治療類風濕關節炎的RITUXAN資源手冊

考慮使用Rituxan並開始治療的完整指南

Rituxan只需要一個療程（2次輸液）便可改善您的症狀，並保持6個月。

什麼是 RITUXAN? Rituxan是一種處方藥，在至少在使用另一種名為腫瘤壞死因數(TNF)的拮抗劑進行治療並且沒有效果之後，與另一種名為甲氨蝶呤的藥品共同使用，以減輕成人中度至重度活動性類風濕關節炎(RA)的病徵或症狀。

有嚴重感染的人不應當使用Rituxan。

Rituxan®
Rituximab
現在開始治療，效果可維持6個月

重要安全資訊: **Rituxan伴隨有輸液反應、腫瘤溶解綜合症、嚴重皮膚反應以及嚴重感染，包括進行性多灶性白質腦病(PML)**。如果需要更多的資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

歡迎使用 Rituxan

我們很高興與您分享關於Rituxan®（莫須瘤注射劑）的資訊，它是一種獨特的治療方法，幫助很多患者長期改善類風濕關節炎症狀。 請記住，Rituxan的藥理與其他類風濕關節炎治療方法不同。 即使其他治療方法對您的效果不明顯，Rituxan可能仍然對您有效。

請閱讀下列資訊，請與您的醫師討論Rituxan。 這可能是重要的一步，使您不再錯過重要的事情。

考慮使用 Rituxan的指南

為什麼Rituxan或許適合我?

- 一個療程（2次輸液）即可改善類風濕關節炎症狀，並保持6個月（第8頁）
- 輸液時間安排很方便： 一年只需要輸液4次（第10頁）
- 延緩類風濕關節的損害，有助於保護關節（第16頁）
- 可以在其他治療方法效果不夠好時對您有好處（第18頁）

在開始治療時，我應當瞭解哪些情況?

- 關於輸液的資訊（第23頁）
- 第一次Rituxan輸液時可能發生的情況（第24頁）
- 您的第二次輸液以及以後的每次輸液（第27頁）

我應當將哪些事情告訴我的醫師?

- 醫療服務提供者/患者討論指南（第31頁）
- 重要的安全資訊，包括可能的副作用（第40頁）
- 幫助您入門的Genentech Rheumatology Access Solutions®表格（第44頁）
- 財務援助資源（第45頁）

在考慮任何治療方法時，與您的醫療服務提供者權衡潛在風險與好處很重要。 要瞭解與Rituxan有關的風全，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

本手冊刊載的使用Rituxan®（莫須瘤注射劑）的人是RISE™ Ambassador計畫的會員，該計畫由Genentech USA, Inc.和Biogen Idec Inc.贊助。 Genentech為Ambassadors介紹其故事所花費的時間和開支向其提供報酬。

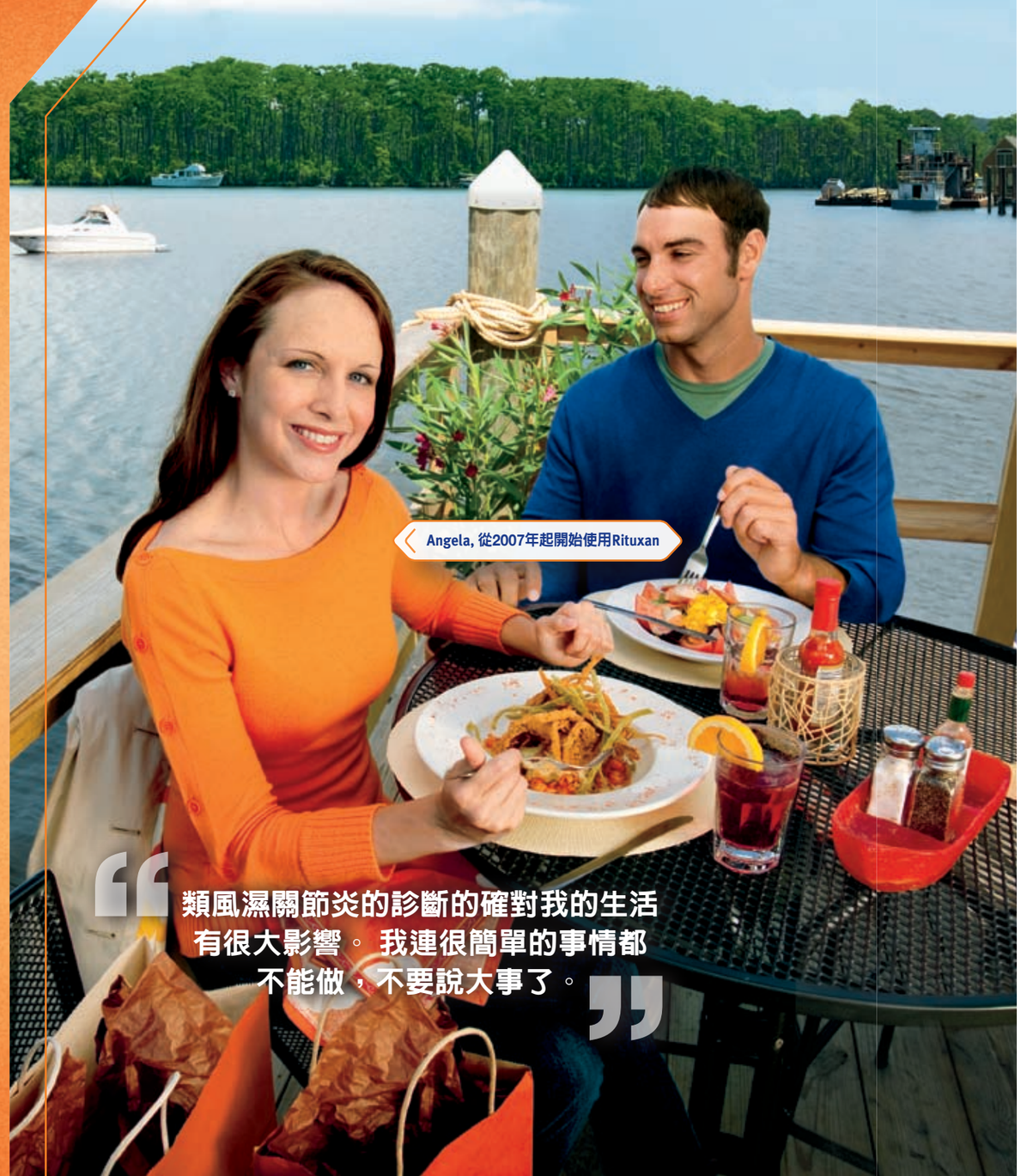
為什麼選擇 Rituxan?

本節內容：

- 一個療程的Rituxan治療（2次輸液）可減輕症狀6個月
- 一年只需要2個療程（4次輸液）即有助於控制您的類風濕關節炎
- Rituxan可延緩類風濕關節炎的損害，有助於保護您的關節
- 為什麼其他治療方法對您沒有作用，Rituxan可能對您有作用

重要安全資訊

與您的醫師討論您的所有醫療狀況、您正在服用的所有藥物、您正在接種或打算接種的任何疫苗。 如果您已經懷孕、打算懷孕或正在哺乳，請告訴您的醫師。



錯過與朋友相聚的時光?
NO WAY, RA.

