severe or life-threatening CAR T cell-induced cytokine release syndrome (CRS) in patients 2 years of age and older.

ACTEMRA by subcutaneous use is indicated for the treatment of pediatric patients with:

- Active polyarticular juvenile idiopathic arthritis in patients 2 years of age and older
- Active systemic juvenile idiopathic arthritis in patients 2 years of age and older

The safety and effectiveness of ACTEMRA in pediatric patients with conditions other than PJIA, SJIA or CRS have not been established. The safety and effectiveness in pediatric patients below the age of 2 have not been established in PJIA, SJIA, or CRS.

Systemic Juvenile Idiopathic Arthritis – Intravenous Use

A multicenter, open-label, single arm study to evaluate the PK, safety and exploratory PD and efficacy of ACTEMRA over 12-weeks in SJIA patients (N=11) under 2 years of age was conducted. Patients received intravenous ACTEMRA 12 mg/kg every two weeks. Concurrent use of stable background treatment with corticosteroids, MTX, and/or non-steroidal anti-inflammatory drugs was permitted. Patients who completed the 12-week period could continue to the optional extension period (a total of 52-weeks or until the age of 2 years, whichever was longer).

The primary PK endpoints (C_{max}, C_{trough} and AUC_{2weeks}) of ACTEMRA at steady-state in this study were within the ranges of these parameters observed in patients with SJIA aged 2 to 17 years.

The safety and immunogenicity of ACTEMRA for patients with SJIA under 2 years of age was assessed descriptively. SAEs, AEs leading to discontinuation, and infectious AEs were reported by 27.3%, 36.4%, and 81.8% of patients. Six patients (54.5%) experienced hypersensitivity reactions, defined as all adverse events

occurring during or within 24 hours after an infusion considered related to ACTEMRA. Three of these patients experienced serious hypersensitivity reactions and were withdrawn from the study. Three patients with hypersensitivity reactions (two with serious hypersensitivity reactions) developed treatment induced anti-tocilizumab antibodies after the event. There were no cases of MAS based on the protocol-specified criteria, but 2 cases of suspected MAS based on Ravelli criteria[1].

Cytokine Release Syndrome – Intravenous Use

In the retrospective analysis of pooled outcome data for patients treated with ACTEMRA for CAR T cell-induced CRS, 25 patients were children (2 years up to 12 years of age), and 17 patients were adolescents (12 years up to 18 years of age). There were no differences between the pediatric patients and the adults for safety or efficacy.

8.5 Geriatric Use

Of the 2644 patients who received ACTEMRA in Studies I to V *[see Clinical Studies (14)]*, a total of 435 rheumatoid arthritis patients were 65 years of age and older, including 50 patients 75 years and older. Of the 1069 patients who received ACTEMRA-SC in studies SC-I and SC-II there were 295 patients 65 years of age and older, including 41 patients 75 years and older. The frequency of serious infection among ACTEMRA treated subjects 65 years of age and older was higher than those under the age of 65. As there is a higher incidence of infections in the elderly population in general, caution should be used when treating the elderly.

Clinical studies that included ACTEMRA for CRS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

In the EMPACTA, COVACTA, and REMDACTA studies, of the 974 COVID-19 patients in the ACTEMRA arm, 375 (39%) were 65 years of age or older. No overall differences in safety or effectiveness of ACTEMRA were observed between patients 65 years of age and older and those under the age of 65 years of age in these studies *[see Adverse Reactions (6.1) and Clinical Studies (14.11)]*.

In the RECOVERY study, of the 2022 COVID-19 patients in the ACTEMRA arm, 930 (46%) were 65 years of age or older. No overall differences in effectiveness of ACTEMRA were observed between patients 65 years of age and older and those under the age 65 years of age in this study *[see Clinical Studies (14.11)]*.

8.6 Hepatic Impairment

The safety and efficacy of ACTEMRA have not been studied in patients with hepatic impairment, including patients with positive HBV and HCV serology *[see Warnings and Precautions (5.8)]*.

8.7 Renal Impairment

No dose adjustment is required in patients with mild or moderate renal impairment. ACTEMRA has not been studied in patients with severe renal impairment *[see Clinical Pharmacology (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

No studies on the potential for ACTEMRA to cause dependence have been performed. However, there is no evidence from the available data that ACTEMRA treatment results in dependence.

[1] Ravelli A, Minoia F, Davì S on behalf of the Paediatric Rheumatology International Trials Organisation, the Childhood Arthritis and Rheumatology Research Alliance, the Pediatric Rheumatology Collaborative Study Group, and the Histiocyte Society, *et al.* 2016 Classification Criteria for Macrophage Activation Syndrome Complicating Systemic Juvenile Idiopathic Arthritis. Annals of the Rheumatic Diseases 2016;75:481-489.

10 OVERDOSAGE

There are limited data available on overdoses with ACTEMRA. One case of accidental overdose was reported with intravenous ACTEMRA in which a patient with multiple myeloma received a dose of 40 mg per kg. No adverse drug reactions were observed. No serious adverse drug reactions were observed in healthy volunteers who received single doses of up to 28 mg per kg, although all 5 patients at the highest dose of 28 mg per kg developed dose-limiting neutropenia.

In case of an overdose, it is recommended that the patient be monitored for signs and symptoms of adverse reactions. Patients who develop adverse reactions should receive appropriate symptomatic treatment.

11 DESCRIPTION

Tocilizumab is a recombinant humanized anti-human interleukin 6 (IL-6) receptor monoclonal antibody of the immunoglobulin IgG1κ (gamma 1, kappa) subclass with a typical H_2L_2 polypeptide structure. Each light chain and heavy chain consists of 214 and 448 amino acids, respectively. The four polypeptide chains are linked intra- and inter-molecularly by disulfide bonds. ACTEMRA has a molecular weight of approximately 148 kDa. The antibody is produced in mammalian (Chinese hamster ovary) cells.

Intravenous Infusion

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to pale yellow, preservative-free solution for further dilution prior to intravenous infusion with a pH of approximately 6.5. Each single-dose vial, formulated with a disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, is available at a concentration of 20 mg/mL containing 80 mg/4 mL, 200 mg/10 mL, or 400 mg/20 mL of ACTEMRA. Each mL of solution contains polysorbate 80 (0.5 mg), sucrose (50 mg), and Water for Injection, USP.

Subcutaneous Injection

ACTEMRA (tocilizumab) injection is a sterile, clear, colorless to slightly yellowish, preservative-free, histidine buffered solution for subcutaneous use with a pH of approximately 6.0.

It is supplied in a ready-to-use, single-dose 0.9 mL prefilled syringe (PFS) with a needle safety device or a ready-to-use, single-dose 0.9 mL autoinjector that delivers 162 mg tocilizumab, L-arginine hydrochloride (19 mg), L-histidine (1.52 mg), L-histidine hydrochloride monohydrate (1.74 mg), L-methionine (4.03 mg), polysorbate 80 (0.18 mg), and Water for Injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tocilizumab binds to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, lymphocytes, monocytes and fibroblasts. IL-6 has been shown to be involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, initiation of hepatic acute phase protein synthesis, and stimulation of hematopoietic precursor cell proliferation and differentiation. IL-6 is also produced by synovial and endothelial cells leading to local production of IL-6 in joints affected by inflammatory processes such as rheumatoid arthritis.

12.2 Pharmacodynamics

In clinical studies in RA patients with the 4 mg per kg and 8 mg per kg intravenous doses or the 162 mg weekly and every other weekly subcutaneous doses of ACTEMRA, decreases in levels of C-reactive protein (CRP) to within normal ranges were seen as early as week 2. Changes in pharmacodynamic parameters were observed (i.e., decreases in rheumatoid factor, erythrocyte sedimentation rate (ESR), serum amyloid A, fibrinogen and increases in hemoglobin) with doses, however the greatest improvements were observed with 8 mg per kg ACTEMRA. Pharmacodynamic changes were also observed to occur after ACTEMRA administration in GCA,

SSc-ILD, PJIA, and SJIA patients (decreases in CRP, ESR, and increases in hemoglobin). The relationship between these pharmacodynamic findings and clinical efficacy is not known.

In healthy subjects administered ACTEMRA in doses from 2 to 28 mg per kg intravenously and 81 to 162 mg subcutaneously, absolute neutrophil counts decreased to the nadir 3 to 5 days following ACTEMRA administration. Thereafter, neutrophils recovered towards baseline in a dose dependent manner. Rheumatoid arthritis and GCA patients demonstrated a similar pattern of absolute neutrophil counts following ACTEMRA administration *[see Warnings and Precautions (5.4)]*.

12.3 Pharmacokinetics

PK of tocilizumab is characterized by nonlinear elimination which is a combination of linear clearance and Michaelis-Menten elimination. The nonlinear part of tocilizumab elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of tocilizumab do not change with time. Due to the dependence of total clearance on tocilizumab serum concentrations, the half-life of tocilizumab is also concentration-dependent and varies depending on the serum concentration level. Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

Rheumatoid Arthritis - Intravenous and Subcutaneous Administration

The pharmacokinetics in healthy subjects and RA patients suggest that PK is similar between the two populations.

The population PK model was developed from an analysis dataset composed of an IV dataset of 1793 patients from Study I, Study III, Study IV, and Study V, and from an IV and SC dataset of 1759 patients from Studies SC-I and SC-II. C_{mean} is included in place of AUC_{tau}, since for dosing regimens with different inter-dose intervals, the mean concentration over the dosing period characterizes the comparative exposure better than $AUC_{tau.}$

At high serum concentrations, when total clearance of tocilizumab is dominated by linear clearance, a terminal half-life of approximately 21.5 days was derived from the population parameter estimates.

For doses of 4 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab at steady state were 86.1 (44.8–202) mcg/mL, 0.1 (0.0–14.6) mcg/mL, and 18.0 (8.9–50.7) mcg/mL, respectively. For doses of 8 mg/kg tocilizumab given every 4 weeks intravenously, the estimated median (range) C_{max}, $C_{trough,}$ and C_{mean} of tocilizumab were 176 (75.4–557) mcg/mL, 13.4 (0.1–154) mcg/mL, and 54.0 (17–260) mcg/mL, respectively. C_{max} increased dose-proportionally between doses of 4 and 8 mg/kg IV every 4 weeks, while a greater than dose-proportional increase was observed in C_{mean} and C_{trough}. At steady-state, C_{mean} and C_{trough} were 3.0 and 134 fold higher at 8 mg/kg as compared to 4 mg/kg, respectively.

The accumulation ratios for AUC and C_{max} after multiple doses of 4 and 8 mg/kg IV Q4W are low, while the accumulation ratios for C_{trough} are higher (2.62 and 2.47, respectively). For C_{max}, greater than 90% of the steady-state value was reached after the 1st IV infusion. For AUC_{tau} and C_{mean}, 90% of the steady-state value was reached after the 1st and 3rd infusion for 4 mg/kg and 8 mg/kg IV, while for C_{trough}, approximately 90% of the steady-state value was reached after the 4th IV infusion after both doses.

For doses of 162 mg given every other week subcutaneously, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 12.1 (0.4–49.3) mcg/mL, 4.1 (0.0–34.2) mcg/mL, and 9.2 (0.2–43.6) mcg/mL, respectively.

For doses of 162 mg given every week subcutaneously, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 49.8 (3–150) mcg/mL, 42.9 (1.3–144) mcg/mL, and 47.3 (2.4–147) mcg/mL,

respectively. Exposures after the 162 mg SC QW regimen were greater by 5.1 (C_{mean}) to 10.5 fold (C_{trough}) compared to the 162 mg SC Q2W regimen.

Accumulation ratios after multiple doses of either SC regimen were higher than after IV regimen with the highest ratios for C_{trough} (6.02 and 6.30, for 162 mg SC Q2W and 162 mg SC QW, respectively). The higher accumulation for C_{trough} was expected based on the nonlinear clearance contribution at lower concentrations. For C_{max}, greater than 90% of the steady-state value was reached after the 5th SC and the 12th SC injection with the Q2W and QW regimens, respectively. For AUC_{tau} and C_{mean}, 90% of the steady-state value was reached after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens, respectively. For C_{trough}, approximately 90% of the steady-state value was reached after the 6th and 12th injections for the 162 mg SC Q2W and QW regimens, respectively.

Population PK analysis identified body weight as a significant covariate impacting the pharmacokinetics of tocilizumab. When given IV on a mg/kg basis, individuals with body weight ≥ 100 kg are predicted to have mean steady-state exposures higher than mean values for the patient population. Therefore, tocilizumab doses exceeding 800 mg per infusion are not recommended in patients with RA *[see Dosage and Administration (2.2)]*. Due to the flat dosing employed for SC administration of tocilizumab, no modifications are necessary by this dosing route.

Giant Cell Arteritis – Subcutaneous and Intravenous Administration

The pharmacokinetics of tocilizumab SC in GCA patients was determined using a population pharmacokinetic analysis on a dataset composed of 149 GCA patients treated with 162 mg subcutaneously every week or with 162 mg subcutaneously every other week.

For the 162 mg every week dose, the estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab SC were 72.1 (12.2–151) mcg/mL, 67.2 (10.7–145) mcg/mL, and 70.6 (11.7–149) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 10.9, 9.6, and 8.9, respectively. Steady state was reached after 17 weeks. For the 162 mg every other week dose, the estimated median (range) steady-state C_{max}, C_{trough}, and C_{mean} of tocilizumab were 17.2 (1.1–56.2) mcg/mL, 7.7 (0.1–37.3) mcg/mL, and 13.7 (0.5–49) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 2.8, 5.6, and 2.3 respectively. Steady-state was reached after 14 weeks.

The pharmacokinetics of tocilizumab IV in GCA patients was characterized by a non-compartmental pharmacokinetic analysis which included 22 patients treated with 6 mg/kg intravenously every 4 weeks for 20 weeks. The median (range) C_{max}, C_{trough} and C_{mean} of tocilizumab at steady state were 178 (115-320) mcg/mL, 22.7 (3.38-54.5) mcg/mL and 57.5 (32.9-110) mcg/mL, respectively. Steady state trough concentrations were within the range observed in GCA patients treated with 162 mg TCZ SC administered every week or every other week.

Based on pharmacokinetic exposure and extrapolation between RA and GCA patients, when given IV on a mg/kg basis, tocilizumab doses exceeding 600 mg per infusion are not recommended in patients with GCA *[see Dosage and Administration (2.3)]*.

Systemic Sclerosis-Associated Interstitial Lung Disease – Subcutaneous Administration

The pharmacokinetics of tocilizumab in SSc-ILD patients was determined using a population pharmacokinetic analysis on a dataset composed of 66 SSc-ILD patients treated with 162 mg tocilizumab SC every week.

The estimated median (range) steady-state C_{max}, C_{trough} and C_{mean} of tocilizumab were 52.5 (14.8-121) mcg/mL, 47.2 (10.8-114) mcg/mL, and 50.4 (13.4-119) mcg/mL, respectively. The accumulation ratios for C_{mean} or AUC_{tau}, C_{trough}, and C_{max} were 7.11, 6.56, and 5.89, respectively. Steady-state was reached after 13 weeks.

Polyarticular Juvenile Idiopathic Arthritis – Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in PJIA patients was characterized by a population pharmacokinetic analysis which included 188 patients who were treated with TCZ IV or 52 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab at steady state were 181 (114–331) mcg/mL, 3.28 (0.02–35.4) mcg/mL, and 38.6 (22.2–83.8) mcg/mL, respectively. For doses of 10 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 4 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 167 (125–220) mcg/mL, 0.35 (0–11.8) mcg/mL, and 30.8 (16.0–48.0) mcg/mL, respectively.

The accumulation ratios were 1.05 and 1.16 for AUC_{4weeks}, and 1.43 and 2.22 for C_{trough} for 10 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. No accumulation for C_{max} was observed. Following 10 mg/kg and 8 mg/kg TCZ IV every 4 weeks doses in PJIA patients (aged 2 to 17 years), steady state concentrations (trough and average) were within the range of exposures in adult RA patients following 4 mg/kg and 8 mg/kg every 4 weeks, and steady state peak concentrations in PJIA patients were comparable to those following 8 mg/kg every 4 weeks in adult RA patients.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 29.7 (7.56–50.3) mcg/mL, 12.7 (0.19–23.8) mcg/mL, and 23.0 (3.86–36.9) mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 3 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 62.4 (39.4–121) mcg/mL, 13.4 (0.21–52.3) mcg/mL, and 35.7 (17.4–91.8) mcg/mL, respectively.

The accumulation ratios were 1.46 and 2.04 for AUC_{4weeks}, 2.08 and 3.58 for C_{trough}, and 1.32 and 1.72 for C_{max}, for 162 mg given every 3 weeks (BW less than 30 kg) and 162 mg given every 2 weeks (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state C_{trough} was comparable for patients in the two body weight groups, while steady-state C_{max} and C_{mean} were higher for patients in the less than 30 kg group compared to the group at or above 30 kg. All patients treated with TCZ SC had steady-state C_{trough} at or higher than that achieved with TCZ IV across the spectrum of body weights. The average and trough concentrations in patients after subcutaneous dosing were within the range of those achieved in adult patients with RA following the subcutaneous administration of the recommended regimens.

Systemic Juvenile Idiopathic Arthritis – Intravenous and Subcutaneous Administration

The pharmacokinetics of tocilizumab (TCZ) in SJIA patients was characterized by a population pharmacokinetic analysis which included 89 patients who were treated with TCZ IV or 51 patients treated with TCZ SC.