如果您有中度至重度活動性類風濕關節炎(RA)，您當然明白自己所面臨的挑戰，也知道自己每天所想的問題。

您是否錯過與家人團聚的時光？ 您是否只能閒居在家，不能去上班？ 您是否錯過與朋友相聚的時光？

Rituxan®（莫須瘤注射劑）治療可改善您的類風濕關節炎症狀，保護您的關節，即使其他治療方法對你無效也不例外。

因此請與您的醫師討論Rituxan。 這可能是重要的一步，使您不再錯過重要的事情。

重要安全資訊

請記住，每個人對Rituxan的反應不盡相同。 有些人在Rituxan治療期間或之後可能出現副作用。

如果需要關於Rituxan的更多的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

我預期多久能看到 Rituxan的效果? 效果能維持多久?

Rituxan®（莫須瘤注射劑）是唯一只需要一個療程（2次輸液，間隔兩個星期）便能改善症狀達6個月的類風濕關節炎治療方法。

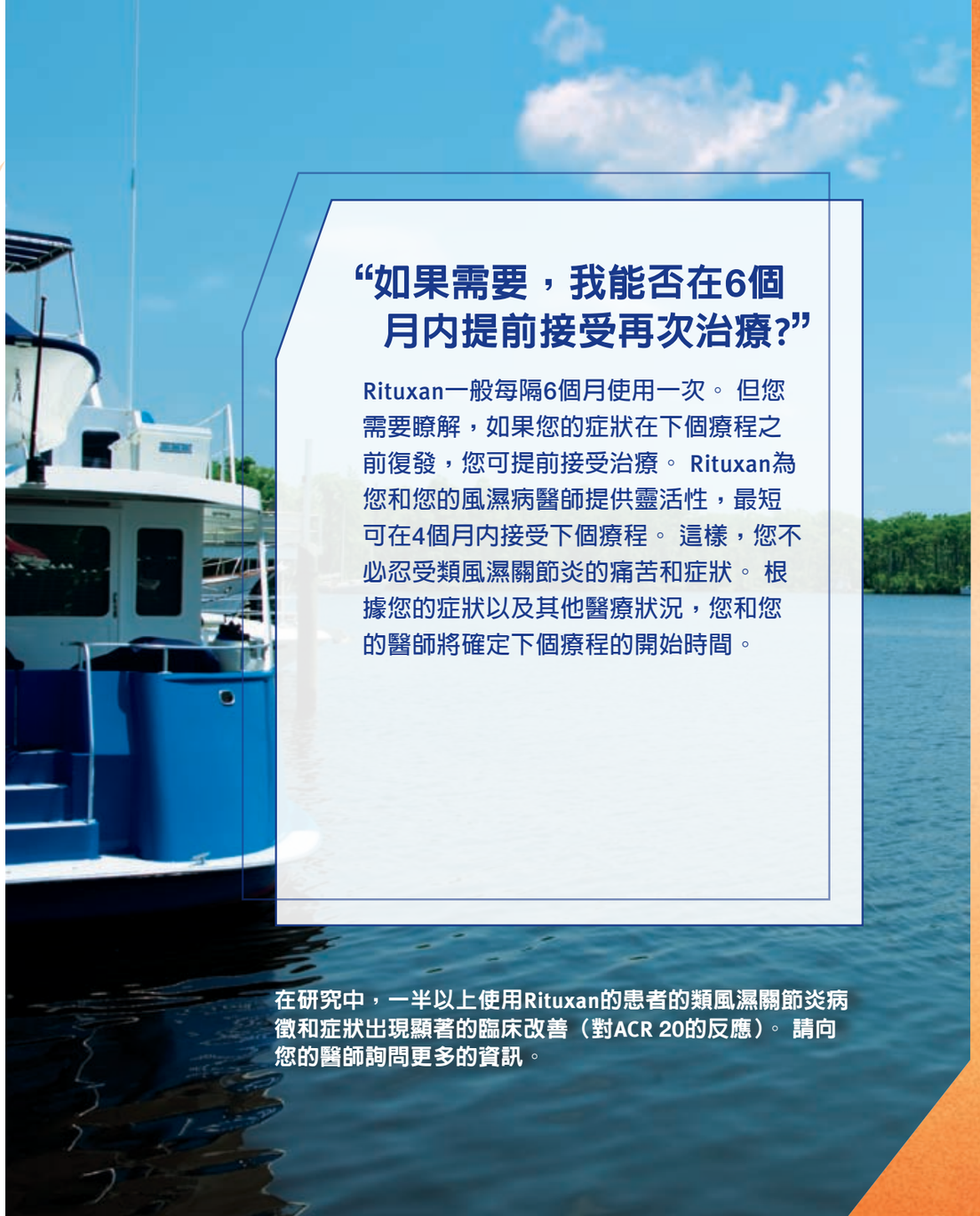
在臨床試驗中，有些使用Rituxan的患者在第一個療程之後2個星期內便可改善症狀。

這些患者在輸液之前還曾接受甲氨蝶呤和甲基潑尼松治療，這些藥物可能在2個星期內影響療效。 但是，與未使用Rituxan的患者相比，使用Rituxan的患者8個星期後的症狀改善更為明顯。很多患者的症狀改善持續達6個月。

療效可能持續超過6個月。 研究顯示，如果持續使用Rituxan，同樣的症狀改善可繼續保持6個月。

重要的副作用資訊

您應當瞭解，Rituxan可能增加您的感染風險。 如果出現持續的咳嗽、發燒、寒戰、鼻塞或任何類似流感的症狀，請告訴您的醫療服務提供者。



“如果需要，我能否在6個月內提前接受再次治療?”

Rituxan一般每隔6個月使用一次。 但您需要瞭解，如果您的症狀在下個療程之前復發，您可提前接受治療。 Rituxan為您和您的風濕病醫師提供靈活性，最短可在4個月內接受下個療程。 這樣，您不必忍受類風濕關節炎的痛苦和症狀。 根據您的症狀以及其他醫療狀況，您和您的醫師將確定下個療程的開始時間。

在研究中，一半以上使用Rituxan的患者的類風濕關節炎病徵和症狀出現顯著的臨床改善（對ACR 20的反應）。 請向您的醫師詢問更多的資訊。

我的治療頻率是什麼?

Rituxan®（莫須瘤注射劑）經過兩次輸液可減輕症狀達6個月，每次輸液間隔2個星期。 因此在一年內，您只需要4次輸液便可控制類風濕關節炎。

與其他類風濕關節炎的用藥時間表相比（見右圖），長期而言，Rituxan的用藥次數更少。

如果需要關於Rituxan的更多的重要安全資訊，包括可能的輸液反應，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

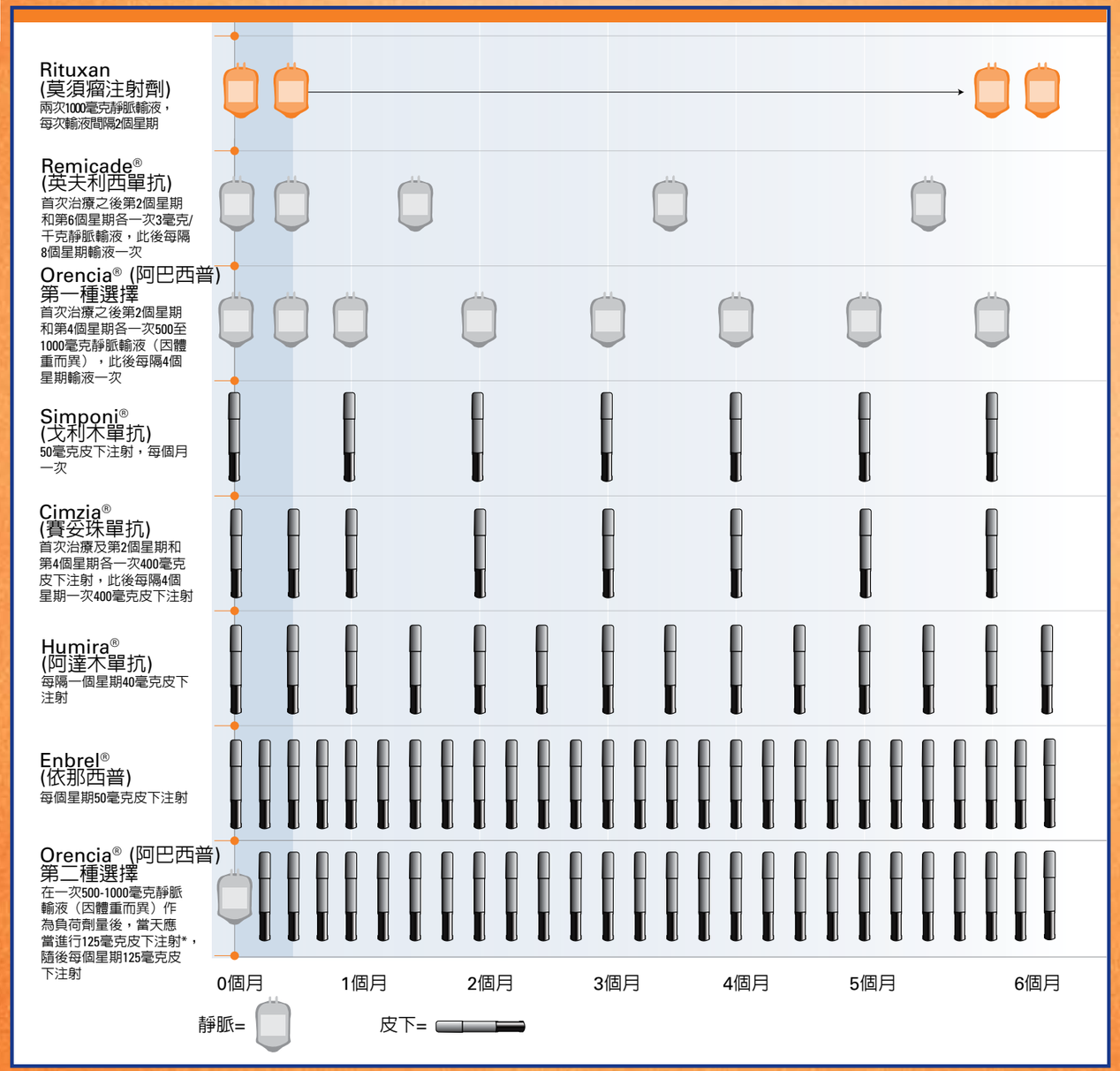
Rituxan可與甲氨蝶呤聯合使用，治療對一種或多種腫瘤壞死因數拮抗劑療法反應不夠大的中度至重度活動性類風濕關節炎成年患者。

我最喜歡Rituxan在輸液方面的靈活性。每6個月輸液一次較方便。

—Kathy, 從2006年起使用Rituxan

部分生物治療方法的用藥時間表

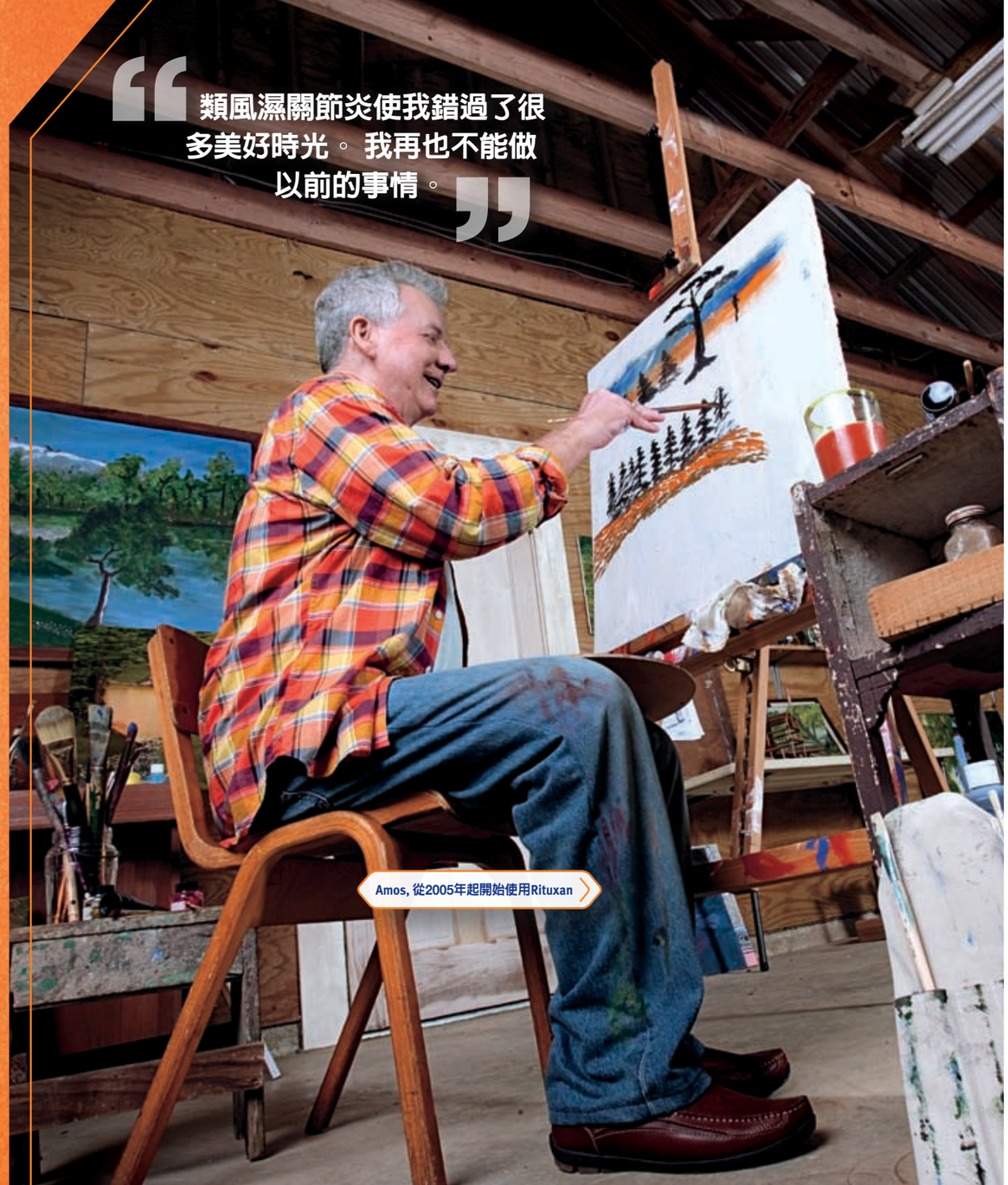
不能根據不同治療方法的用藥時間表的比較而得出關於安全或療效方面的比較結論。



請檢視相關處方資訊，瞭解每種產品的用藥事項。 所有商標均是其各自所有人的財產。

數據摘自Rituxan、Remicade、Orencia、Simponi、Cimzia、Humira和Enbrel的完整處方資訊。

*不能接受靜脈輸液的患者可每個星期進行皮下注射，而不必使用靜脈輸液負荷劑量。



錯過美好時光? NO WAY, RA.