For doses of 8 mg/kg tocilizumab (patients with a body weight at or above 30 kg) given every 2 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 253 (120–404) mcg/mL, 70.7 (5.26–127) mcg/mL, and 117 (37.6–199) mcg/mL, respectively. For doses of 12 mg/kg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks intravenously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 274 (149–444) mcg/mL, 65.9 (19.0–135) mcg/mL, and 124 (60–194) mcg/mL, respectively.

The accumulation ratios were 1.95 and 2.01 for AUC_{4weeks}, and 3.41 and 3.20 for C_{trough} for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Accumulation data for C_{max} were 1.37 and 1.42 for 12 mg/kg (BW less than 30 kg) and 8 mg/kg (BW at or above 30 kg) intravenous doses, respectively. Following every other week dosing with tocilizumab IV, steady state was reached by 8 weeks for

both body weight groups. Mean estimated tocilizumab exposure parameters were similar between the two dose groups defined by body weight.

For doses of 162 mg tocilizumab (patients with a body weight at or above 30 kg) given every week subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 89.8 (26.4–190) mcg/mL, 72.4 (19.5–158) mcg/mL, and 82.4 (23.9–169) mcg/mL, respectively. For doses of 162 mg tocilizumab (patients with a body weight less than 30 kg) given every 2 weeks subcutaneously, the estimated median (range) C_{max}, C_{trough}, and C_{mean} of tocilizumab were 127 (51.7–266) mcg/mL, 64.2 (16.6–136) mcg/mL, and 92.7 (38.5–199) mcg/mL, respectively.

The accumulation ratios were 2.27 and 4.28 for AUC_{4weeks}, 3.21 and 4.39 for C_{trough}, and 1.88 and 3.66 for C_{max}, for 162 mg given every 2 weeks (BW less than 30 kg) and 162 mg given every week (BW at or above 30 kg) subcutaneous doses, respectively. Following subcutaneous dosing, steady state was reached by 12 weeks for both body weight groups. All patients treated with tocilizumab SC had steady-state C_{max} lower than that achieved with tocilizumab IV across the spectrum of body weights. Trough and mean concentrations in patients after SC dosing were similar to those achieved with tocilizumab IV across body weights.

COVID-19 -Intravenous Administration

The pharmacokinetics of tocilizumab in COVID-19 patients was characterized by a population pharmacokinetic analysis of a dataset composed of 380 adult patients treated with tocilizumab 8mg/kg intravenously (IV) in the COVACTA study *[see Clinical Studies (14.11)]* and another clinical study.

For one dose of 8 mg/kg tocilizumab IV, the estimated median (range) C_{max} and C_{day28} of tocilizumab were 151 (77.5-319) mcg/mL and 0.229 (0.00119-19.4) mcg/mL, respectively. For two doses of 8 mg/kg tocilizumab IV separated by at least 8 hours, the estimated median (range) C_{max} and C_{day28} of tocilizumab was 290 (152-604) mcg/mL and 7.04 (0.00474-54.8) mcg/mL, respectively. The weight-tiered dosing used in RECOVERY study, 800 mg for patients >90 kg, 600 mg for patients >65 and ≤90 kg, 400 mg for patients >40 and ≤65 kg, and 8mg/kg for patients ≤40 kg, is comparable to 8 mg/kg dosing and is expected to have similar exposure.

Absorption

Following subcutaneous dosing, the absorption half-life was around 4 days in RA and GCA patients and 3 days in SSc-ILD patients. The bioavailability for the subcutaneous formulation was 80%.

Following subcutaneous dosing in PJIA patients, the absorption half-life was around 2 days, and the bioavailability for the subcutaneous formulation in PJIA patients was 96%.

Following subcutaneous dosing in SJIA patients, the absorption half-life was around 2 days, and the bioavailability for the SC formulation in SJIA patients was 95%.

In RA patients the median values of T_{max} were 2.8 days after the tocilizumab every week dose and 4.7 days after the tocilizumab every other week dose.

In GCA patients, the median values of T_{max} were 3 days after the tocilizumab every week dose and 4.5 days after the tocilizumab every other week dose.

In SSc-ILD patients, the median value of T_{max} was 2.8 days after the tocilizumab every week dose.

Distribution

Following intravenous dosing, tocilizumab undergoes biphasic elimination from the circulation. In rheumatoid arthritis patients the central volume of distribution was 3.5 L and the peripheral volume of distribution was 2.9 L, resulting in a volume of distribution at steady state of 6.4 L.

In GCA patients, the central volume of distribution was 4.09 L, the peripheral volume of distribution was 3.37 L resulting in a volume of distribution at steady state of 7.46 L.

In SSc-ILD patients, the central volume of distribution was 4.16 L, the peripheral volume of distribution was 2.58 L resulting in a volume of distribution at steady state of 6.74 L.

In pediatric patients with PJIA, the central volume of distribution was 1.98 L, the peripheral volume of distribution was 2.1 L, resulting in a volume of distribution at steady state of 4.08 L.

In pediatric patients with SJIA, the central volume of distribution was 1.87 L, the peripheral volume of distribution was 2.14 L resulting in a volume of distribution at steady state of 4.01 L.

In COVID-19 patients treated with one or two infusions of tocilizumab 8 mg/kg intravenously separated by 8 hours, the estimated central volume of distribution was 4.52 L, and the estimated peripheral volume of distribution was 4.23 L, resulting in a volume of distribution of 8.75 L.

Elimination

ACTEMRA is eliminated by a combination of linear clearance and nonlinear elimination. The concentration-dependent nonlinear elimination plays a major role at low tocilizumab concentrations. Once the nonlinear pathway is saturated, at higher tocilizumab concentrations, clearance is mainly determined by the linear clearance. The saturation of the nonlinear elimination leads to an increase in exposure that is more than dose-proportional. The pharmacokinetic parameters of ACTEMRA do not change with time.

Population pharmacokinetic analyses in any patient population tested so far indicate no relationship between apparent clearance and the presence of anti-drug antibodies.

The linear clearance in the population pharmacokinetic analysis was estimated to be 12.5 mL per h in RA patients, 6.7 mL per h in GCA patients, 8.8 mL per h in SSc-ILD patients, 5.8 mL per h in pediatric patients with PJIA, and 5.7 mL per h in pediatric patients with SJIA. In COVID-19 patients, serum concentrations were below the limit of quantification after 35 days on average following one infusion of tocilizumab 8 mg/kg intravenously. The average linear clearance in the population pharmacokinetic analysis was estimated to be 17.6 mL per hour in patients with baseline ordinal scale category 3 (OS 3, patients requiring supplemental oxygen), 22.5 mL per hour in patients with baseline OS 4 (patients requiring high-flow oxygen or non-invasive ventilation), 29 mL per hour in patients with baseline OS 5 (patients requiring mechanical ventilation), and 35.4 mL per hour in patients with baseline OS 6 (patients requiring extracorporeal membrane oxygenation (ECMO) or mechanical ventilation and additional organ support).

Due to the dependence of total clearance on ACTEMRA serum concentrations, the half-life of ACTEMRA is also concentration-dependent and varies depending on the serum concentration level.

For intravenous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 11 days for 4 mg per kg and up to 13 days for 8 mg per kg every 4 weeks in patients with RA at steady-state. For subcutaneous administration in RA patients, the concentration-dependent apparent $t_{1/2}$ is up to 13 days for 162 mg every week and 5 days for 162 mg every other week in patients with RA at steady-state.

In GCA patients at steady state, the effective $t_{1/2}$ of tocilizumab varied between 18.3 and 18.9 days for 162 mg subcutaneously every week dosing regimen and between 4.2 and 7.9 days for 162 mg subcutaneously every other week dosing regimen. For intravenous administration in GCA patients, the TCZ concentration-dependent apparent $t_{1/2}$ was 13.2 days following 6 mg/kg every 4 weeks.

In SSc-ILD patients at steady state, the effective $t_{1/2}$ of tocilizumab varied between 12.1 and 13.0 days for the 162 mg subcutaneous every week dosing regimen.

The $t_{1/2}$ of tocilizumab in children with PJIA is up to 17 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg or 10 mg/kg for body weight below 30 kg) during a dosing interval at steady state. For subcutaneous administration, the $t_{1/2}$ of tocilizumab in PJIA patients is up to 10 days for the two body weight categories (every other week regimen for body weight at or above 30 kg or every 3 week regimen for body weight less than 30 kg) during a dosing interval at steady state.

The $t_{1/2}$ of tocilizumab intravenous in pediatric patients with SJIA is up to 16 days for the two body weight categories (8 mg/kg for body weight at or above 30 kg and 12 mg/kg for body weight below 30 kg every other week) during a dosing interval at steady-state. Following subcutaneous administration, the effective $t_{1/2}$ of tocilizumab subcutaneous in SJIA patients is up to 14 days for both the body weight categories (162 mg every week for body weight at or above 30 kg and 162 mg every two weeks for body weight below 30 kg) during a dosing interval at steady state.

Specific Populations

Population pharmacokinetic analyses in adult rheumatoid arthritis patients and GCA patients showed that age, gender and race did not affect the pharmacokinetics of tocilizumab. Linear clearance was found to increase with body size. In RA patients, the body weight-based dose (8 mg per kg) resulted in approximately 86% higher exposure in patients who are greater than 100 kg in comparison to patients who are less than 60 kg. There was an inverse relationship between tocilizumab exposure and body weight for flat dose subcutaneous regimens.

In GCA patients treated with ACTEMRA-SC, higher exposure was observed in patients with lower body weight. For the 162 mg every week subcutaneous dosing regimen, the steady-state C_{mean} was 51% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. For the 162 mg every other week subcutaneous regimen, the steady-state C_{mean} was 129% higher in patients with body weight less than 60 kg compared to patients weighing between 60 to 100 kg. There is limited data for patients above 100 kg (n=7).

In COVID-19 patients, exposure following body-weight-based intravenous dosing (8 mg per kg tocilizumab up to 100 kg body weight with a maximum dose of 800 mg) was dependent on body weight and disease severity assessed by an ordinal scale (OS). Within an OS category, compared to patients with a mean body weight of 80 kg, exposure was 20% lower in patients weighing less than 60 kg. Exposure in patients weighing more than 100 kg was in the same range as exposure in patients with a mean body weight of 80 kg. For an 80 kg patient, exposure decreases as OS category increases; for each category increase, exposure decreases by 13%.

Patients with Hepatic Impairment

No formal study of the effect of hepatic impairment on the pharmacokinetics of tocilizumab was conducted.

Patients with Renal Impairment

No formal study of the effect of renal impairment on the pharmacokinetics of tocilizumab was conducted.

Most of the RA, GCA, and SSc-ILD patients in the population pharmacokinetic analysis had normal renal function or mild renal impairment. Mild renal impairment (estimated creatinine clearance less than 80 mL per min and at or above 50 mL per min based on Cockcroft-Gault formula) did not impact the pharmacokinetics of tocilizumab.

Approximately one-third of the patients in the ACTEMRA-SC GCA clinical trial had moderate renal impairment at baseline (estimated creatinine clearance of 30-59 mL/min). No impact on tocilizumab exposure was noted in these patients.

No dose adjustment is required in patients with mild or moderate renal impairment.

Drug Interaction Studies

In vitro data suggested that IL-6 reduced mRNA expression for several CYP450 isoenzymes including CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP3A4, and this reduced expression was reversed by co-incubation with tocilizumab at clinically relevant concentrations. Accordingly, inhibition of IL-6 signaling in RA patients treated with tocilizumab may restore CYP450 activities to higher levels than those in the absence of tocilizumab leading to increased metabolism of drugs that are CYP450 substrates. Its effect on CYP2C8 or transporters (e.g., P-gp) is unknown. This is clinically relevant for CYP450 substrates with a narrow therapeutic index, where the dose is individually adjusted. Upon initiation of ACTEMRA, in patients being treated with these types of medicinal products, therapeutic monitoring of the effect (e.g., warfarin) or drug concentration (e.g., cyclosporine or theophylline) should be performed and the individual dose of the medicinal product adjusted as needed. Caution should be exercised when ACTEMRA is coadministered with drugs where decrease in effectiveness is undesirable, e.g., oral contraceptives (CYP3A4 substrates) *[see Drug Interactions (7.2)]*.

Simvastatin

Simvastatin is a CYP3A4 and OATP1B1 substrate. In 12 RA patients not treated with ACTEMRA, receiving 40 mg simvastatin, exposures of simvastatin and its metabolite, simvastatin acid, was 4- to 10-fold and 2-fold higher, respectively, than the exposures observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (10 mg per kg), exposure of simvastatin and simvastatin acid decreased by 57% and 39%, respectively, to exposures that were similar or slightly higher than those observed in healthy subjects. Exposures of simvastatin and simvastatin acid increased upon withdrawal of ACTEMRA in RA patients. Selection of a particular dose of simvastatin in RA patients should take into account the potentially lower exposures that may result after initiation of ACTEMRA (due to normalization of CYP3A4) or higher exposures after discontinuation of ACTEMRA.

Omeprazole

Omeprazole is a CYP2C19 and CYP3A4 substrate. In RA patients receiving 10 mg omeprazole, exposure to omeprazole was approximately 2 fold higher than that observed in healthy subjects. In RA patients receiving 10 mg omeprazole, before and one week after ACTEMRA infusion (8 mg per kg), the omeprazole AUC_{inf} decreased by 12% for poor (N=5) and intermediate metabolizers (N=5) and by 28% for extensive metabolizers (N=8) and were slightly higher than those observed in healthy subjects.

Dextromethorphan

Dextromethorphan is a CYP2D6 and CYP3A4 substrate. In 13 RA patients receiving 30 mg dextromethorphan, exposure to dextromethorphan was comparable to that in healthy subjects. However, exposure to its metabolite, dextrorphan (a CYP3A4 substrate), was a fraction of that observed in healthy subjects. One week following administration of a single infusion of ACTEMRA (8 mg per kg), dextromethorphan exposure was decreased by approximately 5%. However, a larger decrease (29%) in dextrorphan levels was noted after ACTEMRA infusion.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenicity potential of tocilizumab. Literature indicates that the IL-6 pathway can mediate anti-tumor responses by promoting increased immune cell surveillance of the tumor microenvironment. However, available published evidence also supports that IL-6 signaling through the IL-6 receptor may be involved in pathways that lead to tumorigenesis. The malignancy risk in humans from an antibody that disrupts signaling through the IL-6 receptor, such as tocilizumab, is presently unknown.

Fertility and reproductive performance were unaffected in male and female mice that received a murine analogue of tocilizumab administered by the intravenous route at a dose of 50 mg/kg every three days.

14 CLINICAL STUDIES

14.1 Rheumatoid Arthritis – Intravenous Administration

The efficacy and safety of intravenously administered ACTEMRA was assessed in five randomized, double-blind, multicenter studies in patients greater than 18 years with active rheumatoid arthritis diagnosed according to American College of Rheumatology (ACR) criteria. Patients had at least 8 tender and 6 swollen joints at baseline. ACTEMRA was given intravenously every 4 weeks as monotherapy (Study I), in combination with methotrexate (MTX) (Studies II and III) or other disease-modifying anti-rheumatic drugs (DMARDs) (Study IV) in patients with an inadequate response to those drugs, or in combination with MTX in patients with an inadequate response to TNF antagonists (Study V).

Study I (NCT00109408) evaluated patients with moderate to severe active rheumatoid arthritis who had not been treated with MTX within 24 weeks prior to randomization, or who had not discontinued previous methotrexate treatment as a result of clinically important toxic effects or lack of response. In this study, 67% of patients were MTX-naïve, and over 40% of patients had rheumatoid arthritis less than 2 years. Patients received ACTEMRA 8 mg per kg monotherapy or MTX alone (dose titrated over 8 weeks from 7.5 mg to a maximum of 20 mg weekly). The primary endpoint was the proportion of ACTEMRA patients who achieved an ACR 20 response at Week 24.

Study II (NCT00106535) was a 104-week study with an optional 156-week extension phase that evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). Upon completion of 52-weeks, patients received open-label treatment with ACTEMRA 8 mg per kg through 104 weeks or they had the option to continue their double-blind treatment if they maintained a greater than 70% improvement in swollen/tender joint count. Two pre-specified interim analyses at week 24 and week 52 were conducted. The primary endpoint at week 24 was the proportion of patients who achieved an ACR 20 response. At weeks 52 and 104, the primary endpoints were change from baseline in modified total Sharp-Genant score and the area under the curve (AUC) of the change from baseline in HAQ-DI score.

Study III (NCT00106548) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response to MTX. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study IV (NCT00106574) evaluated patients who had an inadequate response to their existing therapy, including one or more DMARDs. Patients received ACTEMRA 8 mg per kg or placebo every four weeks, in combination with the stable DMARDs. The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Study V (NCT00106522) evaluated patients with moderate to severe active rheumatoid arthritis who had an inadequate clinical response or were intolerant to one or more TNF antagonist therapies. The TNF antagonist therapy was discontinued prior to randomization. Patients received ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, or placebo every four weeks, in combination with MTX (10 to 25 mg weekly). The primary endpoint was the proportion of patients who achieved an ACR 20 response at week 24.

Clinical Response

The percentages of intravenous ACTEMRA-treated patients achieving ACR 20, 50 and 70 responses are shown in **Table 4.** In all intravenous studies, patients treated with 8 mg per kg ACTEMRA had higher ACR 20, ACR 50, and ACR 70 response rates versus MTX- or placebo-treated patients at week 24.

During the 24 week controlled portions of Studies I to V, patients treated with ACTEMRA at a dose of 4 mg per kg in patients with inadequate response to DMARDs or TNF antagonist therapy had lower response rates compared to patients treated with ACTEMRA 8 mg per kg.