Amos於1996年被診斷出類風濕關節炎。隨著病情發展，他身體的很多關節都受到影響。「它讓我的膝蓋受到損害。 我的兩個髖關節都換了。」

2005年，Amos參加一項Rituxan®（莫須瘤注射劑）的臨床試驗。「在我開始使用Rituxan之後，情況開始好轉，」Amos說。「最終，我的症狀得到改善。我現在可握拳了。」

請注意，Rituxan對您的治療效果可能與Amos不同。常見的副作用包括感染和輸液反應。 如果需要關於Rituxan的更多的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

對Amos而言，現在他已經把繪畫當成了自己的愛好。他喜歡與妻子一起散步和購物。 有了Rituxan，Amos找到了一種方法，不再錯過對他最重要的事情。

“我現在能和妻子一起做事情了。我們一起購物，我還學會了繪畫。”

請注意，您對Rituxan®（莫須瘤注射劑）的反應可能不同。如果需要關於Rituxan的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

Rituxan如何保護我的關節?

除了能將症狀減輕6個月之外，Rituxan®（莫須瘤注射劑）還可延緩類風濕關節炎的損害，保護您的關節。

類風濕關節炎對您身體關節的侵害可能導致它們感覺僵硬、疼痛和腫大。 類風濕關節炎還會隨時間削弱周圍的骨頭和軟骨。

即使您沒有類風濕關節炎的症狀，它仍然可能對您的關節造成永久損害。 請與您的醫師討論如何用Rituxan治療類風濕關節炎，保護您的關節。

研究顯示，如果您持續使用Rituxan，它能夠持續保護您的關節。

重要的副作用資訊

Rituxan的副作用包括乙型肝炎復發、心臟問題和感染。如果需要更多的資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

「為什麼在其他治療方法無效時，Rituxan或許對我有效?」

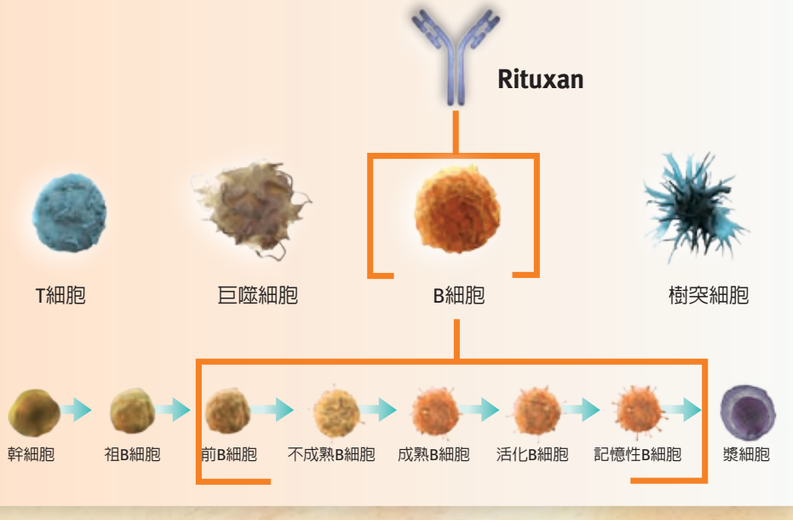
Rituxan®（莫須瘤注射劑）針對免疫系統中一種特定類型的細胞，而其他類風濕治療方法並不針對這種細胞。 由於藥理不同，當其他治療方法無效時，Rituxan可能對您有效。

雖然Rituxan與其他類風濕關節炎治療方法的藥理不同，但它經過了廣泛的測試和使用。事實上，十多年來，Rituxan已經用於治療超過1,000,000名各種症狀的患者。

請將您的所有醫療狀況告訴您的醫師，包括您是否計畫接種任何疫苗。 在使用Rituxan之後，您不應當接種活疫苗。

Rituxan針對免疫系統中的特定細胞，以治療類風濕關節炎。

與其他治療方法不同，Rituxan有選擇性地針對B細胞，我們相信這種細胞在免疫系統對關節的侵害中起到了重要作用。



Rituxan能夠限制這種侵害，從而限制類風濕關節炎的疼痛、症狀和關節損害。

您的 Rituxan治療

本節內容：

- 瞭解關於輸液的重要事實
- 瞭解第一個療程（2次輸液）以及後來各療程的預期情況

如果需要關於Rituxan®（莫須瘤注射劑）的更多的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

關於輸液，我應當瞭解哪些情況？

Rituxan®（莫須瘤注射劑）用輸液方式使用。 如果您不熟悉輸液，則您應當瞭解下面這些事情：

- 輸液是一種用於治療各種症狀的方式。
- 它們需要的時間可能比其他治療方式長，但就治療類風濕關節炎而言，您通常不需要輸那麼多次。
- 與其他治療方式不同，輸液由經過訓練醫療專家來完成，他們將幫助您控制輸液過程，並監控副作用。
- Rituxan可能發生輸液反應，包括發燒、寒戰和發抖、發癢以及咳嗽。在研究中，大多數均為輕度可控的副作用，嚴重副作用不到1%。

如果需要關於Rituxan的更多的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

在第一次Rituxan輸液時，我預期會發生什麼情況?

- 您的醫師診所將安排預約，為您進行第一個療程的2次Rituxan®（莫須瘤注射劑）輸液，輸液可在您的醫師診所、輸液中心或醫院完成。
- 每次輸液可能需要4至6個小時，因此請做好相應的計畫。請帶上一些幫助您打發時間的東西，例如書籍或音樂。
- 在輸液之前，請閱讀《Rituxan藥品說明書》，並與您的醫療服務提供者討論。
- 在每次輸液之前，您可能需要使用其他藥物，以降低副作用的風險。 如果您在治療期間發生任何不適，請立即叫醫護人員處理。
- 如果發生輸液反應，它們通常在首次輸液後24小時內發生。 請參閱「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書，查看潛在反應的清單。

在第二次輸液時，我預期會發生什麼情況?

第二次輸液的時間可能比第一次略短，但也會持續幾個小時。 如果您第一次輸液沒有出現任何副作用，則第二次輸液可能很順利。 但您仍然需要留意輸液期間的感覺。

如果您在第一次輸液時發生副作用，請務必告訴您的醫師。

在第二次輸液之後，您可能開始看到症狀的改善，並且在下一個療程之前能夠持續6個月。

重要的副作用資訊

注射反應是Rituxan®（莫須瘤注射劑）的常見副作用。請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

請注意，您對Rituxan®（莫須瘤注射劑）的反應可能不同。如果需要關於Rituxan的更多的重要安全資訊，請參閱本手冊「與您的醫師商量」一節、隨附的完整處方資訊，以及隨附的藥品說明書。

與您的醫師討論Rituxan

本節內容：

- 與您的醫療服務提供者討論Rituxan®（莫須瘤注射劑）的談話指南。
- 幫助您瞭解Rituxan的安全資訊
- 如果您需要申請共付額和保險援助，Genentech Rheumatology Access Solutions®可提供一份表格幫助您開始申請。
- 財務援助資源

與您的醫師討論
Rituxan

無論您正在考慮使用Rituxan®（莫須瘤注射劑），或正在接受Rituxan治療，都可參照本節內容，與您的醫療服務提供者進行討論。 下面有若干建議，可幫助您充分利用本節內容。

- 在與您的醫師見面時，請帶上本《資源手冊》。
- 請閱讀本手冊其他章節中對您的討論有幫助的相關資訊。要瞭解Rituxan的安全資訊，包括可能的副作用，請參閱本節第42至44頁。 請務必與您的醫療服務提供者一起閱讀這些資訊，以及隨附的完整處方資訊和隨附的藥品說明書。
- 您可在隨附的「備註」一節記下討論過程中的重要資訊。

考慮使用 Rituxan

評估您目前的治療方法

請閱讀下列問題，並與您的醫療服務提供者討論，幫助確定Rituxan®（莫須瘤注射劑）是否適合您。

- 類風濕關節炎對您的日常活動有多大影響？ 您是否不能上班？您是否錯過家庭或社交活動？
- 儘管已經接受目前的治療，但您的類風濕關節炎最近的發作次數是否比以前更頻繁，或更為嚴重？
- 您的關節每天是否腫大和僵硬？
- 您是否將自己目前為了治療類風濕關節炎而服用的任何處方藥、非處方藥、維生素或草藥告訴您的醫師？ 哪一種藥物對您的類風濕關節炎有效？
- 您對目前的類風濕關節炎治療方法的方便性是否滿意？
- 您過去曾嘗試使用哪些藥物？其中是否有任何藥物對您的類風濕關節炎有效？

備註

Rituxan是否適合我?

請閱讀下列問題，並與您的醫療服務提供者討論。 您可利用右邊的部分記下筆記。

- Rituxan®（莫須瘤注射劑）與您曾使用的其他治療方法或可用的其他治療方法有什麼不同？（請參閱第11頁和第18頁瞭解更多的資訊。）
- 針對B細胞的療法如何工作？（見第19頁。）
- Rituxan治療的風險與好處是什麼？它們與您有什麼關係？（見第40至43頁。）
- Rituxan預期對您有什麼作用（例如症狀改善、您多久可看到改善以及可能的副作用）？（見第8頁以及第40至43頁。）

您還應當告訴您的醫療服務提供者下列內容：

- 您是否有任何持續不退或復發的感染症狀
- 您是否計畫做手術或接種任何疫苗
- 您是否有心臟或肺部問題
- 您是否正在哺乳、懷孕或打算懷孕
- 您是否有乙型肝炎或者是乙型肝炎病毒的攜帶者。 在Rituxan治療期間以及治療結束後幾個月內，您的醫師應當密切關注您的肝炎感染症狀。
- 您以前是否經歷過輸液反應

備註

開始治療

開始Rituxan輸液

請閱讀下列問題，並與您的醫療服務提供者討論。 您可利用右邊的部分記下筆記。（請參閱第26頁和第29頁瞭解關於輸液的更多資訊。）

- 您應當為輸液做哪些準備？
- 您應當如何跟蹤兩次Rituxan®（莫須瘤注射劑）治療之間健康狀況？
- 您的醫療服務提供者對於在輸液之前使用藥物有哪些說明，包括血壓藥、抗生素和疫苗？
- 您的醫療服務提供者對於跟蹤輸液期間或之後可能發生的副作用有哪些說明？

備註

瞭解Rituxan的安全資訊

在考慮任何治療方法時，瞭解潛在風險與好處，並與您的醫療服務提供者進行權衡很重要。 藥品說明書有關於治療方法的安全資訊，向您說明潛在風險。

與Rituxan®（莫須瘤注射劑）有關的風險包括某些可能很嚴重和危及生命的副作用，包括：

- 嚴重感染，包括進行性多灶性白質腦病(PML)
- 嚴重輸液反應
- 腫瘤溶解綜合症(TLS).
- 嚴重皮膚反應

需要注意的是，雖然這些都被視為是治療類風濕關節炎的風險，但有些副作用只發生在患有非霍奇金淋巴瘤(NHL)的人身上。

“我認為始終閱讀您正在服用的藥物的藥品說明書很重要。”

—Kathy, 從2006年起使用Rituxan

嚴重感染，包括進行性多灶性白質

Rituxan可能增加感染機率。 在臨床研究中，2%使用Rituxan的患者發生嚴重感染。最常見的感染是肺炎。

使用Rituxan的患者曾發生一種名為進行性多灶性白質腦病（簡稱PML）的罕見腦感染。 儘管進行性多灶性白質腦病在使用Rituxan治療類風濕關節炎的患者身上很罕見，但仍然是一種風險，您應當與您的醫師討論這種風險。 進行性多灶性白質腦病沒有已知的治療、預防或治癒方法。 進行性多灶性白質腦病可能在Rituxan治療期間或治療結束之後發生。

嚴重輸液反應

輸液反應是Rituxan最常見的副作用，需要注意的是，在輸液期間或輸液之後24小內均可能發生嚴重、可能危及生命的反應。在研究中，不到1%的反應屬於嚴重反應。 您的醫療服務提供者應當在輸液之前為您提供藥物，以降低發生嚴重輸液反應的概率。 您應當與自己的醫師討論這些反應的風險。

腫瘤溶解綜合症和嚴重皮膚反應

使用Rituxan治療非霍奇金淋巴瘤的患者曾發生腫瘤溶解綜合症和嚴重皮膚反應，但類風濕關節炎患者未報告這類反應。 腫瘤溶解綜合症是一種可能導致腎衰竭並且需要透析治療的症狀。

如果您有任何問題，請告訴您的醫療服務提供者。他們可根據您的個人健康狀況提供具體的建議。

其他潛在嚴重副作用

- **乙型肝炎病毒(HBV)復發**。 如果您曾患過乙型肝炎，並且是乙型肝炎病毒的攜帶者，使用Rituxan可能導致病毒再次成為活動性感染。 乙型肝炎復發可能導致嚴重的肝臟問題，包括肝功能衰竭和死亡。 如果您有活動性乙型肝炎，您不應當使用Rituxan。 在您使用Rituxan期間和結束後幾個月內，您的醫生應當觀察您的乙型肝炎感染情況。

- **嚴重感染**。Rituxan治療期間和其後可能發生嚴重感染，並可能導致死亡。Rituxan可降低您的免疫系統抵抗感染的能力。使用Rituxan可能發生的嚴重感染類型包括細菌、真菌和病毒感染。使用Rituxan後，某些患者血液中的某些抗體水準長期較低（超過11個月）。這些抗體水準低的患者中，有些人會感染。 如果您有下列任何感染症狀，請立即聯絡您的醫師：
  - 發燒
  - 感冒症狀，例如流鼻涕或咽喉痛，並且持續不退
  - 流感症狀，例如咳嗽、疲倦和身體疼痛
  - 耳痛或頭痛
  - 小便疼痛
  - 口腔或咽喉出現白斑
  - 出現紅色、鮮豔、腫大或疼痛的傷口、擦痕或創口

- **心臟問題**。Rituxan可能導致胸痛和心律不齊，並且可能需要治療，或者您的醫師可能決定停止您的Rituxan治療。

- **腎臟問題**，特別是在您因為非霍奇金淋巴瘤而使用Rituxan時。您的醫師應當進行驗血，以檢查您的腎臟健康狀況。

- **胃髒問題和嚴重的腸道問題，有時可能導致死亡**。 如果您與化療藥物一起使用Rituxan，以治療非霍奇金淋巴瘤，則可能發生腸道問題，包括腸道阻塞或裂傷。 如果您在Rituxan治療期間有任何胃部疼痛，請立即告訴您的醫師。