Table 4 Clinical Response at Weeks 24 and 52 in Active and Placebo Controlled Trials of Intravenous ACTEMRA (Percent of Patients)

Percent of Patients												
	Study I		Study II			Study III			Study IV		Study V		
Response Rate	MTX N=284	ACTEMRA 8 mg per kg N=286 (95% CI)[a]	Placebo + MTX N=393	ACTEMRA 4 mg per kg + MTX N=399 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=398 (95% CI)[a]	Placebo + MTX N=204	ACTEMRA 4 mg per kg + MTX N=213 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=205 (95% CI)[a]	Placebo + DMARDs N=413	ACTEMRA 8 mg per kg + DMARDs N=803 (95% CI)[a]	Placebo + MTX N=158	ACTEMRA 4 mg per kg + MTX N=161 (95% CI)[a]	ACTEMRA 8 mg per kg + MTX N=170 (95% CI)[a]
ACR 20													
Week 24	53%	70% (0.11, 0.27)	27%	51% (0.17, 0.29)	56% (0.23, 0.35)	27%	48% (0.15, 0.32)	59% (0.23, 0.41)	24%	61% (0.30, 0.40)	10%	30% (0.15, 0.36)	50% (0.36, 0.56)
Week 52	N/A	N/A	25%	47% (0.15, 0.28)	56% (0.25, 0.38)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 50													
Week 24	34%	44% (0.04, 0.20)	10%	25% (0.09, 0.20)	32% (0.16, 0.28)	11%	32% (0.13, 0.29)	44% (0.25, 0.41)	9%	38% (0.23, 0.33)	4%	17% (0.05, 0.25)	29% (0.21, 0.41)
Week 52	N/A	N/A	10%	29% (0.14, 0.25)	36% (0.21, 0.32)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
ACR 70													
Week 24	15%	28% (0.07, 0.22)	2%	11% (0.03, 0.13)	13% (0.05, 0.15)	2%	12% (0.04, 0.18)	22% (0.12, 0.27)	3%	21% (0.13, 0.21)	1%	5% (-0.06, 0.14)	12% (0.03, 0.22)
Week 52	N/A	N/A	4%	16% (0.08, 0.17)	20% (0.12, 0.21)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Major Clinical Responses[b]													
Week 52	N/A	N/A	1%	4% (0.01, 0.06)	7% (0.03, 0.09)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] CI: 95% confidence interval of the weighted difference to placebo adjusted for site (and disease duration for Study I only)

[b] Major clinical response is defined as achieving an ACR 70 response for a continuous 24 week period

In study II, a greater proportion of patients treated with 4 mg per kg and 8 mg per kg ACTEMRA + MTX achieved a low level of disease activity as measured by a DAS 28-ESR less than 2.6 compared with placebo +MTX treated patients at week 52. The proportion of ACTEMRA-treated patients achieving DAS 28-ESR less than 2.6, and the number of residual active joints in these responders in Study II are shown in **5**.

Table 5 Proportion of Patients with DAS28-ESR Less Than 2.6 with Number of Residual Active Joints in Trials of Intravenous ACTEMRA

Study II			
	Placebo + MTX N = 393	**ACTEMRA 4 mg per kg + MTX N = 399**	**ACTEMRA 8 mg per kg + MTX N = 398**
DAS28-ESR less than 2.6			
Proportion of responders at week 52 (n) 95% confidence interval	3% (12)	18% (70) 0.10, 0.19	32% (127) 0.24, 0.34
Of responders, proportion with 0 active joints (n)	33% (4)	27% (19)	21% (27)
Of responders, proportion with 1 active joint (n)	8% (1)	19% (13)	13% (16)
Of responders, proportion with 2 active joints (n)	25% (3)	13% (9)	20% (25)
Of responders, proportion with 3 or more active joints (n)	33% (4)	41% (29)	47% (59)

*n denotes numerator of all the percentage. Denominator is the intent-to-treat population. Not all patients received DAS28 assessments at Week 52.

The results of the components of the ACR response criteria for Studies III and V are shown in **Table 6**. Similar results to Study III were observed in Studies I, II and IV.

Table 6 Components of ACR Response at Week 24 in Trials of Intravenous ACTEMRA

	Study III						**Study V**					
	ACTEMRA 4 mg per kg + MTX N=213		**ACTEMRA 8 mg per kg + MTX N=205**		**Placebo + MTX N=204**		**ACTEMRA 4 mg per kg + MTX N=161**		**ACTEMRA 8 mg per kg + MTX N=170**		**Placebo + MTX N=158**	
Component (mean)	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24[a]**	**Baseline**	**Week 24**
Number of tender joints (0-68)	33	19 -7.0 (-10.0, -4.1)	32	14.5 -9.6 (-12.6, -6.7)	33	25	31	21 -10.8 (-14.6, -7.1)	32	17 -15.1 (-18.8, -11.4)	30	30
Number of swollen joints (0-66)	20	10 -4.2 (-6.1, -2.3)	19.5	8 -6.2 (-8.1, -4.2)	21	15	19.5	13 -6.2 (-9.0, -3.5)	19	11 -7.2 (-9.9, -4.5)	19	18
Pain[b]	61	33 -11.0 (-17.0, -5.0)	60	30 -15.8 (-21.7, -9.9)	57	43	63.5	43 -12.4 (-22.1, -2.1)	65	33 -23.9 (-33.7, -14.1)	64	48
Patient global assessment[b]	66	34 -10.9 (-17.1, -4.8)	65	31 -14.9 (-20.9, -8.9)	64	45	70	46 -10.0 (-20.3, 0.3)	70	36 -17.4 (-27.8, -7.0)	71	51
Physician global assessment[b]	64	26 -5.6 (-10.5, -0.8)	64	23 -9.0 (-13.8, -4.2)	64	32	66.5	39 -10.5 (-18.6, -2.5)	66	28 -18.2 (-26.3, -10.0)	67.5	43
Disability index (HAQ)[c]	1.64	1.01 -0.18 (-0.34, -0.02)	1.55	0.96 -0.21 (-0.37, -0.05)	1.55	1.21	1.67	1.39 -0.25 (-0.42, -0.09)	1.75	1.34 -0.34 (-0.51, -0.17)	1.70	1.58
CRP (mg per dL)	2.79	1.17 -1.30 (-2.0, -0.59)	2.61	0.25 -2.156 (-2.86, -1.46)	2.36	1.89	3.11	1.77 -1.34 (-2.5, -0.15)	2.80	0.28 -2.52 (-3.72, -1.32)	3.705	3.06

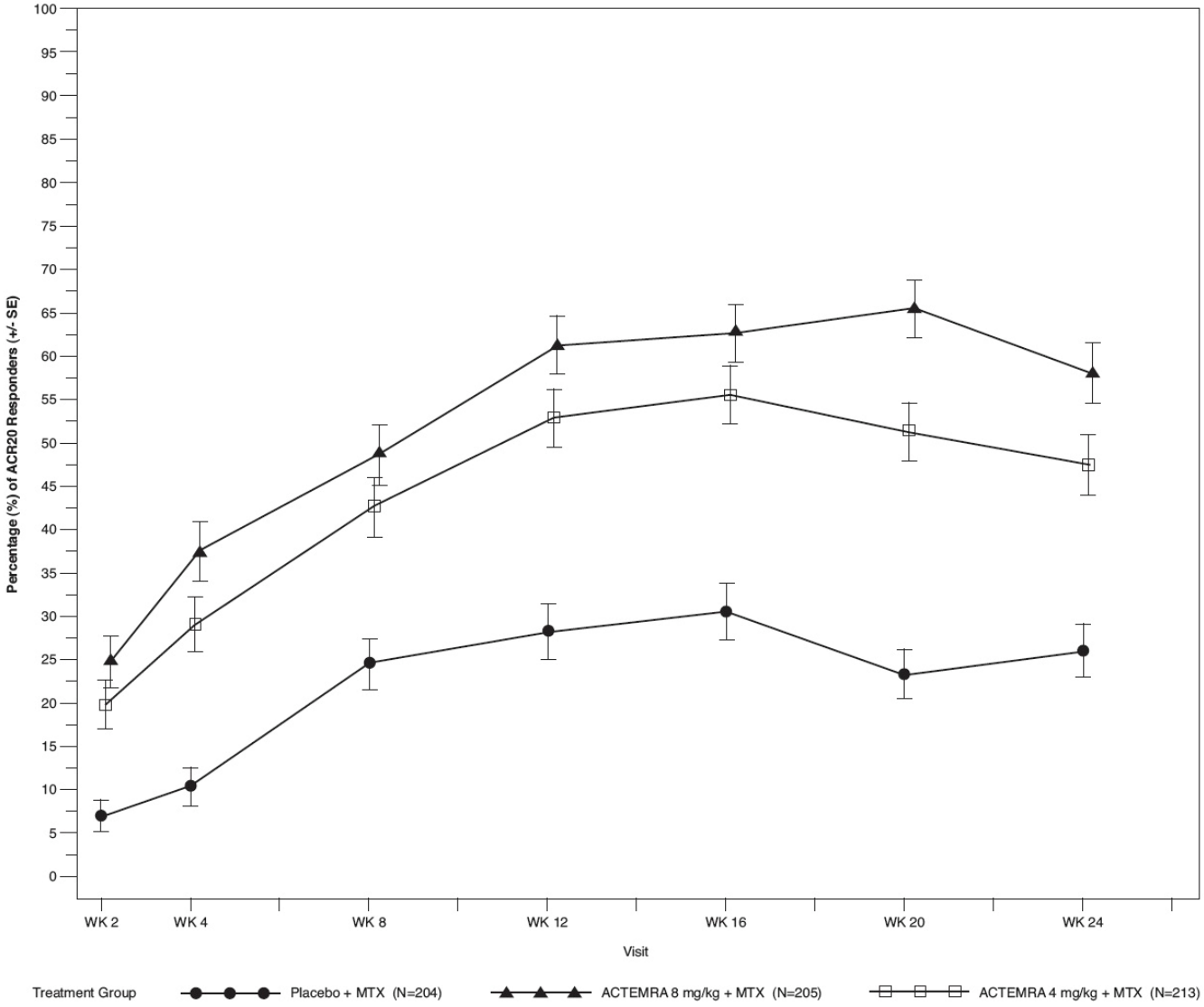
[a] Data shown is mean at week 24, difference in adjusted mean change from baseline compared with placebo + MTX at week 24 and 95% confidence interval for that difference

[b] Visual analog scale: 0 = best, 100 = worst

[c] Health Assessment Questionnaire: 0 = best, 3 = worst; 20 questions; 8 categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities

The percent of ACR 20 responders by visit for Study III is shown in **Figure 1**. Similar response curves were observed in studies I, II, IV, and V.

Figure 1 Percent of ACR 20 Responders by Visit for Study III (Inadequate Response to MTX)*



*The same patients may not have responded at each timepoint.

Radiographic Response

In Study II, structural joint damage was assessed radiographically and expressed as change in total Sharp-Genant score and its components, the erosion score and joint space narrowing score. Radiographs of hands/wrists and forefeet were obtained at baseline, 24 weeks, 52 weeks, and 104 weeks and scored by readers unaware of treatments group and visit number. The results from baseline to week 52 are shown in **Table 7**. ACTEMRA 4 mg per kg slowed (less than 75% inhibition compared to the control group) and ACTEMRA 8 mg per kg inhibited (at least 75% inhibition compared to the control group) the progression of structural damage compared to placebo plus MTX at week 52.

Table 7 Mean Radiographic Change from Baseline to Week 52 in Study II

	Placebo + MTX N=294	**ACTEMRA 4 mg per kg + MTX N=343**	**ACTEMRA 8 mg per kg + MTX N=353**
Week 52*			
Total Sharp-Genant Score, Mean (SD)	1.17 (3.14)	0.33 (1.30)	0.25 (0.98)
Adjusted Mean difference (95%CI)**		-0.83 (-1.13, -0.52)	-0.90 (-1.20, -0.59)
Erosion Score, Mean (SD)	0.76 (2.14)	0.20 (0.83)	0.15 (0.77)
Adjusted Mean difference (95%CI)**		-0.55 (-0.76, -0.34)	-0.60 (-0.80, -0.39)
Joint Space Narrowing Score, Mean (SD)	0.41 (1.71)	0.13 (0.72)	0.10 (0.49)
Adjusted Mean difference (95%CI)**		-0.28 (-0.44, -0.11)	-0.30 (-0.46, -0.14)

* Week 52 analysis employs linearly extrapolated data for patients after escape, withdrawal, or loss to follow up.
** Difference between the adjusted means (ACTEMRA + MTX - Placebo + MTX)
SD = standard deviation

The mean change from baseline to week 104 in Total Sharp-Genant Score for the ACTEMRA 4 mg per kg groups was 0.47 (SD = 1.47) and for the 8 mg per kg groups was 0.34 (SD = 1.24). By the week 104, most patients in the control (placebo + MTX) group had crossed over to active treatment, and results are therefore not included for comparison. Patients in the active groups may have crossed over to the alternate active dose group, and results are reported per original randomized dose group.

In the placebo group, 66% of patients experienced no radiographic progression (Total Sharp-Genant Score change ≤ 0) at week 52 compared to 78% and 83% in the ACTEMRA 4 mg per kg and 8 mg per kg, respectively. Following 104 weeks of treatment, 75% and 83% of patients initially randomized to ACTEMRA 4 mg per kg and 8 mg per kg, respectively, experienced no progression of structural damage compared to 66% of placebo treated patients.

Health Related Outcomes

In Study II, physical function and disability were assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI). Both dosing groups of ACTEMRA demonstrated a greater improvement compared to the placebo group in the AUC of change from baseline in the HAQ-DI through week 52. The mean change from baseline to week 52 in HAQ-DI was 0.6, 0.5, and 0.4 for ACTEMRA 8 mg per kg, ACTEMRA 4 mg per kg, and placebo treatment groups, respectively. Sixty-three percent (63%) and sixty percent (60%) of patients in the ACTEMRA 8 mg per kg and ACTEMRA 4 mg per kg treatment groups, respectively, achieved a clinically relevant improvement in HAQ-DI (change from baseline of ≥ 0.3 units) at week 52 compared to 53% in the placebo treatment group.

Other Health-Related Outcomes

General health status was assessed by the Short Form Health Survey (SF-36) in Studies I – V. Patients receiving ACTEMRA demonstrated greater improvement from baseline compared to placebo in the Physical Component Summary (PCS), Mental Component Summary (MCS), and in all 8 domains of the SF-36.

Cardiovascular Outcomes

Study WA25204 (NCT01331837) was a randomized, open-label (sponsor-blinded), 2-arm parallel-group, multicenter, non-inferiority, cardiovascular (CV) outcomes trial in patients with a diagnosis of moderate to severe RA. This CV safety study was designed to exclude a moderate increase in CV risk in patients treated with ACTEMRA compared with a TNF inhibitor standard of care (etanercept).

The study included 3,080 seropositive RA patients with active disease and an inadequate response to non-biologic disease-modifying anti-rheumatic drugs, who were aged ≥50 years with at least one additional CV risk factor beyond RA. Patients were randomized 1:1 to IV ACTEMRA 8 mg/kg Q4W or SC etanercept 50 mg QW and followed for an average of 3.2 years. The primary endpoint was the comparison of the time-to-first occurrence of any component of a composite of major adverse CV events (MACE; non-fatal myocardial infarction, non-fatal stroke, or CV death), with the final intent-to-treat analysis based on a total of 161 confirmed CV events (83/1538 [5.4%] for ACTEMRA; 78/1542 [5.1%] for etanercept) reviewed by an independent and blinded adjudication committee.

Non-inferiority of ACTEMRA to etanercept for cardiovascular risk was determined by excluding >80% relative increase in the risk of MACE. The estimated hazard ratio (HR) for the risk of MACE comparing ACTEMRA to etanercept was 1.05; 95% CI (0.77, 1.43).

14.2 Rheumatoid Arthritis – Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in two double-blind, controlled, multicenter studies in patients with active RA. One study, SC-I (NCT01194414), was a non-inferiority study that compared the efficacy and safety of ACTEMRA 162 mg administered every week subcutaneously to 8 mg per kg intravenously every four weeks. The second study, SC-II (NCT01232569), was a placebo controlled superiority study that evaluated the safety and efficacy of ACTEMRA 162 mg administered every other week subcutaneously to placebo. Both SC-I and SC-II required patients to be >18 years of age with moderate to severe active rheumatoid arthritis diagnosed according to ACR criteria who had at least 4 tender and 4 swollen joints at baseline (SC-I) or at least 8 tender and 6 swollen joints at baseline (SC-II), and an inadequate response to their existing DMARD therapy, where approximately 20% also had a history of inadequate response to at least one TNF inhibitor. All patients in both SC studies received background non-biologic DMARD(s).

In SC-I, 1262 patients were randomized 1:1 to receive ACTEMRA-SC 162 mg every week or intravenous ACTEMRA 8 mg/kg every four weeks in combination with DMARD(s). In SC-II, 656 patients were randomized 2:1 to ACTEMRA-SC 162 mg every other week or placebo, in combination with DMARD(s). The primary endpoint in both studies was the proportion of patients who achieved an ACR20 response at Week 24.