- **血球數目低**。您的醫師可能在Rituxan治療期間進行驗血，以檢查您的血球數目。
  - **白血球**。白血球可抵抗細菌感染。白血球數目低可能導致您發生感染，並且可能是嚴重的感染。 請參閱前頁「嚴重感染」，查看感染症狀的清單。
  - **紅血球**。 紅血球為您的身體組織和器官輸送氧氣。
  - **血小板**。血小板是幫助血液凝結的血細胞。

常見副作用

Rituxan安全資訊還包括一些不太嚴重，但更為常見的副作用風險，例如伴隨發燒、寒戰、發抖、發癢、蕁麻疹、打噴嚏、咽喉疼痛或發緊、頭痛、噁心和咳嗽等症狀的嚴重輸液反應。 如果發生這些反應，它們通常在首次輸液後24小時內發生。

其他副作用包括關節疼痛、上呼吸道感染、血球數減少以及肺部問題。

儘管出現這些症狀可能不是Rituxan治療引起的，但如果您有任何此類症狀，應告訴您的醫療服務提供者，這很重要。

如果需要關於Rituxan的更多的更多資訊，請參閱隨附的完整處方資訊，以及隨附的藥品說明書。

“我的醫師和我對Rituxan的風險與好處談得很多。”

—Maria, 從2006年起使用Rituxan

「幫助您入門的表格」

如果您和您的醫師確定Rituxan®（莫須瘤注射劑）適合您，Genentech Rheumatology Access Solutions®計畫可在幫助您獲得必要的治療時發揮重要作用。

請與您的醫療服務提供者一起填寫下頁表格，立即申請Genentech Rheumatology Access Solutions。

關於資訊披露的患者授權與通知 (PAN)

電話：(866) 681-3261 **傳真：**(866) 681-3288 **GenentechAccessSolutions.com**

Genentech Access Solutions是Genentech為您提供的一項免費計畫。

我們致力於幫您支付Rituxan®（莫須瘤注射劑）或ACTEMRA®（托珠單抗）的費用。我們可透過很多不同的方法幫助您。我們為有醫療保健計畫以及沒有醫療保健計畫的人士提供援助。

如果您沒有醫療保健計畫，或者您的醫療保健計畫不支付Genentech產品的費用，我們或許可幫助您。如果您符合若干財務和醫療標準，我們可提供免費藥品。這透過Genentech® Access to Care基金會(GATCF)來完成。

為了獲得我們的幫助，我們需要檢視、使用和披露您的個人健康資訊 (PHI)。只有經您書面同意，您的醫師及醫療保健計畫才可向我們披露您的個人健康資訊。一旦簽署本表格並交還給我們，我們就可開始提供這些服務。我們可為您提供本披露書的副本。您需要先向我們索取副本，我們才可將副本寄還給您。

您可不必同意本披露書。但如果沒有您的同意，我們無法提供服務。這表示您可能需要自己支付某些藥品的費用。

請仔細通讀本表格。如有問題，請與您的醫師診所討論，或按本頁開頭所列電話號碼與我們聯絡。

1. 需要披露或使用的資訊

這份經簽字的表格允許我的醫師和醫療保健計畫向Genentech Access Solutions和/或GATCF發送我的個人健康資訊。這包括：

- 與我的冶療有關的所有健康記錄
- 關於我的醫療保健計畫福利的資訊
- 我的醫療保健計畫終生承保總額的餘額（如果適用於我的醫療保健計畫）
- 任何與我的健康或與我對治療方案的遵守情況有關的資訊

所有上述資訊均視為個人健康資訊的一部分。我瞭解這可能包括與下列事項有關的資訊：

- 性傳播疾病
- 精神健康狀況
- 基因檢驗結果

我們不要求提供這類資訊。這些資訊可能是發送給我們的醫療記錄的一部分。

2. 誰可檢視和使用我的個人健康資訊 (PHI)

Genentech Access Solutions和/或GATCF可檢視我的個人健康資訊。這些是由Genentech發起的計畫。其地址是：1 DNA Way, Mail Stop #858a, South San Francisco, CA 94080-4990。任何幫助Genentech Access Solutions履行服務的人士也可檢視這些資訊，包括Genentech的員工以及Genentech的任何合作夥伴。

我的個人健康資訊只能以下列方式使用：

- 協助我的醫療保健計畫支付Rituxan或ACTEMRA的費用
- 應用於GATCF
- 跟蹤我對Rituxan或ACTEMRA的使用情況
- 用於Genentech的一般行政用途

3. 失效日期

本披露書在我簽字後1年內有效。我可隨時以書面形式撤銷本披露書。

4. 通知

我瞭解，一旦簽署本表格，我的個人健康資訊可能不受關於使用我的個人健康資訊及其披露方式的聯邦法律的保護。不保證我的個人健康資訊不會披露給第三方。該第三方可能不需要遵守本披露書的條件。

我瞭解，我可拒絕簽署本表格。我可隨時以任何理由撤銷本表格。這不會影響我的治療的開始或延續。這對我的治療品質沒有影響。

我瞭解，本披露書的有效期為1年，或者到我以書面形式撤銷為止。為了撤銷，我必須向Genentech發送書面通知。通知可用傳真發送，或郵寄至本頁尾部所示地址。撤銷通知在Genentech收到之後生效。該通知不會影響醫師對我的治療。

如果我不簽署本表格，或者我撤銷本表格，我可能需要負責支付治療費用。

5. 同意不傳播

如果我收到GATCF提供的免費產品，我將遵照醫囑使用Rituxan或ACTEMRA。我不會出售或傳播Rituxan或ACTEMRA。我瞭解，這屬於違法行為。我有責任確保Rituxan或ACTEMRA在發運給我時寄送至正確的地址。我瞭解，在我持有Rituxan或ACTEMRA期間，我有責任控制它們。

下頁第6節為必填項。
該書面通知必須簽字、註明日期，用郵寄或傳真發送到：

Genentech Access Solutions
1 DNA Way, Mail Stop #858a
South San Francisco, CA 94080-4990

Fax: (866) 681-3288

6. 簽名與日期（必填）

我已經閱讀和瞭解本披露書的條款。我已經獲得提出問題的機會，瞭解我的個人健康資訊 (PHI) 的使用以及誰可檢視這些資訊。在下面簽署本表格，表示我瞭解我同意按本表格所述條款披露我的個人健康資訊。**（請填寫下列所有資訊。請務必簽署本表格，並註明日期。否則，這可能導致您無法獲得幫助。）**

您必須在這裏簽字並註明日期

患者或監護人簽字* _____ 許可權說明 _____ 日期 _____

您必須在這裏填寫您的正楷姓名

患者正楷姓名 _____

患者/監護人地址 _____

*如果患者是未脫離監護的未成年人或因其他原因不具備行為能力（身體或精神上的行為能力）。

7. 財務資訊

如果您想申請GATCF的幫助，請填寫本節。

家庭經調整總收入

☐ 0-25,000美元/年 ☐ 25,001-50,000美元/年
☐ 50,001-75,000美元/年 ☐ 75,001-100,000美元/年 ☐ 其他：_____

我瞭解，為了獲得免費藥品，我的家庭經調整總收入不得超過每年100,000美元。我證明上文所述我去年的收入屬實。我證明，我沒有承保Rituxan或ACTEMRA費用的醫療保健計畫。這包括Medicare、Medicaid或其他公共計畫。我沒有支付Rituxan或ACTEMRA費用的財務資源。我同意為GATCF提供我的收入證明。這可是我去年的IRS 1040表格。它也可以是我的其他收入證明。我將在提交本表格之後45天內向GATCF發送證明。我瞭解，如果不提供該證明，GATCF將無法繼續幫助我。

在此簽署姓名及日期 (如需要)