The clinical response to 24 weeks of ACTEMRA-SC therapy is shown in **Table 8**. In SC-I, the primary outcome measure was ACR20 at Week 24. The pre-specified non-inferiority margin was a treatment difference of 12%. The study demonstrated non-inferiority of ACTEMRA with respect to ACR20 at Week 24; ACR50, ACR70, and DAS28 responses are also shown in **Table 8**. In SC-II, a greater portion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved ACR20, ACR50, and ACR70 responses compared to placebo-treated patients (Table 8). Further, a greater proportion of patients treated with ACTEMRA 162 mg subcutaneously every other week achieved a low level of disease activity as measured by a DAS28-ESR less than 2.6 at Week 24 compared to those treated with placebo (Table 8).

Table 8 Clinical Response at Week 24 in Trials of Subcutaneous ACTEMRA (Percent of Patients)

	SC-I[a]		SC-II[b]	
	TCZ SC 162 mg every week + DMARD N=558	TCZ IV 8mg/kg + DMARD N=537	TCZ SC 162 mg every other week + DMARD N=437	Placebo + DMARD N=219
ACR20				
Week 24	69%	73.4%	61%	32%
Weighted difference (95% CI)	-4% (-9.2, 1.2)		30% (22.0, 37.0)	
ACR50				
Week 24	47%	49%	40%	12%
Weighted difference (95% CI)	-2% (-7.5, 4.0)		28% (21.5, 34.4)	
ACR70				
Week 24	24%	28%	20%	5%
Weighted difference (95% CI)	-4% (-9.0, 1.3)		15% (9.8, 19.9)	
Change in DAS28 [Adjusted mean]				
Week 24	-3.5	-3.5	-3.1	-1.7
Adjusted mean difference (95% CI)	0 (-0.2, 0.1)		-1.4 (-1.7; -1.1)	
DAS28 < 2.6				
Week 24	38.4%	36.9%	32.0%	4.0%
Weighted difference (95% CI)	0.9 (-5.0, 6.8)		28.6 (22.0, 35.2)	

TCZ = tocilizumab

[a] Per Protocol Population

[b] Intent To Treat Population

The results of the components of the ACR response criteria and the percent of ACR20 responders by visit for ACTEMRA-SC in Studies SC-I and SC-II were consistent with those observed for ACTEMRA-IV.

Radiographic Response

In study SC-II, the progression of structural joint damage was assessed radiographically and expressed as a change from baseline in the van der Heijde modified total Sharp score (mTSS). At week 24, significantly less radiographic progression was observed in patients receiving ACTEMRA-SC every other week plus DMARD(s) compared to placebo plus DMARD(s); mean change from baseline in mTSS of 0.62 vs. 1.23, respectively, with an adjusted mean difference of -0.60 (-1.1, -0.1). These results are consistent with those observed in patients treated with intravenous ACTEMRA.

Health Related Outcomes

In studies SC-I and SC-II, the mean decrease from baseline to week 24 in HAQ-DI was 0.6, 0.6, 0.4 and 0.3, and the proportion of patients who achieved a clinically relevant improvement in HAQ-DI (change from baseline of $\geq$ 0.3 units) was 65%, 67%, 58% and 47%, for the subcutaneous every week, intravenous 8 mg/kg, subcutaneous every other week, and placebo treatment groups, respectively.

Other Health-Related Outcomes

General health status was assessed by the SF-36 in Studies SC-I and SC-II. In Study SC-II, patients receiving ACTEMRA every other week demonstrated greater improvement from baseline compared to placebo in the PCS, MCS, and in all 8 domains of the SF-36. In Study SC-I, improvements in these scores were similar between ACTEMRA-SC every week and ACTEMRA-IV 8 mg/kg.

14.3 Giant Cell Arteritis – Subcutaneous Administration

The efficacy and safety of subcutaneously administered ACTEMRA was assessed in a single, randomized, double-blind, multicenter study in patients with active GCA. In Study WA28119 (NCT01791153), 251 screened patients with new-onset or relapsing GCA were randomized to one of four treatment arms. Two subcutaneous doses of ACTEMRA (162 mg every week and 162 mg every other week) were compared to two different placebo control groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks) randomized 2:1:1:1. The study consisted of a 52-week blinded period, followed by a 104-week open-label extension.

All patients received background glucocorticoid (prednisone) therapy. Each of the ACTEMRA-treated groups and one of the placebo-treated groups followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 26 weeks, while the second placebo-treated group followed a pre-specified prednisone-taper regimen with the aim to reach 0 mg by 52 weeks designed to be more in keeping with standard practice.

The primary efficacy endpoint was the proportion of patients achieving sustained remission from Week 12 through Week 52. Sustained remission was defined by a patient attaining a sustained (1) absence of GCA signs and symptoms from Week 12 through Week 52, (2) normalization of erythrocyte sedimentation rate (ESR) (to < 30 mm/hr without an elevation to ≥ 30 mm/hr attributable to GCA) from Week 12 through Week 52, (3) normalization of C-reactive protein (CRP) (to < 1 mg/dL, with an absence of successive elevations to ≥ 1mg/dL) from Week 12 through Week 52, and (4) successful adherence to the prednisone taper defined by not more than 100 mg of excess prednisone from Week 12 through Week 52. ACTEMRA 162 mg weekly and 162 mg every other week + 26 weeks prednisone taper both showed superiority in achieving sustained remission from Week 12 through Week 52 compared with placebo + 26 weeks prednisone taper (Table 9). Both ACTEMRA treatment arms also showed superiority compared to the placebo + 52 weeks prednisone taper (Table 9).

Table 9 Efficacy Results from Study WA28119

	PBO + 26 weeks prednisone taper N=50	**PBO + 52 weeks prednisone taper N=51**	**TCZ 162mg SC QW + 26 weeks prednisone taper N=100**	**TCZ 162 mg SC Q2W + 26 weeks prednisone taper N=49**
Sustained remission [a]				
Responders, n (%)	7 (14.0%)	9 (17.6%)	56 (56.0%)	26 (53.1%)
Unadjusted difference in proportions vs PBO + 26 weeks taper (99.5% CI)	N/A	N/A	42.0% (18.0, 66.0)	39.1% (12.5 , 65.7)
Unadjusted difference in proportions vs PBO + 52 weeks taper (99.5% CI)	N/A	N/A	38.4% (14.4, 62.3)	35.4% (8.6, 62.2)
Components of Sustained Remission				
Sustained absence of GCA signs and symptoms[b], n (%)	20 (40.0%)	23 (45.1%)	69 (69.0%)	28 (57.1%)
Sustained ESR<30 mm/hr[c], n (%)	20 (40.0%)	22 (43.1%)	83 (83.0%)	37 (75.5%)
Sustained CRP normalization[d], n (%)	17 (34.0%)	13 (25.5%)	72 (72.0%)	34 (69.4%)
Successful prednisone tapering[e], n (%)	10 (20.0%)	20 (39.2%)	60 (60.0%)	28 (57.1%)

[a] Sustained remission was achieved by a patient meeting all of the following components: absence of GCA signs and symptoms[b], normalization of ESR[c], normalization of CRP[d] and adherence to the prednisone taper regimen[e].
[b] Patients who did not have any signs or symptoms of GCA recorded from Week 12 up to Week 52.

[c] Patients who did not have an elevated ESR ≥30 mm/hr which was classified as attributed to GCA from Week 12 up to Week 52.
[d] Patients who did not have two or more consecutive CRP records of ≥ 1mg/dL from Week 12 up to Week 52.
[e] Patients who did not enter escape therapy and received ≤ 100mg of additional concomitant prednisone from Week 12 up to Week 52.
Patients not completing the study to week 52 were classified as non-responders in the primary and key secondary analysis: PBO+26: 6 (12.0%), PBO+52: 5 (9.8%), TCZ QW: 15 (15.0%), TCZ Q2W: 9 (18.4%).
CRP = C-reactive protein
ESR = erythrocyte sedimentation rate
PBO = placebo
Q2W = every other week dose
QW = every week dose
TCZ = tocilizumab

The estimated annual cumulative prednisone dose was lower in the two ACTEMRA dose groups (medians of 1887 mg and 2207 mg on ACTEMRA QW and Q2W, respectively) relative to the placebo arms (medians of 3804 mg and 3902 mg on placebo + 26 weeks prednisone and placebo + 52 weeks prednisone taper, respectively).

14.4 Giant Cell Arteritis – Intravenous Administration

Intravenously administered ACTEMRA in patients with GCA was assessed in WP41152 (NCT03923738), an open-label PK-PD and safety study to determine the appropriate intravenous dose of ACTEMRA that achieved comparable PK-PD profiles to the ACTEMRA-SC regimen.

At enrollment, all patients (n=24) were in remission on ACTEMRA-IV. In Period 1, all patients received open-label ACTEMRA-IV 7 mg/kg every 4 weeks for 20 weeks. Patients who completed Period 1 and remained in remission (n=22) were eligible to enter Period 2, and received open-label ACTEMRA-IV 6 mg/kg every 4 weeks for 20 weeks.

The efficacy of intravenous ACTEMRA 6 mg/kg in adult patients with GCA is based on pharmacokinetic exposure and extrapolation to the efficacy established for subcutaneous ACTEMRA in patients with GCA *[see Clinical Pharmacology (12.3) and Clinical Studies (14.3)]*.

14.5 Systemic Sclerosis-Associated Interstitial Lung Disease – Subcutaneous Administration

The clinical efficacy of ACTEMRA was assessed in a phase 3 multicenter, randomized, double-blind, placebo controlled study in patients with SSc (Study WA29767). A phase 2/3 multicenter, randomized, double-blind, placebo controlled study in patients with SSc (Study WA27788) provided supportive information. Study WA29767 (NCT02453256) enrolled adult patients with SSc defined by the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc, with onset of disease (first non-Raynaud symptom) of ≤ 5 years, modified Rodnan Skin Score (mRSS) of ≥ 10 and ≤ 35 at screening, elevated inflammatory markers (or platelets), and active disease based on at least one of the following: disease duration ≤ 18 months, increase in mRSS ≥ 3 units over 6 months, involvement of one new body area and an increase in mRSS of ≥ 2 over 6 months, or involvement of two new body areas within the previous 6 months, or presence of at least one tendon friction rub. Study WA27788 (NCT01532869) enrolled adult patients with SSc with onset of disease ≤ 5 years, mRSS of ≥ 15 and ≤ 40 at screening, active disease, and elevated inflammatory markers or platelets. Patients in both studies were not permitted to use biologic agents (such as TNF antagonists), alkylating agents, or cyclophosphamide.

In Study WA29767, 212 patients were randomized in a 1:1 ratio to receive weekly SC injections of 162 mg of ACTEMRA or placebo during the 48-week, double-blinded, placebo controlled period. Rescue treatment was allowed during the treatment period after 16 weeks for >10% percent predicted FVC (ppFVC) decline or after 24 weeks for worsening skin fibrosis. The primary efficacy endpoint was change from baseline at Week 48 in mRSS. Change from baseline in FVC at Week 48 was a key secondary endpoint.

In the overall population of Study WA29767, there was not a statistically significant difference in the mean change from baseline to Week 48 in mRSS (primary endpoint) in patients receiving ACTEMRA compared to placebo (difference: -1.73; 95% CI: -3.78, 0.32). There also was not a statistically significant effect on the primary endpoint of mRSS in Study WA27788.

In the overall population of Study WA29767, patients treated with ACTEMRA, as compared to placebo treated patients, were observed to have less decline from baseline in ppFVC and observed FVC at 48 weeks. FVC results from Study WA27788 were similar.

Of the 212 patients who were randomized in Study WA29767, 68 patients (65%) in the ACTEMRA arm and 68 patients (64%) in the placebo arm had SSc-ILD at baseline, as confirmed by a visual read of high resolution computed tomograph (HRCT) by blinded thoracic radiologists. The mean ppFVC at baseline for patients with SSc-ILD identified by HRCT was 79.6% (median 80.5%). Post-hoc analyses were performed to evaluate results within the subgroups of patients with and without SSc-ILD.

Table 10 shows results from Study WA29767 for the changes from baseline to Week 48 in ppFVC, observed FVC, and mRSS both in the overall population and within subgroups based on SSc-ILD status at baseline. The ppFVC and observed FVC results in the overall population were primarily driven by results in the SSc-ILD subgroup. In the SSc-ILD subgroup, the differences in mean changes from baseline to Week 48 for ACTEMRA, as compared to placebo, were 6.47% and 241 mL for ppFVC and observed FVC, respectively. Figure 2 illustrates the mean change from baseline through Week 48 in observed FVC in patients with SSc-ILD.

The results of the key FVC secondary endpoints from Study WA29767 support a conclusion of effectiveness of ACTEMRA in reducing the rate of progressive loss of lung function in the study population. However, in settings where a trial does not provide evidence of an effect on the primary endpoint, the estimated magnitude of effect on other endpoints should be interpreted with caution, and comparisons to results of other products and studies may be misleading.

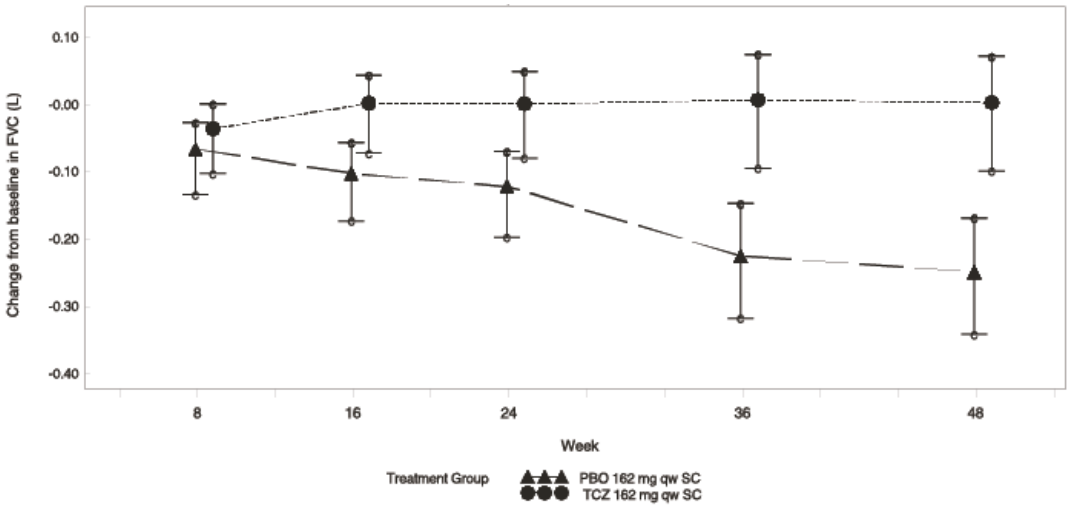
Table 10 Efficacy Results from Study WA29767

	Overall Population		**Subgroup Without SSc-ILD***		**SSc-ILD Subgroup***	
	PBO QW	**TCZ 162 mg QW**	**PBO QW**	**TCZ 162 mg QW**	**PBO QW**	**TCZ 162 mg QW**
Number of patients	**106**	**104**	**36**	**34**	**68**	**68**
Change from Baseline in mRSS at Week 48						
LSM	-4.41	-6.14	-6.16	-8.56	-3.77	-5.88
Difference in LSM, TCZ-placebo (95% CI)	-1.73 (-3.78, 0.32)		-2.40 (-5.59, 0.79)		-2.11 (-4.89, 0.67)	
Change from Baseline in ppFVC at Week 48						
LSM	-4.58	-0.38	-0.82	-0.32	-6.40	0.07
Difference in LSM, TCZ-placebo (95% CI)	4.20 (2.00, 6.40)		0.50 (-2.27, 3.27)		6.47 (3.43, 9.50)	
Change from Baseline in Observed FVC (mL) at Week 48						
LSM	-190	-24	-53	-11	-255	-14
Difference in LSM, TCZ-placebo (95% CI)	167 (83, 250)		43 (-60, 145)		241 (124, 358)	

PBO=placebo; TCZ=tocilizumab; ppFVC = percent predicted forced vital capacity; LSM=least squares mean; mRSS = modified Rodnan skin score; CI=confidence interval

*Post-hoc results are shown for these subgroups. Four patients had ILD status missing at baseline.

Figure 2 Mean Change from Baseline to Week 48 in Observed Forced Vital Capacity in SSc-ILD Patients from Study WA29767



PBO = placebo; TCZ = tocilizumab; QW = every week dose

14.6 Polyarticular Juvenile Idiopathic Arthritis – Intravenous Administration

The efficacy of ACTEMRA was assessed in a three-part study, WA19977 (NCT00988221), including an open-label extension in children 2 to 17 years of age with active polyarticular juvenile idiopathic arthritis (PJIA), who had an inadequate response to methotrexate or inability to tolerate methotrexate. Patients had at least 6 months of active disease (mean disease duration of 4.2 ± 3.7 years), with at least five joints with active arthritis (swollen or limitation of movement accompanied by pain and/or tenderness) and/or at least 3 active joints having limitation of motion (mean, 20 ± 14 active joints). The patients treated had subtypes of JIA that at disease onset included Rheumatoid Factor Positive or Negative Polyarticular JIA, or Extended Oligoarticular JIA. Treatment with a stable dose of methotrexate was permitted but was not required during the study. Concurrent use of disease modifying antirheumatic drugs (DMARDs), other than methotrexate, or other biologics (e.g., TNF antagonists or T cell costimulation modulator) were not permitted in the study.

Part I consisted of a 16-week active ACTEMRA treatment lead-in period (n=188) followed by Part II, a 24-week randomized double-blind placebo-controlled withdrawal period, followed by Part III, a 64-week open-label period. Eligible patients weighing at or above 30 kg received ACTEMRA at 8 mg/kg intravenously once every four weeks. Patients weighing less than 30 kg were randomized 1:1 to receive either ACTEMRA 8 mg/kg or 10 mg/kg intravenously every four weeks. At the conclusion of the open-label Part I, 91% of patients taking background MTX in addition to tocilizumab and 83% of patients on tocilizumab monotherapy achieved an ACR 30 response at week 16 compared to baseline and entered the blinded withdrawal period (Part II) of the study. The proportions of patients with JIA ACR 50/70 responses in Part I were 84.0%, and 64%, respectively for patients taking background MTX in addition to tocilizumab and 80% and 55% respectively for patients on tocilizumab monotherapy.

In Part II, patients (ITT, n=163) were randomized to ACTEMRA (same dose received in Part I) or placebo in a 1:1 ratio that was stratified by concurrent methotrexate use and concurrent corticosteroid use. Each patient continued in Part II of the study until Week 40 or until the patient satisfied JIA ACR 30 flare criteria (relative to Week 16) and qualified for escape.

The primary endpoint was the proportion of patients with a JIA ACR 30 flare at week 40 relative to week 16. JIA ACR 30 flare was defined as 3 or more of the 6 core outcome variables worsening by at least 30% with no more than 1 of the remaining variables improving by more than 30% relative to Week 16.

ACTEMRA treated patients experienced significantly fewer disease flares compared to placebo-treated patients (26% [21/82] versus 48% [39/81]; adjusted difference in proportions -21%, 95% CI: -35%, -8%).

During the withdrawal phase (Part II), more patients treated with ACTEMRA showed JIA ACR 30/50/70 responses at Week 40 compared to patients withdrawn to placebo.

14.7 Polyarticular Juvenile Idiopathic Arthritis – Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with polyarticular juvenile idiopathic arthritis (PJIA) was assessed in WA28117 (NCT01904279), a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen. PJIA patients aged 1 to 17 years with an inadequate response or inability to tolerate MTX, including patients with well-controlled disease on treatment with ACTEMRA-IV and ACTEMRA-naïve patients with active disease, were treated with subcutaneous ACTEMRA based on body weight.

Patients weighing at or above 30 kg (n = 25) were treated with 162 mg of ACTEMRA-SC every 2 weeks and patients weighing less than 30 kg (n = 27) received 162 mg of ACTEMRA-SC every 3 weeks for 52 weeks. Of these 52 patients, 37 (71%) were naive to ACTEMRA and 15 (29%) had been receiving ACTEMRA-IV and switched to ACTEMRA-SC at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in polyarticular JIA patients and subcutaneous ACTEMRA in patients with RA *[see Clinical Pharmacology (12.3) and Clinical Studies (14.2 and 14.6)]*.

14.8 Systemic Juvenile Idiopathic Arthritis – Intravenous Administration

The efficacy of ACTEMRA for the treatment of active SJIA was assessed in WA18221 (NCT00642460), a 12-week randomized, double blind, placebo-controlled, parallel group, 2-arm study. Patients treated with or without MTX, were randomized (ACTEMRA:placebo = 2:1) to one of two treatment groups: 75 patients received ACTEMRA infusions every two weeks at either 8 mg per kg for patients at or above 30 kg or 12 mg per kg for patients less than 30 kg and 37 were randomized to receive placebo infusions every two weeks. Corticosteroid tapering could occur from week six for patients who achieved a JIA ACR 70 response. After 12 weeks or at the time of escape, due to disease worsening, patients were treated with ACTEMRA in the open-label extension phase at weight appropriate dosing.

The primary endpoint was the proportion of patients with at least 30% improvement in JIA ACR core set (JIA ACR 30 response) at Week 12 and absence of fever (no temperature at or above 37.5°C in the preceding 7 days). JIA ACR (American College of Rheumatology) responses are defined as the percentage improvement (e.g., 30%, 50%, 70%) in 3 of any 6 core outcome variables compared to baseline, with worsening in no more than 1 of the remaining variables by 30% or more. Core outcome variables consist of physician global assessment, parent per patient global assessment, number of joints with active arthritis, number of joints with limitation of movement, erythrocyte sedimentation rate (ESR), and functional ability (childhood health assessment questionnaire-CHAQ).

Primary endpoint result and JIA ACR response rates at Week 12 are shown in **Table 11**.

Table 11 Efficacy Findings at Week 12

	ACTEMRA N=75	**Placebo N=37**
Primary Endpoint: JIA ACR 30 response + absence of fever		
Responders	**85%**	**24%**
Weighted difference (95% CI)	**62 (45, 78)**	**-**
JIA ACR Response Rates at Week 12		
JIA ACR 30		
Responders	91%	24%
Weighted difference[a] (95% CI)[b]	67 (51, 83)	-
JIA ACR 50		
Responders	85%	11%
Weighted difference[a] (95% CI) [b]	74 (58, 90)	-
JIA ACR 70		
Responders	71%	8%
Weighted difference[a] (95% CI) [b]	63 (46, 80)	-

[a]The weighted difference is the difference between the ACTEMRA and Placebo response rates, adjusted for the stratification factors (weight, disease duration, background oral corticosteroid dose and background methotrexate use).
[b] CI: confidence interval of the weighted difference.

The treatment effect of ACTEMRA was consistent across all components of the JIA ACR response core variables. JIA ACR scores and absence of fever responses in the open label extension were consistent with the controlled portion of the study (data available through 44 weeks).

Systemic Features

Of patients with fever or rash at baseline, those treated with ACTEMRA had fewer systemic features; 35 out of 41 (85%) became fever free (no temperature recording at or above 37.5°C in the preceding 14 days) compared to 5 out of 24 (21%) of placebo-treated patients, and 14 out of 22 (64%) became free of rash compared to 2 out of 18 (11%) of placebo-treated patients. Responses were consistent in the open label extension (data available through 44 weeks).

Corticosteroid Tapering

Of the patients receiving oral corticosteroids at baseline, 8 out of 31 (26%) placebo and 48 out of 70 (69%), ACTEMRA patients achieved a JIA ACR 70 response at week 6 or 8 enabling corticosteroid dose reduction. Seventeen (24%) ACTEMRA patients versus 1 (3%) placebo patient were able to reduce the dose of corticosteroid by at least 20% without experiencing a subsequent JIA ACR 30 flare or occurrence of systemic symptoms to week 12. In the open label portion of the study, by week 44, there were 44 out of 103 (43%) ACTEMRA patients off oral corticosteroids. Of these 44 patients 50% were off corticosteroids 18 weeks or more.

Health Related Outcomes

Physical function and disability were assessed using the Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI). Seventy-seven percent (58 out of 75) of patients in the ACTEMRA treatment group

achieved a minimal clinically important improvement in CHAQ-DI (change from baseline of ≥ 0.13 units) at week 12 compared to 19% (7 out of 37) in the placebo treatment group.

14.9 Systemic Juvenile Idiopathic Arthritis – Subcutaneous Administration

Subcutaneously administered ACTEMRA in pediatric patients with systemic juvenile idiopathic arthritis (SJIA) was assessed in WA28118 (NCT01904292), a 52-week, open-label, multicenter, PK-PD and safety study to determine the appropriate subcutaneous dose of ACTEMRA that achieved comparable PK/PD profiles to the ACTEMRA-IV regimen.

Eligible patients received ACTEMRA subcutaneously dosed according to body weight, with patients weighing at or above 30 kg (n = 26) dosed with 162 mg of ACTEMRA every week and patients weighing below 30 kg (n = 25) dosed with 162 mg of ACTEMRA every 10 days (n=8) or every 2 weeks (n=17) for 52 weeks. Of these 51 patients, 26 (51%) were naive to subcutaneous ACTEMRA and 25 (49%) had been receiving ACTEMRA intravenously and switched to subcutaneous ACTEMRA at baseline.

The efficacy of subcutaneous ACTEMRA in children 2 to 17 years of age is based on pharmacokinetic exposure and extrapolation of the established efficacy of intravenous ACTEMRA in systemic JIA patients *[see Clinical Pharmacology (12.3) and Clinical Studies (14.8)]*.

14.10 Cytokine Release Syndrome – Intravenous Administration

The efficacy of ACTEMRA for the treatment of CRS was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies. Evaluable patients had been treated with tocilizumab 8 mg/kg (12 mg/kg for patients < 30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS; only the first episode of CRS was included in the analysis. The study population included 24 males and 21 females (total 45 patients) of median age 12 years (range, 3–23 years); 82% were Caucasian. The median time from start of CRS to first dose of tocilizumab was 4 days (range, 0-18 days). Resolution of CRS was defined as lack of fever and off vasopressors for at least 24 hours. Patients were considered responders if CRS resolved within 14 days of the first dose of tocilizumab, if no more than 2 doses of tocilizumab were needed, and if no drugs other than tocilizumab and corticosteroids were used for treatment.

Thirty-one patients (69%; 95% CI: 53%–82%) achieved a response. Achievement of resolution of CRS within 14 days was confirmed in a second study using an independent cohort that included 15 patients (range: 9–75 years old) with CAR T cell-induced CRS.

14.11 COVID-19 – Intravenous Administration

The efficacy of ACTEMRA for the treatment of COVID-19 was based on RECOVERY (NCT04381936), a randomized, controlled, open-label, platform study, and supported by the results from EMPACTA (NCT04372186), a randomized, double-blind, placebo-controlled study. Results of two other randomized, double-blind, placebo-controlled studies, COVACTA (NCT04320615) and REMDACTA (NCT04409262**)**, which evaluated the efficacy of ACTEMRA for the treatment of COVID-19 are also summarized.

RECOVERY (Randomised Evaluation of COVID-19 Therapy) Collaborative Group Study in Hospitalized Adults Diagnosed with COVID-19

RECOVERY was a randomized, controlled, open-label, multicenter platform study conducted in the United Kingdom to evaluate the efficacy and safety of potential treatments in hospitalized adult patients with severe COVID-19 pneumonia. Eligible patients for the ACTEMRA portion of the study had clinically suspected or laboratory-confirmed SARS-CoV-2 infection and no medical contraindications to any of the treatments and had clinical evidence of progressive COVID-19 (defined as oxygen saturation <92% on room air or receiving oxygen therapy, and CRP ≥75 mg/L). Patients were then randomized to receive either standard of care (SoC) or

intravenous ACTEMRA at a weight-tiered dosing comparable to the recommended dosage *[see Clinical Pharmacology (12.3)]* in addition to SoC.

Efficacy analyses were performed in the intent-to-treat (ITT) population comprising 4116 adult patients who were randomized to the ACTEMRA + SoC arm (n=2022) or to the SoC arm (n=2094). The mean age of participants was 64 years (range: 20 to 101), and patients were 67% male, 76% White, 11% Asian, 3% Black or African American, and 1% mixed race. At baseline, 0.2% of patients were not on supplemental oxygen, 45% of patients required low flow oxygen, 41% of patients required non-invasive ventilation or high-flow oxygen, and 14% of patients required invasive mechanical ventilation; 82% of patients were reported to be receiving systemic corticosteroids.

The primary efficacy endpoint was time to death through Day 28. The results for the overall population and the subgroups of patients who were or were not receiving systemic corticosteroids at time of randomization are summarized in Table 12.

Table 12 Mortality through Day 28 in RECOVERY

	ACTEMRA+ SoC N=2022 n (%)[1]	**SoC N=2094 n (%)[1]**	**Hazard Ratio (95% CI)**	**Risk Difference (95% CI)**
Mortality	621 (30.7%)	729 (34.9%)	0.85 (0.76, 0.94) p= 0.0028[1]	-4.1% (-7.0, -1.3)
By baseline receipt of corticosteroid use				
Mortality for patients receiving systemic corticosteroids at randomization[2]	482/1664 (29.0%)	600/1721 (34.9%)	0.79 (0.70, 0.89)	-5.9% (-9.1, -2.8)
Mortality for patients not receiving systemic corticosteroids at randomization[2]	139/357 (39.0%)	127/367 (34.6%)	1.16 (0.91, 1.48)	4.4% (-2.6, 11.5)

[1] P-value reflects that the RECOVERY trial primary analysis results were statistically significant at the two-sided significance level of $\alpha = 0.05$.

[2] Probabilities of dying by Day 28 were estimated by the Kaplan-Meier method.

EMPACTA

EMPACTA was a randomized, double-blind, placebo-controlled, multicenter study to evaluate intravenous ACTEMRA 8 mg/kg in combination with SoC in hospitalized, non-ventilated adult patients with COVID-19 pneumonia. Eligible patients were at least 18 years of age, had confirmed SARS-CoV-2 infection by a positive reverse-transcriptase polymerase chain reaction (RT-PCR) result, had pneumonia confirmed by radiography, and had SpO2 < 94% on ambient air.

Of the 389 patients randomized, efficacy analyses were performed in the modified intent-to-treat (mITT) population comprising 377 patients who were randomized and received study medication (249 in the ACTEMRA arm; 128 in the placebo arm). The mean age of participants was 56 years (range: 20 to 95); 59% of

patients were male, 56% were of Hispanic or Latino ethnicity, 53% were White, 20% were American Indian/Alaska Native, 15% were Black/African American and 2% were Asian. At baseline, 9% patients were not on supplemental oxygen, 64% patients required low flow oxygen, 27% patients required high-flow oxygen, and 73% were on corticosteroids.

The primary efficacy endpoint evaluated time to progression to mechanical ventilation or death through Day 28. The hazard ratio comparing ACTEMRA to placebo was 0.56 (95% CI, 0.33 to 0.97), a statistically significant result (log-rank, p-value = 0.036). The cumulative proportion of patients who required mechanical ventilation or died by Day 28 was 12.0% (95% CI, 8.5% to 16.9%) in the ACTEMRA arm and 19.3% (95% CI, 13.3% to 27.4%) in the placebo arm.

Mortality at Day 28 was 10.4% in the ACTEMRA arm versus 8.6% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 2.0% [95% CI, -5.2% to 7.8%]).

COVACTA

COVACTA was a randomized, double-blind, placebo-controlled, multicenter study to evaluate intravenous ACTEMRA 8 mg/kg in combination with SoC for the treatment of adult patients hospitalized with severe COVID-19 pneumonia. The study randomized 452 patients who were at least 18 years of age with confirmed SARS-CoV-2 infection by a positive RT-PCR result, had pneumonia confirmed by radiography, and had oxygen saturation of 93% or lower on ambient air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mmHg or less. At baseline, 3% of patients were not on supplemental oxygen, 28% were on low flow oxygen, 30% were on non-invasive ventilation or high flow oxygen, 38% were on invasive mechanical ventilation, and 22% were on corticosteroids.

The primary efficacy endpoint was clinical status on Day 28 assessed on a 7-category ordinal scale that ranged from “discharged” to “death.” There were no statistically significant differences observed in the distributions of clinical status on the 7-category ordinal scale at Day 28 when comparing the ACTEMRA arm to the placebo arm.

Mortality at Day 28 was 19.7% in the ACTEMRA arm versus 19.4% in the placebo arm (weighted difference (ACTEMRA arm - placebo arm): 0.3% [95% CI, -7.6 to 8.2]).

REMDACTA

REMDACTA was a randomized, double-blind, placebo-controlled, multicenter study to evaluate intravenous ACTEMRA 8 mg/kg in combination with intravenous remdesivir (RDV) 200 mg on Day 1 followed by 100 mg once daily for a total of 10 days in hospitalized patients with severe COVID-19 pneumonia. The study randomized 649 adult patients with SARS-CoV-2 infection confirmed by a positive polymerase chain reaction (PCR) result, pneumonia confirmed by radiography, and who required supplemental oxygen > 6 L/min to maintain SpO2 >93%. At baseline, 7% of patients were on low flow oxygen, 80% were on non-invasive ventilation or high flow oxygen, 14% were on invasive mechanical ventilation, and 84% were on corticosteroids.

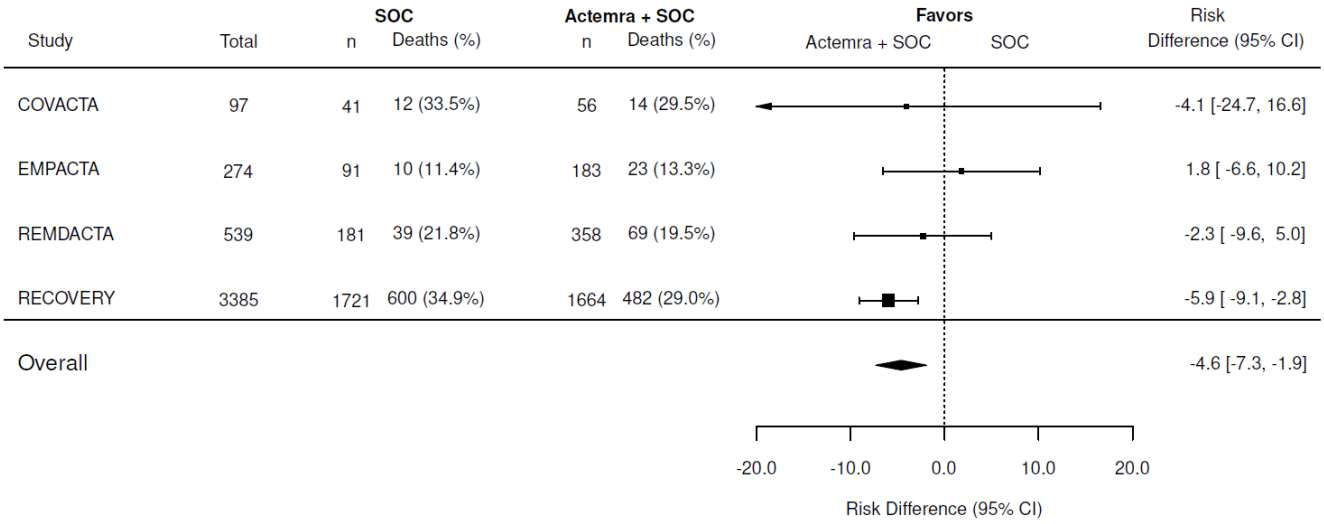
The primary efficacy endpoint was time from randomization to hospital discharge or ‘ready for discharge’ up to Day 28. There was no statistically significant difference between the treatment arms with respect to time to hospital discharge or “ready for discharge” through Day 28.

Mortality at Day 28 was 18.1% in the ACTEMRA+ RDV arm versus 19.5% in the placebo +RDV arm (weighted difference (ACTEMRA arm - placebo arm): -1.3% [95% CI, -7.8% to 5.2%]).

Mortality Across Studies in Patients Receiving Baseline Corticosteroids

A study-level meta-analysis was conducted on EMPACTA, COVACTA, REMDACTA and RECOVERY studies. For each of the four studies, the risk difference through Day 28 was estimated by the Kaplan-Meier method in the subgroup of patients receiving baseline corticosteroids, summarized in Figure 3. Patients from the RECOVERY trial represent 78.8% of the total sample size in this meta-analysis. The combined risk difference showed that ACTEMRA treatment (n=2261) resulted in a 4.61% absolute reduction in the risk of death at Day 28 (risk difference=-4.6%; 95% CI: -7.3% to -1.9%) compared to SoC (n=2034).

Figure 3 Risk Differences Through Day 28 for Baseline Corticosteroid Use Subpopulation in RECOVERY, EMPACTA, COVACTA and REMDACTA studies



16 HOW SUPPLIED/STORAGE AND HANDLING

For Intravenous Infusion

ACTEMRA (tocilizumab) injection is a preservative-free, sterile clear, colorless to pale yellow solution. ACTEMRA is supplied as 80 mg/4 mL (NDC 50242-135-01), 200 mg/10 mL (NDC 50242-136-01), and 400 mg/20 mL (NDC 50242-137-01) individually packaged 20 mg/mL single-dose vials for further dilution prior to intravenous infusion.

For Subcutaneous Injection

ACTEMRA (tocilizumab) injection is supplied as a preservative-free, sterile, clear, colorless to slightly yellowish solution for subcutaneous administration. The following packaging configurations are available:

- Each single-dose prefilled syringe delivers 162 mg/0.9 mL (NDC 50242-138-01).
- Each single-dose ACTPen® autoinjector delivers 162 mg/0.9 mL (NDC 50242-143-01).

Storage and Handling: Do not use beyond expiration date on the container, package, prefilled syringe, or autoinjector. ACTEMRA must be refrigerated at 36°F to 46°F (2ºC to 8ºC). Do not freeze. Protect the vials, syringes, and autoinjectors from light by storage in the original package until time of use, and keep syringes and autoinjectors dry. Once removed from the refrigerator, the prefilled syringe and autoinjector can be stored up to 2 weeks at or below 86°F (30°C). The prefilled syringe and autoinjector must always be kept in the carton.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Serious Infections

Inform patients that ACTEMRA may lower their resistance to infections *[see Warnings and Precautions (5.1)]*. Instruct the patient of the importance of contacting their doctor immediately when symptoms suggesting infection appear in order to assure rapid evaluation and appropriate treatment.

Gastrointestinal Perforation

Inform patients that some patients who have been treated with ACTEMRA have had serious side effects in the stomach and intestines *[see Warnings and Precautions (5.2)]*. Instruct the patient of the importance of contacting their doctor immediately when symptoms of fever, severe, persistent abdominal pain, and change in bowel habits appear to assure rapid evaluation and appropriate treatment.

Hypersensitivity and Serious Allergic Reactions

Inform patients that some patients who have been treated with ACTEMRA have developed serious allergic reactions, including anaphylaxis, as well as serious skin reactions [see Warnings and Precautions (5.6)]. Advise patients to stop taking ACTEMRA and seek immediate medical attention if they experience any symptom of serious allergic reactions (including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing).

Instruction on Injection Technique

Assess patient suitability for home use for subcutaneous injection. Perform the first injection under the supervision of a qualified healthcare professional. If a patient or caregiver is to administer subcutaneous ACTEMRA, instruct him/her in injection techniques and assess his/her ability to inject subcutaneously to ensure proper administration of subcutaneous ACTEMRA and the suitability for home use *[see Instructions for Use]*.

Prior to use, remove the prefilled syringe (PFS) or autoinjector from the refrigerator and allow to sit at room temperature outside of the carton for 30 minutes (PFS) or 45 minutes (autoinjector), out of the reach of children. Do not warm ACTEMRA in any other way.

Advise patients to consult their healthcare provider if the full dose is not received.

A puncture-resistant container for disposal of needles, syringes and autoinjectors should be used and should be kept out of the reach of children. Instruct patients or caregivers in the technique as well as proper needle, syringe and autoinjector disposal, and caution against reuse of these items.

Pregnancy

Inform female patients of reproductive potential that ACTEMRA may cause fetal harm and to inform their prescriber of a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

ACTEMRA® (tocilizumab)

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
1 DNA Way
South San Francisco, CA 94080-4990

U.S. License No.: 1048

Medication Guide

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for intravenous use

ACTEMRA® (AC-TEM-RA)
(tocilizumab) injection
for subcutaneous use

What is the most important information I should know about ACTEMRA?

ACTEMRA can cause serious side effects including:

1. **Serious Infections**. ACTEMRA is a medicine that affects your immune system. ACTEMRA can lower the ability of your immune system to fight infections. Some people have serious infections while taking ACTEMRA, including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body. Some people have died from these infections. Your healthcare provider should assess you for TB before starting ACTEMRA (except if you have COVID-19).

   If you have COVID-19, your healthcare provider should monitor you for signs and symptoms of new infections during and after treatment with ACTEMRA.

   Your healthcare provider should monitor you closely for signs and symptoms of TB during and after treatment with ACTEMRA.

   - You should not start taking ACTEMRA if you have any kind of infection unless your healthcare provider says it is okay.

   Before starting ACTEMRA, tell your healthcare provider if you:

   - think you have an infection or have symptoms of an infection, with or without a fever, such as:
     - sweating or chills
     - shortness of breath
     - warm, red, or painful skin or sores on your body
     - feel very tired
     - muscle aches
     - blood in phlegm
     - diarrhea or stomach pain
     - cough
     - weight loss
     - burning when you urinate or urinating more often than normal
   - are being treated for an infection.
   - get a lot of infections or have infections that keep coming back.
   - have diabetes, HIV, or a weak immune system. People with these conditions have a higher chance for infections.
   - have TB, or have been in close contact with someone with TB.
   - live or have lived, or have traveled to certain parts of the country (such as the Ohio and Mississippi River valleys and the Southwest) where there is an increased chance for getting certain kinds of fungal infections (histoplasmosis, coccidiomycosis, or blastomycosis). These infections may happen or become more severe if you use ACTEMRA. Ask your healthcare provider, if you do not know if you have lived in an area where these infections are common.
   - have or have had hepatitis B.

   After starting ACTEMRA, call your healthcare provider right away if you have any symptoms of an infection. ACTEMRA can make you more likely to get infections or make worse any infection that you have.

2. **Tears (perforation) of the stomach or intestines.**
   - Tell your healthcare provider if you have had diverticulitis (inflammation in parts of the large intestine) or ulcers in your stomach or intestines. Some people taking ACTEMRA get tears in their stomach or intestine. This happens most often in people who also take nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or methotrexate.
   - Tell your healthcare provider right away if you have fever and new onset stomach-area pain that does not go away, and a change in your bowel habits.

3. **Liver problems (Hepatotoxicity):** Some people have experienced serious life-threatening liver problems, which required a liver transplant or led to death. Your healthcare provider may tell you to stop taking ACTEMRA if you develop new or worse liver problems during treatment with ACTEMRA. Tell your healthcare provider right away if you have any of the following symptoms:
   - feeling tired (fatigue)
   - weakness

- lack of appetite for several days or longer (anorexia)
- yellowing of your skin or the whites of your eyes (jaundice)
- abdominal swelling and pain on the right side of your stomach-area
- light colored stools
- nausea and vomiting
- confusion
- dark “tea-colored” urine

4. **Changes in certain laboratory test results**. Your healthcare provider should do blood tests before you start receiving ACTEMRA. If you have rheumatoid arthritis (RA), giant cell arteritis (GCA), or systemic sclerosis-interstitial lung disease (SSc-ILD) your healthcare provider should do blood tests every 4 to 8 weeks after you start receiving ACTEMRA for the first 6 months and then every 3 months after that. If you have polyarticular juvenile idiopathic arthritis (PJIA) you will have blood tests done every 4 to 8 weeks during treatment. If you have systemic juvenile idiopathic arthritis (SJIA) you will have blood tests done every 2 to 4 weeks during treatment. These blood tests are to check for the following side effects of ACTEMRA:
   - low neutrophil count. Neutrophils are white blood cells that help the body fight off bacterial infections.
   - low platelet count. Platelets are blood cells that help with blood clotting and stop bleeding.
   - increase in certain liver function tests.
   - increase in blood cholesterol levels. You may also have changes in other laboratory tests, such as your blood cholesterol levels. Your healthcare provider should do blood tests to check your cholesterol levels 4 to 8 weeks after you start receiving ACTEMRA.

   Your healthcare provider will determine how often you will have follow-up blood tests. Make sure you get all your follow-up blood tests done as ordered by your healthcare provider.
   You should not receive ACTEMRA if your neutrophil or platelet counts are too low or your liver function tests are too high.

   Your healthcare provider may stop your ACTEMRA treatment for a period of time or change your dose of medicine if needed because of changes in these blood test results.
5. **Cancer.** ACTEMRA may increase your risk of certain cancers by changing the way your immune system works. Tell your healthcare provider if you have ever had any type of cancer.

See **“What are the possible side effects with ACTEMRA?”** for more information about side effects.

What is ACTEMRA?

ACTEMRA is a prescription medicine called an Interleukin-6 (IL-6) receptor antagonist. ACTEMRA is used:

- To treat adults with moderately to severely active rheumatoid arthritis (RA), after at least one other medicine called a Disease-Modifying Anti-Rheumatic Drug (DMARD) has been used and did not work well.
- To treat adults with giant cell arteritis (GCA).
- For slowing the rate of decline in lung function in adults with systemic sclerosis-associated interstitial lung disease (SSc-ILD) (also known as scleroderma associated ILD).
- To treat people with active PJIA ages 2 and above.
- To treat people with active SJIA ages 2 and above.
- To treat people age 2 years and above who experience severe or life-threatening Cytokine Release Syndrome (CRS) following chimeric antigen receptor (CAR) T cell treatment.
- To treat hospitalized adults with coronavirus disease 2019 (COVID-19) receiving systemic corticosteroids and requiring supplemental oxygen or mechanical ventilation.
- ACTEMRA is not approved for subcutaneous use in people with CRS or COVID-19.

It is not known if ACTEMRA is safe and effective in children with PJIA, SJIA, or CRS under 2 years of age or in children with conditions other than PJIA, SJIA or CRS.

Do not take ACTEMRA: if you are allergic to tocilizumab, or any of the ingredients in ACTEMRA. See the end of this Medication Guide for a complete list of ingredients in ACTEMRA.

Before you receive ACTEMRA, tell your healthcare provider about all of your medical conditions, including if you:

- have an infection. **See “What is the most important information I should know about ACTEMRA?”**
- have liver problems.

- have any stomach-area (abdominal) pain or been diagnosed with diverticulitis or ulcers in your stomach or intestines.
- have had a reaction to tocilizumab or any of the ingredients in ACTEMRA before.
- have or had a condition that affects your nervous system, such as multiple sclerosis.
- have recently received or are scheduled to receive a vaccine:
  - All vaccines should be brought up-to-date before starting ACTEMRA, unless urgent treatment initiation is required.
  - People who take ACTEMRA should not receive live vaccines.
  - People taking ACTEMRA can receive non-live vaccines.
- plan to have surgery or a medical procedure.
- are pregnant or plan to become pregnant. ACTEMRA may harm your unborn baby. Tell your healthcare provider if you become pregnant or think you may be pregnant during treatment with ACTEMRA.
- are breastfeeding or plan to breastfeed. It is not known if ACTEMRA passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take ACTEMRA.

Tell your healthcare provider about all of the medicines you take, including prescription, over-the-counter medicines, vitamins and herbal supplements. ACTEMRA and other medicines may affect each other causing side effects.

Especially tell your healthcare provider if you take:

- any other medicines to treat your RA. Taking ACTEMRA with these medicines may increase your risk of infection.
- medicines that affect the way certain liver enzymes work. Ask your healthcare provider if you are not sure if your medicine is one of these.

Know the medicines you take. Keep a list of them to show to your healthcare provider and pharmacist when you get a new medicine.

How will I receive ACTEMRA?

Into a vein (IV or intravenous infusion) for Rheumatoid Arthritis, Giant Cell Arteritis, PJIA, SJIA, CRS or COVID-19:

- If your healthcare provider prescribes ACTEMRA as an IV infusion, you will receive ACTEMRA from a healthcare provider through a needle placed in a vein in your arm. The infusion will take about 1 hour to give you the full dose of medicine.
- For rheumatoid arthritis, giant cell arteritis or PJIA you will receive a dose of ACTEMRA about every 4 weeks.
- For SJIA you will receive a dose of ACTEMRA about every 2 weeks.
- For CRS you will receive a single dose of ACTEMRA, and if needed, additional doses.
- For COVID-19, you will receive a single dose of ACTEMRA, and if needed one additional dose.
- While taking ACTEMRA, you may continue to use other medicines that help treat your rheumatoid arthritis, PJIA, SJIA or COVID-19 such as methotrexate, non-steroidal anti-inflammatory drugs (NSAIDs) and prescription steroids, as instructed by your healthcare provider.
- Keep all of your follow-up appointments and get your blood tests as ordered by your healthcare provider.

Under the skin (SC or subcutaneous injection) for Rheumatoid Arthritis, Giant Cell Arteritis, SSc-ILD, PJIA or SJIA:

- **See the Instructions for Use at the end of this Medication Guide for instructions about the right way to prepare and give your ACTEMRA injections at home.**
- ACTEMRA is available as a single-dose Prefilled Syringe or single-dose prefilled ACTPen® autoinjector.
- You may also receive ACTEMRA as an injection under your skin (subcutaneous). If your healthcare provider decides that you or a caregiver can give your injections of ACTEMRA at home, you or your caregiver should receive training on the right way to prepare and inject ACTEMRA. Do not try to inject ACTEMRA until you have been shown the right way to give the injections by your healthcare provider.
- For PJIA or SJIA, you may self-inject with the Prefilled Syringe or prefilled ACTPen® autoinjector, or your caregiver can give you ACTEMRA, if both your healthcare provider and parent/legal guardian find it appropriate.
- Your healthcare provider will tell you how much ACTEMRA to use and when to use it.

What are the possible side effects with ACTEMRA?

ACTEMRA can cause serious side effects, including:

- See **"What is the most important information I should know about ACTEMRA?"**
- **Hepatitis B infection** in people who carry the virus in their blood. If you are a carrier of the hepatitis B virus (a virus that affects the liver), the virus may become active while you use ACTEMRA. Your healthcare provider may

do blood tests before you start treatment with ACTEMRA and while you are using ACTEMRA. Tell your healthcare provider if you have any of the following symptoms of a possible hepatitis B infection:

- feel very tired
- vomiting
- chills
- dark urine
- skin or eyes look yellow
- clay-colored bowel movements
- stomach discomfort
- skin rash
- little or no appetite
- fevers
- muscle aches

- **Serious Allergic Reactions.** Serious allergic reactions, including death, can happen with ACTEMRA. These reactions can happen with any infusion or injection of ACTEMRA, even if they did not occur with an earlier infusion or injection. Stop taking ACTEMRA, contact your healthcare provider, and get emergency help right away if you have any of the following signs of a serious allergic reaction:
  - swelling of your face, lips, mouth, or tongue
  - trouble breathing
  - wheezing
  - severe itching
  - skin rash, hives, redness, or swelling outside of the injection site area
  - dizziness or fainting
  - fast heartbeat or pounding in your chest (tachycardia)
  - sweating
- **Nervous system problems**. While rare, Multiple Sclerosis has been diagnosed in people who take ACTEMRA. It is not known what effect ACTEMRA may have on some nervous system disorders.

The most common side effects of ACTEMRA include:

- upper respiratory tract infections (common cold, sinus infections)
- headache
- increased blood pressure (hypertension)
- injection site reactions

Tell your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of ACTEMRA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also report side effects to Genentech at 1-888-835-2555.

General information about the safe and effective use of ACTEMRA.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not give ACTEMRA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about ACTEMRA that is written for health professionals.

What are the ingredients in ACTEMRA?

Active ingredient: tocilizumab.
Inactive ingredients of Intravenous ACTEMRA: disodium phosphate dodecahydrate/sodium dihydrogen phosphate dihydrate buffered solution, polysorbate 80, sucrose, and water for Injection.
Inactive ingredients of Subcutaneous ACTEMRA: L-arginine hydrochloride, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, and water for Injection.

Genentech, Inc., A Member of the Roche Group, 1 DNA Way, South San Francisco, CA 94080-4990 U.S. License No.: 1048

For more information, go to www.ACTEMRA.com or call 1-800-ACTEMRA.

Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 09/2024

Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Injection, For Subcutaneous Use
Single-dose Prefilled Syringe

Read and follow the Instructions for Use that come with your ACTEMRA prefilled syringe before you start using it and each time you get a prescription refill. Before you use ACTEMRA prefilled syringe for the first time, make sure your healthcare provider shows you the right way to use it.

- **Do not remove the needle cap until you are ready to inject ACTEMRA.**
- **Do not try to take apart the syringe at any time.**
- **Do not reuse the same syringe.**

Parts of your ACTEMRA Prefilled Syringe **(See Figure A).**

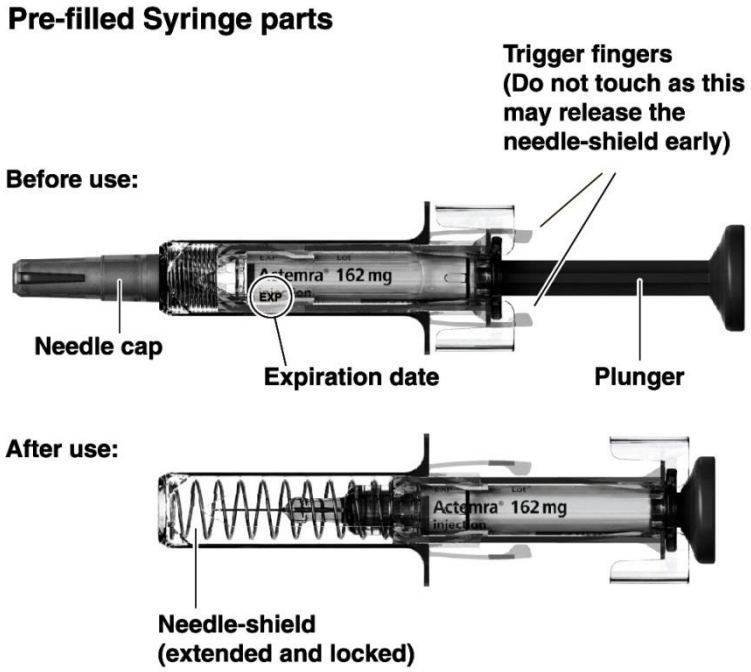


Figure A

Supplies needed for your ACTEMRA Prefilled Syringe Injection (See Figure B):

- ACTEMRA prefilled syringe
- alcohol pad
- sterile cotton ball or gauze
- puncture-resistant container or sharps container for safe disposal of needle cap and used syringe **(See Step 4 "Dispose of the syringe")**

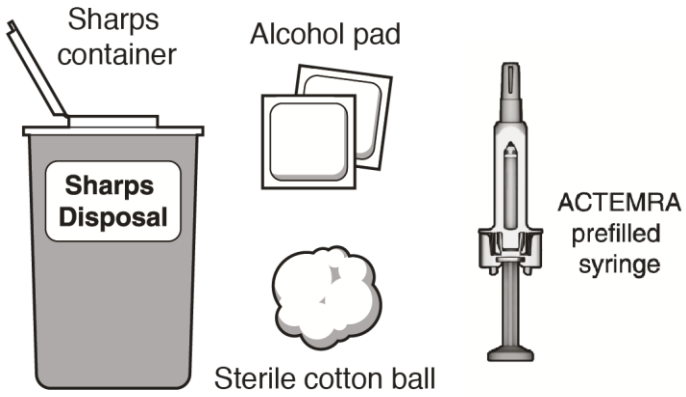


Figure B

Step 1. Preparing for an ACTEMRA Injection

Find a comfortable space with a clean, flat, working surface.

- Take the box containing the syringe out of the refrigerator and open the box. **Do not** touch the trigger fingers on the syringe as this may damage the syringe.
- Remove 1 single-use ACTEMRA prefilled syringe from the box and let it warm up for 30 minutes to allow it to reach room temperature. If the syringe does not reach room temperature, this could cause your injection to feel uncomfortable and make it difficult to push the plunger in.
- **Do not** speed up the warming process in any way, such as using the microwave or placing the syringe in warm water.
- Check the expiration date on the ACTEMRA prefilled syringe **(See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed safely dispose of the syringe in a sharps container and get a new one.

Do not remove the needle cap while allowing your ACTEMRA prefilled syringe to reach room temperature.

- Keep your unused syringes in the original carton and keep in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** freeze.
- Once removed from the refrigerator, your prefilled syringe can be stored up to 2 weeks at or below 86°F (30°C). Your prefilled syringe must always be kept in the original carton in order to protect from light and moisture. Hold your ACTEMRA prefilled syringe with the covered needle pointing down **(See Figure C).**

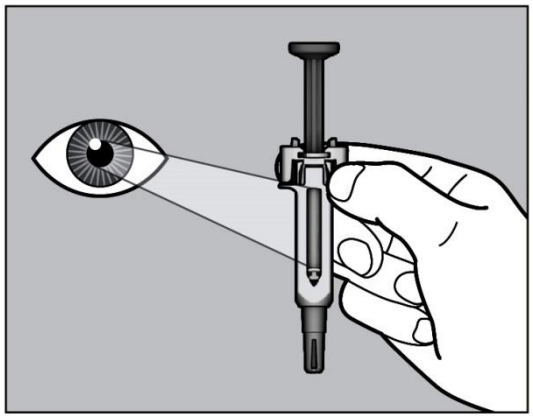


Figure C

- Check the liquid in the ACTEMRA prefilled syringe. It should be clear and colorless to pale yellow. Do not inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the syringe in a sharps container and get a new one.
- Wash your hands well with soap and water.

Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh and your abdomen except for the 2-inch area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. Do not attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1-inch from the last area you injected.
- Do not inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

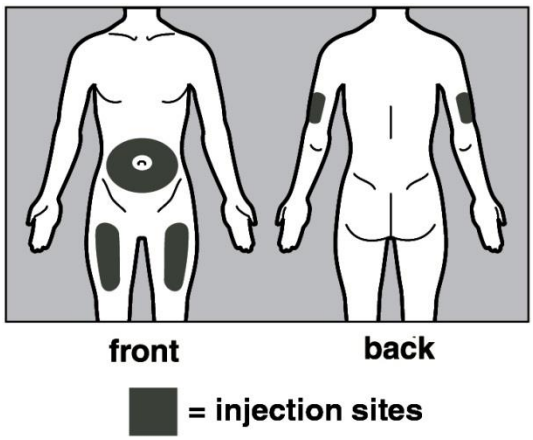


Figure D

Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

Step 3. Inject ACTEMRA

- Hold the ACTEMRA prefilled syringe with 1 hand and pull the needle cap straight off with your other hand **(See Figure E). Do not** hold the plunger while you remove the needle cap. If you cannot remove the needle cap you should ask a caregiver for help or contact your healthcare provider.

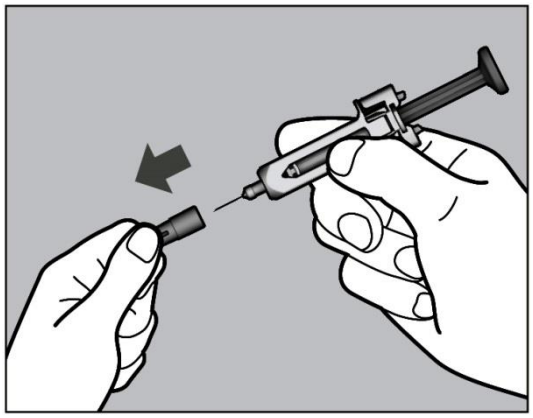


Figure E

- Throw away the needle cap in a sharps container.
- There may be a small air bubble in the ACTEMRA prefilled syringe. You do not need to remove it.
- You may see a drop of liquid at the end of the needle. This is normal and will not affect your dose.
- **Do not** touch the needle or let it touch any surfaces.
- **Do not** use the prefilled syringe if it is dropped.
- If it is not used within 5 minutes of needle cap removal, the syringe should be disposed of in the puncture resistant container or sharps container and a new syringe should be used.
- Never reattach the needle cap after removal.
- Hold the ACTEMRA prefilled syringe in 1 hand between the thumb and index finger **(See Figure F).**

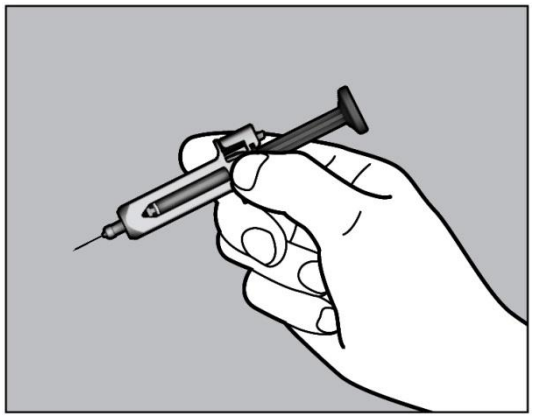


Figure F

- **Do not** pull back on the plunger of the syringe.
- Use your other hand and gently pinch the area of skin you cleaned. Hold the pinched skin firmly. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.
- **Do not** hold or push on the plunger while inserting the needle into the skin.
- Use a quick, dart-like motion to insert the needle all the way into the pinched skin at an angle between 45° to 90° **(See Figure G).** It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.

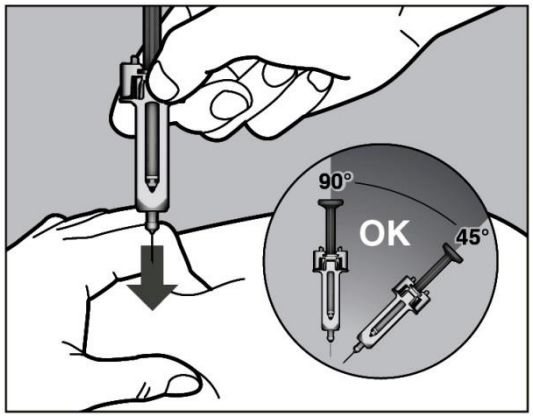


Figure G

- Keep the syringe in position and let go of the pinch of skin.
- Slowly inject all of the medicine by gently pushing the plunger all the way down **(See Figure H).** You must press the plunger all the way down to get the full dose of medicine and to ensure the trigger fingers are completely pushed to the side. If the plunger is not fully depressed the needle shield will not extend to cover the needle when it is removed. If the needle is not covered, carefully place the syringe into the puncture resistant container to avoid injury with the needle.

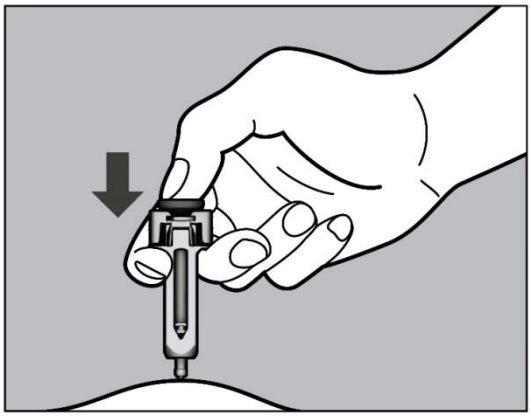


Figure H

- After the plunger is pushed all the way down, keep pressing down on the plunger to be sure all of the medicine is injected before taking the needle out of the skin.
- Keep pressing down on the plunger while you take the needle out of the skin at the same angle as inserted **(See Figure I).**

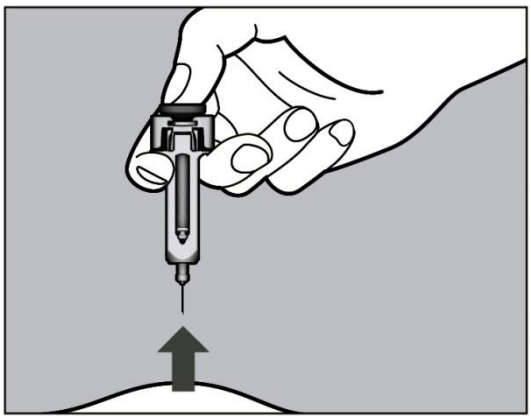


Figure I

- After the needle is removed completely from the skin, release the plunger, allowing the needle-shield to protect the needle **(See Figure J).**

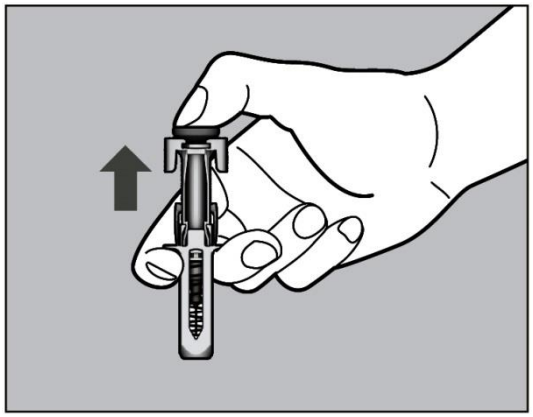


Figure J

After the Injection

- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the syringe

- The ACTEMRA prefilled syringe should not be reused.
- Put the used syringe into your puncture resistant container **(See "How do I throw away used syringes?")**
- **Do not** put the needle cap back on the needle.
- **If your injection is given by another person, this person must also be careful when removing the syringe and disposing of the syringe to prevent accidental needle stick injury and passing infection.**

How do I throw away used syringes?

- Put your used needles and syringes including ACTEMRA in a FDA-cleared sharps disposal container right away after use **(See Figure K). Do not throw away (dispose of) loose needles and syringes in your household trash.**

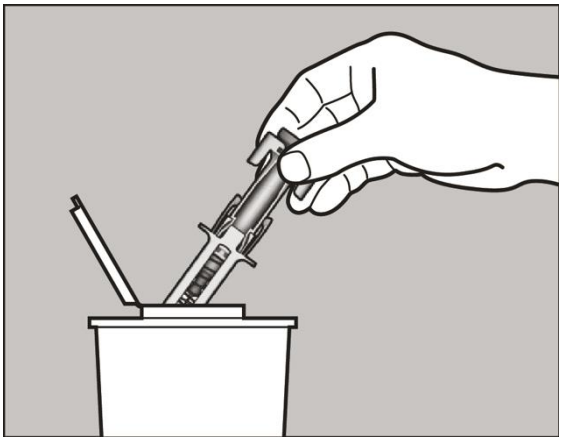


Figure K

- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic

- can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
- upright stable during use
- leak-resistant
- properly labeled to warn of hazardous waste inside the container
    - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should throw away used needles and syringes. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
    - Do not dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. Do not recycle your used sharps disposal container.

- **Keep ACTEMRA prefilled syringes and the disposal container out of the reach of children.**

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have questions or concerns about your ACTEMRA prefilled syringe, please contact your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.
Medication Guide Revised: 09/2024

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Instructions for Use
ACTEMRA® (AC-TEM-RA)
(tocilizumab)
Injection, For Subcutaneous Use
Single-dose Prefilled ACTPen® (AKT-PEN) Autoinjector

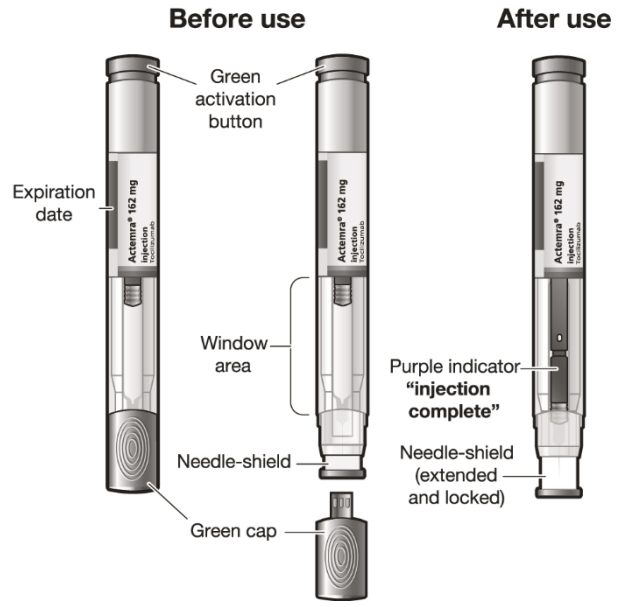
Read and follow the Instructions for Use that come with your ACTEMRA ACTPen autoinjector before you start using it and each time you get a prescription refill. Before you use the ACTEMRA ACTPen autoinjector for the first time, make sure your healthcare provider shows you the right way to use it.

Important: Keep your unused Autoinjectors in the original carton and keep in the refrigerator at 36˚F to 46˚F (2˚C to 8˚C). **Do not** freeze. Once removed from the refrigerator, your Autoinjector can be stored up to 2 weeks at or below 86°F (30°C). Your Autoinjector must always be kept in the original carton in order to protect from light and moisture.

- **Do not** remove the Autoinjector cap until you are ready to inject ACTEMRA.
- **Do not** try to take apart the Autoinjector at any time.
- **Do not** reuse the same Autoinjector.
- **Do not** use the Autoinjector through clothing.
- **Do not** leave the Autoinjector unattended.
- **Do not** use the Autoinjector if it appears to be damaged or if you have accidentally dropped the Autoinjector.
- Keep out of the reach of children.

Parts of your ACTEMRA ACTPen autoinjector **(See Figure A).**

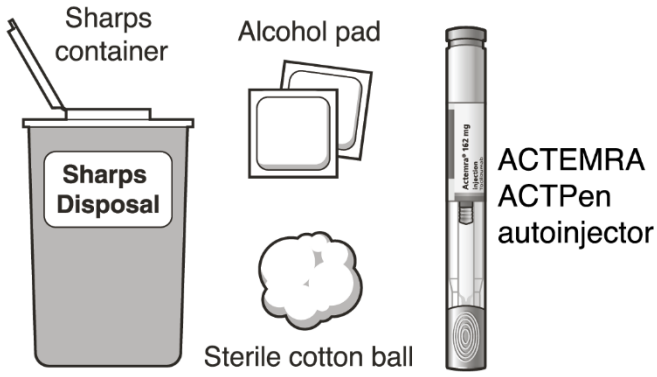
Figure A



Supplies needed for an injection using your ACTEMRA ACTPen autoinjector (See Figure B):

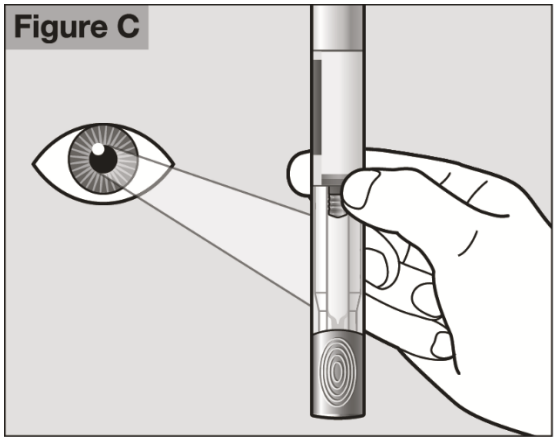
- 1 ACTEMRA ACTPen autoinjector
- 1 Alcohol pad
- 1 Sterile cotton ball or gauze
- 1 Puncture-resistant container or sharps container for safe disposal of Autoinjector cap and used Autoinjector **(See Step 4 "Dispose of the Autoinjector")**

Figure B



Step 1. Preparing for an ACTEMRA Injection
Find a comfortable space with a clean, flat, working surface.

- Take the box containing the Autoinjector out of the refrigerator.
- If you are opening the box for the first time, check to make sure that it is properly sealed. **Do not** use the Autoinjector if the box looks like it has already been opened.
- Check that the Autoinjector box is not damaged. **Do not** use ACTEMRA ACTPen autoinjector if the box looks damaged.
- **Check the expiration date on the Autoinjector box**. **Do not** use the Autoinjector if the expiration date has passed because it may not be safe to use.
- Open the box, and remove 1 single-use ACTEMRA ACTPen autoinjector from the box.
- Return any remaining autoinjectors in the box to the refrigerator.
- **Check the expiration date on the ACTEMRA ACTPen autoinjector (See Figure A). Do not** use it if the expiration date has passed because it may not be safe to use. If the expiration date has passed, safely dispose of the Autoinjector in a sharps container and get a new one.
- **Check the Autoinjector to make sure it is not damaged. Do not** use the Autoinjector if it appears to be damaged or if you have accidentally dropped the Autoinjector.
- Place the Autoinjector on a clean, flat surface and let the Autoinjector warm up for 45 minutes to allow it to reach room temperature. If the Autoinjector does not reach room temperature, this could cause your injection to feel uncomfortable and it could take longer to inject.
    - **Do not** speed up the warming process in any way, such as using the microwave or placing the Autoinjector in warm water.
    - **Do not** leave the Autoinjector to warm up in direct sunlight.
    - **Do not** remove the green cap while allowing your ACTEMRA ACTPen autoinjector to reach room temperature.
- Hold your ACTEMRA ACTPen autoinjector with the green cap pointing down **(See Figure C).**
- Look in the clear Window area. Check the liquid in the ACTEMRA ACTPen autoinjector **(See Figure C)**. It should be clear and colorless to pale yellow. **Do not** inject ACTEMRA if the liquid is cloudy, discolored, or has lumps or particles in it because it may not be safe to use. Safely dispose of the Autoinjector in a sharps container and get a new one.



- Wash your hands well with soap and water.

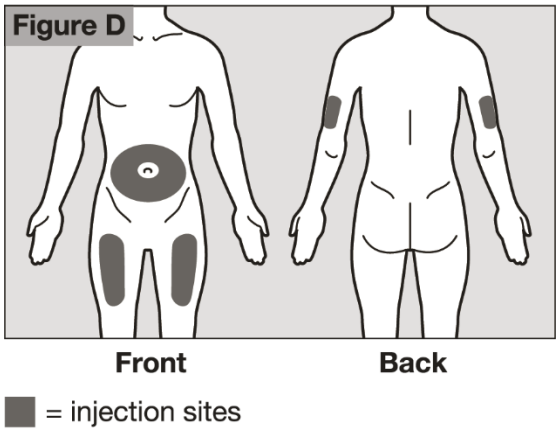
Step 2. Choose and Prepare an Injection Site

Choose an Injection Site

- The front of your thigh or your abdomen except for the 2-inch (5cm) area around your navel are the recommended injection sites **(See Figure D).**
- The outer area of the upper arms may also be used only if the injection is being given by a caregiver. **Do not** attempt to use the upper arm area by yourself **(See Figure D).**

Rotate Injection Site

- Choose a different injection site for each new injection at least 1 inch (2.5cm) from the last area you injected.
- **Do not** inject into moles, scars, bruises, or areas where the skin is tender, red, hard or not intact.

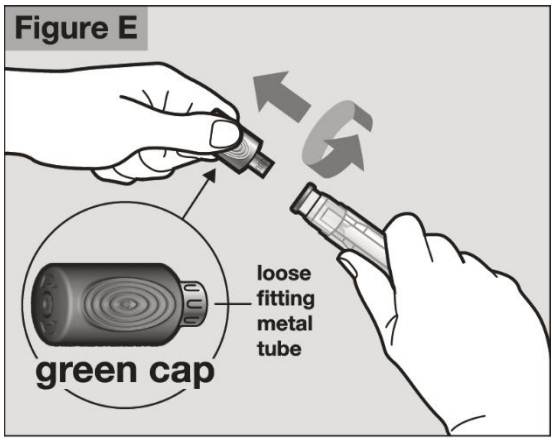


Prepare the Injection Site

- Wipe the injection site with an alcohol pad in a circular motion and let it air dry to reduce the chance of getting an infection. **Do not** touch the injection site again before giving the injection.
- **Do not** fan or blow on the clean area.

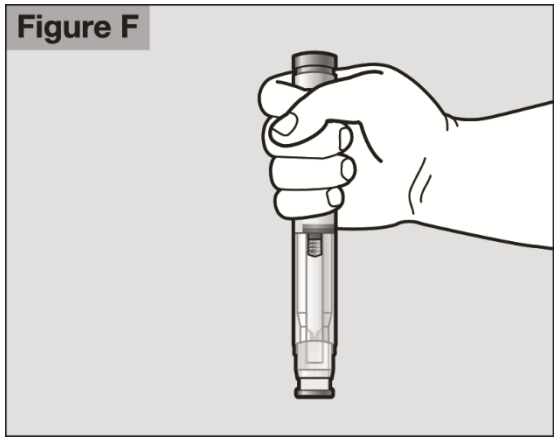
Step 3. Inject ACTEMRA

- Hold the ACTEMRA ACTPen autoinjector firmly with one hand. Twist and pull off the green cap with the other hand **(See Figure E).** The green cap contains a loose fitting metal tube.
- If you cannot remove the green cap you should ask a caregiver for help or contact your healthcare provider.

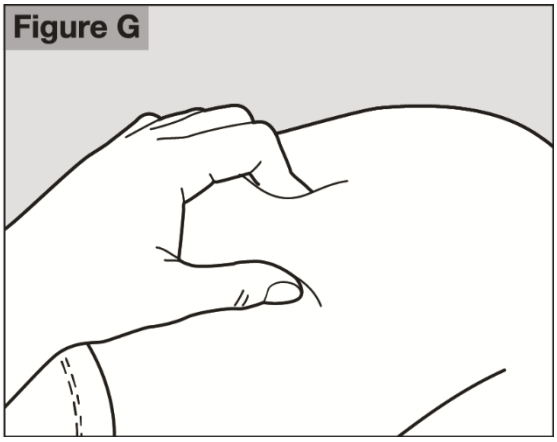


Important: Do not touch the needle shield which is located at the tip of the Autoinjector below the Window area (See Figure A), to avoid accidental needle stick injury.

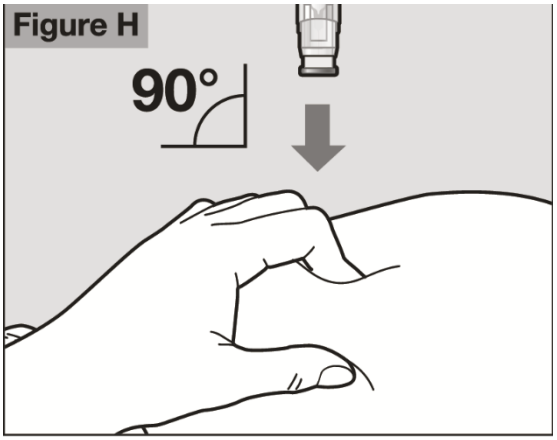
- Throw away the green cap in a sharps container.
- After you remove the green cap, the Autoinjector is ready for use. **If the Autoinjector is not used within 3 minutes of the cap removal, the Autoinjector should be disposed of in the sharps container and a new Autoinjector should be used.**
- Never reattach the green cap after removal.
- Hold the Autoinjector comfortably in 1 hand by the upper part, so that you can see the Window area of the Autoinjector **(See Figure F)**.



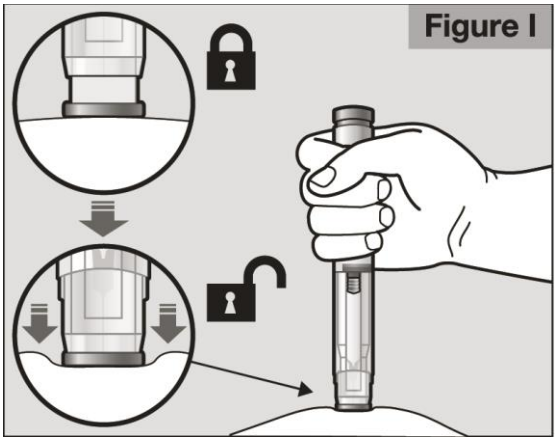
- Use your other hand to gently pinch the area of skin you cleaned, to prepare a firm injection site **(See Figure G)**. The Autoinjector requires a firm injection site to properly activate. Pinching the skin is important to make sure that you inject under the skin (into fatty tissue) but not any deeper (into muscle). Injection into muscle could cause the injection to feel uncomfortable.



- **Do not** press the green Activation button yet.
  Place the needle-shield of the Autoinjector against your pinched skin at a 90° angle **(See Figure H)**.
- It is important to use the correct angle to make sure the medicine is delivered under the skin (into fatty tissue), or the injection could be painful and the medicine may not work.
- **Continue to gently pinch throughout the injection procedure**.

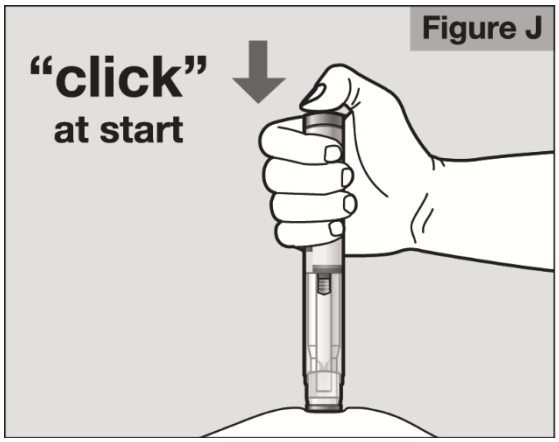


- To use the Autoinjector, you first have to unlock the green Activation button. To unlock it, press the Autoinjector firmly against your pinched skin until the needle-shield is completely pushed in **(See Figure I)**.

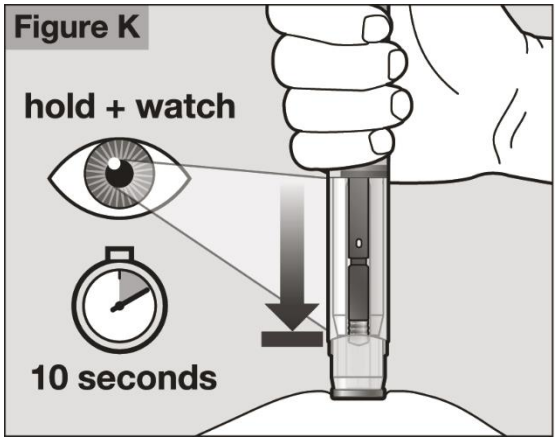


- Continue to keep the needle-shield pushed in. If you do not keep the needle-shield completely pushed against the skin, the green Activation button will not work. Continue to pinch the skin while you keep the Autoinjector in place.

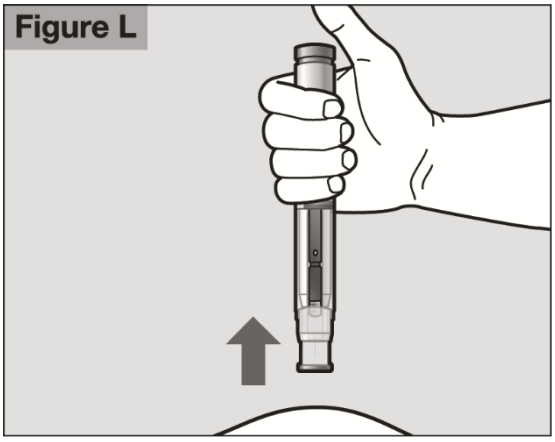
- Press the green Activation button to start the injection. A “click” sound indicates the **start** of the injection. Keep the green button pressed in and continue holding the Autoinjector pressed firmly against your skin **(See Figure J)**. If you cannot start the injection you should ask for help from a caregiver or contact your healthcare provider.



- The purple indicator will move along the Window area during the injection **(See Figure K)**.
- **Watch the purple indicator until it stops moving** to be sure the full dose of medicine is injected. This may take up to **10 seconds**.



- You may hear a second “click” during the injection but you should continue to hold the Autoinjector firmly against your skin until the purple indicator stops moving.
- When the purple indicator has stopped moving, release the green button. Lift the Autoinjector straight off of the injection site at a 90° angle to remove the needle from the skin. The needle-shield will then move out and lock into place covering the needle **(See Figure L)**.



- Check the Window area to see that it is filled with the purple indicator **(See Figure L).**
- If the Window area is not filled by the purple indicator then:
  - The needle-shield may not have locked. **Do not** touch the needle-shield of the Autoinjector, because you may stick yourself with the needle. If the needle is not covered, carefully place the Autoinjector into the sharps container to avoid any injury with the needle.
  - You may not have received your full dose of ACTEMRA. **Do not** try to re-use the Autoinjector. **Do not** repeat the injection with another Autoinjector. Call your healthcare provider for help.

After the Injection

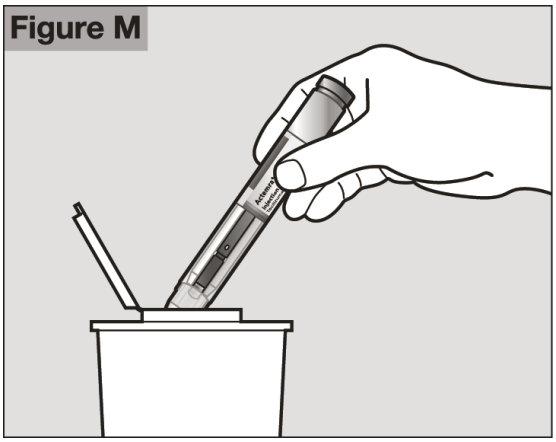
- There may be a little bleeding at the injection site. You can press a cotton ball or gauze over the injection site.
- **Do not** rub the injection site.
- If needed, you may cover the injection site with a small bandage.

Step 4. Dispose of the Autoinjector

- The ACTEMRA ACTPen autoinjector should not be reused.
- Put the used Autoinjector into your sharps container **(See "How do I dispose of used Autoinjectors?").**
- **Do not** put the cap back on the Autoinjector.
- **If your injection is given by another person, this person must also be careful when removing the Autoinjector and disposing of it to prevent accidental needle stick injury and passing infection.**

How do I dispose of used Autoinjectors?

- Put your used ACTEMRA ACTPen autoinjector and green cap in a FDA-cleared sharps disposal container right away after use **(See Figure M)**.
- **Do not** throw away (dispose of) the Autoinjector and the green cap in your household trash.



- If you do not have a FDA-cleared sharps disposal container, you may use a household container that is:
    - made of a heavy-duty plastic
    - can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out
    - upright stable during use
    - leak-resistant
    - properly labeled to warn of hazardous waste inside the container
        - When your sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of your sharps disposal container. There may be state or local laws about how you should dispose of used Autoinjectors. For more information about the safe sharps disposal, and for specific information about sharps disposal in the state that you live in, go to the FDA's website at: http://www.fda.gov/safesharpsdisposal.
        - **Do not** dispose of your used sharps disposal container in your household trash unless your community guidelines permit this. **Do not** recycle your used sharps disposal container.

Keep the ACTEMRA ACTPen autoinjector and disposal container out of the reach of children.

Record your Injection

- Write the date, time, and specific part of your body where you injected yourself. It may also be helpful to write any questions or concerns about the injection so you can ask your healthcare provider.

If you have any questions or concerns about your ACTEMRA ACTPen autoinjector, talk to your healthcare provider familiar with ACTEMRA or call 1-800-ACTEMRA.

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Medication Guide Revised: 09/2024

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