患者或監護人簽字 _____ 日期 _____

8. 任選的免費患者支持計畫

我想登記參加Genentech提供的一項任選的免費患者支援計畫。我瞭解，我需要提供自己的個人健康資訊，才能參加該計畫。我還瞭解，我的個人健康資訊將與Genentech Access Solutions以及患者健康計畫分享。我可選擇用郵件、電子郵件或電話與我聯絡。我瞭解，我的個人健康資訊不會在Genentech之外分享，或由其代理人分享。我同意讓Genentech或其代理人將來就該計畫與我聯絡。Genentech隱私政策可在GenentechAccessSolutions.com瀏覽。我瞭解，我可不必簽署本表格的這部分內容。這對於我獲得藥品沒有任何影響。它與我獲得Genentech Access Solutions的幫助無關。我還瞭解，我可隨時取消參與該患者支持計畫。要取消參與，我可透過其代理人寫信給Genentech，寄至5901B Peachtree Dunwoody Rd., Suite 380, Atlanta, GA 30328。

我的首選聯絡方式（請核選合適的方框，並填寫您的資訊。您可核選多個方框。）：

☐ 電子郵件：_____ ☐ 電話號碼：_____ 是否允許留言？ ☐ 是 ☐ 否

☐ 地址：_____

在這裏簽字表示選擇參與計畫

患者簽字（你必須在這裏簽字，才可參與患者支持計畫）。 _____ 日期 _____

Access Solutions標記是Genentech, Inc.的註冊商標。

財務援助資源

有3項重要的計畫對於幫助您獲得您需要的Rituxan®（莫須瘤注射劑）治療有重要作用：

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Rituxan safely and effectively. See full prescribing information for Rituxan.

Rituxan (rituximab)
Injection for Intravenous Use
Initial U.S. Approval: 1997

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

See full prescribing information for complete boxed warning.

- **Fatal infusion reactions within 24 hours of Rituxan infusion occur; approximately 80% of fatal reactions occurred with first infusion. Monitor patients and discontinue Rituxan infusion for severe reactions (5.1).**
- **Tumor lysis syndrome (5.2).**
- **Severe mucocutaneous reactions, some with fatal outcomes (5.3).**
- **PML resulting in death (5.4).**

----------RECENT MAJOR CHANGES----------

Indications and Usage, WG and MPA (1.4)	04/2011
Dosage and Administration, WG and MPA (2.6)	04/2011
Dosage and Administration, Recommended Concomitant Medications (2.7)	04/2011
Warnings and Precautions, Infections (5.6)	02/2012
Warnings and Precautions, Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, WG and MPA (5.12)	04/2011
Warnings and Precautions, Retreatment in Patients with WG and MPA (5.14)	04/2011

----------INDICATIONS AND USAGE----------

Rituxan is a CD20-directed cytolytic antibody indicated for the treatment of patients with:

- Non-Hodgkin's Lymphoma (NHL) (1.1)
- Chronic Lymphocytic Leukemia (CLL) (1.2)
- Rheumatoid Arthritis (RA) in combination with methotrexate in adult patients with moderately-to severely-active RA who have inadequate response to one or more TNF antagonist therapies (1.3)
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) in adult patients in combination with glucocorticoids (1.4)

Limitations of Use: Rituxan is not recommended for use in patients with severe, active infections (1.5).

----------DOSAGE AND ADMINISTRATION----------

DO NOT ADMINISTER AS AN IV PUSH OR BOLUS.

- The dose for NHL is 375 mg/m^2 (2.2).
- The dose for CLL is 375 mg/m^2 in the first cycle and 500 mg/m^2 in cycles 2–6, in combination with FC, administered every 28 days (2.3).
- The dose as a component of Zevalin® (Ibritumomab tiuxetan) Therapeutic Regimen is 250 mg/m^2 (2.4).
- The dose for RA in combination with methotrexate is two-1000 mg IV infusions separated by 2 weeks (one course) every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks. Methylprednisolone 100 mg IV or equivalent glucocorticoid is recommended 30 minutes prior to each infusion (2.5).
- The dose for WG and MPA in combination with glucocorticoids is 375 mg/m^2 once weekly for 4 weeks (2.6).

----------DOSAGE FORMS AND STRENGTHS----------

- 100 mg/10 mL and 500 mg/50 mL solution in a single-use vial (3).

----------CONTRAINDICATIONS----------

None.

----------WARNINGS AND PRECAUTIONS----------

- Tumor lysis syndrome - administer aggressive intravenous hydration, anti-hyperuricemic agents, and monitor renal function (5.2).
- PML - monitor neurologic function. Discontinue Rituxan (5.4).
- Hepatitis B reactivation with fulminant hepatitis, sometimes fatal - screen high risk patients and monitor HBV carriers during and several months after therapy. Discontinue Rituxan if reactivation occurs (5.5).
- Infections - withhold Rituxan and institute appropriate anti-infective therapy (5.6).
- Cardiac arrhythmias and angina can occur and can be life threatening. Monitor patients with these conditions closely (5.7).
- Bowel obstruction and perforation - evaluate complaints of abdominal pain (5.9).
- Do not administer live virus vaccines prior to or during Rituxan (5.10).
- Monitor CBC at regular intervals for severe cytopenias (5.11, 6.1).

----------ADVERSE REACTIONS----------

- Lymphoid Malignancies: Common adverse reactions (≥25%) in clinical trials of NHL were: infusion reactions, fever, lymphopenia, chills, infection and asthenia. Common adverse reactions (≥25%) in clinical trials of CLL were: infusion reactions and neutropenia (6.1).
- Rheumatoid Arthritis (RA): Common adverse reactions (≥10%) in clinical trials: upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis (6.2). Other important adverse reactions include infusion reactions, serious infections, and cardiovascular events (6.2).
- Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA): Common adverse reactions (≥15 %) in the clinical study were infections, nausea, diarrhea, headache, muscle spasms, anemia, peripheral edema (6.3). Other important adverse reactions include infusion reactions (6.3).

To report SUSPECTED ADVERSE REACTIONS, contact Genentech at 1-888-835-2555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Renal toxicity when used in combination with cisplatin (5.8).

----------USE IN SPECIFIC POPULATIONS----------

- Pregnancy: Limited human data; B-cell lymphocytopenia occurred in infants exposed in utero (8.1).
- Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3).
- Geriatric Use: In CLL patients older than 70 years of age, exploratory analyses suggest no benefit with the addition of Rituxan to FC (8.5).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: FATAL INFUSION REACTIONS, TUMOR LYSIS SYNDROME (TLS), SEVERE MUCOCUTANEOUS REACTIONS, and PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

Infusion Reactions

Rituxan administration can result in serious, including fatal infusion reactions. Deaths within 24 hours of Rituxan infusion have occurred. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. Carefully monitor patients during infusions. Discontinue Rituxan infusion and provide medical treatment for Grade 3 or 4 infusion reactions [*see Warnings and Precautions (5.1), Adverse Reactions (6.1)*].

Tumor Lysis Syndrome (TLS)

Acute renal failure requiring dialysis with instances of fatal outcome can occur in the setting of TLS following treatment of non-Hodgkin's lymphoma (NHL) with Rituxan monotherapy [*see Warnings and Precautions (5.2), Adverse Reactions (6)*].

Severe Mucocutaneous Reactions

Severe, including fatal, mucocutaneous reactions can occur in patients receiving Rituxan [*see Warnings and Precautions (5.3), Adverse Reactions (6)*].

Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in patients receiving Rituxan [*see Warnings and Precautions (5.4), Adverse Reactions (6)*].

1 INDICATIONS AND USAGE

1.1 Non–Hodgkin's Lymphoma (NHL)

Rituxan® (rituximab) is indicated for the treatment of patients with:

- Relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL as a single agent
- Previously untreated follicular, CD20-positive, B-cell NHL in combination with first line chemotherapy and, in patients achieving a complete or partial response to Rituxan in combination with chemotherapy, as single-agent maintenance therapy.
- Non-progressing (including stable disease), low-grade, CD20-positive, B-cell NHL as a single agent after first-line CVP chemotherapy
- Previously untreated diffuse large B-cell, CD20-positive NHL in combination with CHOP or other anthracycline-based chemotherapy regimens

1.2 Chronic Lymphocytic Leukemia (CLL)

Rituxan® (rituximab) is indicated, in combination with fludarabine and cyclophosphamide (FC), for the treatment of patients with previously untreated and previously treated CD20-positive CLL.

1.3 Rheumatoid Arthritis (RA)

Rituxan® (rituximab) in combination with methotrexate 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 TNF antagonist therapies.

1.4 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Rituxan® (rituximab), in combination with glucocorticoids, is indicated for the treatment of adult patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA).

1.5 Limitations of Use

Rituxan is not recommended for use in patients with severe, active infections.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

Premedicate before each infusion [*see Dosage and Administration (2.7)*]. Administer only as an intravenous (IV) infusion [*see Dosage and Administration (2.7)*].

- **First Infusion**: Initiate infusion at a rate of 50 mg/hr. In the absence of infusion toxicity, increase infusion rate by 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr.
- **Subsequent Infusions**: Initiate infusion at a rate of 100 mg/hr. In the absence of infusion toxicity, increase rate by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr.
- Interrupt the infusion or slow the infusion rate for infusion reactions [*see Boxed Warning, Warnings and Precautions (5.1)*]. Continue the infusion at one-half the previous rate upon improvement of symptoms.

2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)

The recommended dose is 375 mg/m^2 as an intravenous infusion according to the following schedules:

- **Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 or 8 doses.
- **Retreatment for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL**
  Administer once weekly for 4 doses.
- **Previously Untreated, Follicular, CD20-Positive, B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy, for up to 8 doses. In patients with complete or partial response, initiate Rituxan maintenance eight weeks following completion of Rituxan in combination with chemotherapy. Administer Rituxan as a single-agent every 8 weeks for 12 doses.
- **Non-progressing, Low-Grade, CD20-Positive, B-cell NHL, after first-line CVP chemotherapy**
  Following completion of 6–8 cycles of CVP chemotherapy, administer once weekly for 4 doses at 6-month intervals to a maximum of 16 doses.
- **Diffuse Large B-Cell NHL**
  Administer on Day 1 of each cycle of chemotherapy for up to 8 infusions.

2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)

The recommended dose is:

- 375 mg/m^2 the day prior to the initiation of FC chemotherapy, then 500 mg/m^2 on Day 1 of cycles 2–6 (every 28 days).

2.4 Recommended Dose as a Component of Zevalin®

- Infuse rituximab 250 mg/m^2 within 4 hours prior to the administration of Indium-111-(In-111-) Zevalin and within 4 hours prior to the administration of Yttrium-90- (Y-90-) Zevalin.
- Administer Rituxan and In-111-Zevalin 7–9 days prior to Rituxan and Y-90- Zevalin.
- Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

2.5 Recommended Dose for Rheumatoid Arthritis (RA)

- Administer Rituxan as two-1000 mg intravenous infusions separated by 2 weeks.
- Glucocorticoids administered as methylprednisolone 100 mg intravenous or its equivalent 30 minutes prior to each infusion are recommended to reduce the incidence and severity of infusion reactions.
- Subsequent courses should be administered every 24 weeks or based on clinical evaluation, but not sooner than every 16 weeks.
- Rituxan is given in combination with methotrexate.

2.6 Recommended Dose for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

- Administer Rituxan as a 375 mg/m^2 intravenous infusion once weekly for 4 weeks.
- Glucocorticoids administered as methylprednisolone 1000 mg intravenously per day for 1 to 3 days followed by oral prednisone 1 mg/kg/day (not to exceed 80 mg/day and tapered per clinical need) are recommended to treat severe vasculitis symptoms. This regimen should begin within 14 days prior to or with the initiation of Rituxan and may continue during and after the 4 week course of Rituximab treatment.
- Safety and efficacy of treatment with subsequent courses of Rituxan have not been established [*see Warnings and Precautions (5.14)*].

2.7 Recommended Concomitant Medications

Premedicate before each infusion with acetaminophen and an antihistamine.

For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion.

For WG and MPA patients, glucocorticoids are given in combination with Rituxan [*see Dosage and Administration (2.6)*].

Pneumocystis jiroveci pneumonia (PCP) and anti-herpetic viral prophylaxis is recommended for patients with CLL during treatment and for up to 12 months following treatment as appropriate.

PCP prophylaxis is also recommended for patients with WG and MPA during treatment and for at least 6 months following the last Rituxan infusion.

2.8 Preparation for Administration

Use appropriate aseptic technique. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use vial if particulates or discoloration is present. Withdraw the necessary amount of Rituxan and dilute to a final concentration of 1 to 4 mg/mL in an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Do not mix or dilute with other drugs. Discard any unused portion left in the vial.

3 DOSAGE FORMS AND STRENGTHS

100 mg/10 mL single-use vial
500 mg/50 mL single-use vial

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions

Rituxan can cause severe, including fatal, infusion reactions. Severe reactions typically occurred during the first infusion with time to onset of 30–120 minutes. Rituxan-induced infusion reactions and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. For RA patients, methylprednisolone 100 mg intravenously or its equivalent is recommended 30 minutes prior to each infusion. Institute medical management (e.g. glucocorticoids, epinephrine, bronchodilators, or oxygen) for infusion reactions as needed. Depending on the severity of the infusion reaction and the required interventions, temporarily or permanently discontinue Rituxan. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells ($\geq$25,000/mm^3). [*See Boxed Warning, Warnings and Precautions (5.7), Adverse Reactions (6.1).*]

5.2 Tumor Lysis Syndrome (TLS)

Acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatemia from tumor lysis, some fatal, can occur within 12–24 hours after the first infusion of Rituxan in patients with NHL. A high number of circulating malignant cells ($\geq$25,000/mm^3) or high tumor burden, confers a greater risk of TLS.

Administer aggressive intravenous hydration and anti-hyperuricemic therapy in patients at high risk for TLS. Correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated. [*See Boxed Warning, Warnings and Precautions (5.8)*.]

5.3 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with Rituxan. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has varied from 1–13 weeks following Rituxan exposure. Discontinue Rituxan in patients who experience a severe mucocutaneous reaction. The safety of readministration of Rituxan to patients with severe mucocutaneous reactions has not been determined. [*See Boxed Warning, Adverse Reactions (6, 6.1).*]

5.4 Progressive Multifocal Leukoencephalopathy (PML)

JC virus infection resulting in PML and death can occur in Rituxan-treated patients with hematologic malignancies or with autoimmune diseases. The majority of patients with hematologic malignancies diagnosed with PML received Rituxan in combination with chemotherapy or as part of a hematopoietic stem cell transplant. The patients with autoimmune diseases had prior or concurrent immunosuppressive therapy. Most cases of PML were diagnosed within 12 months of their last infusion of Rituxan.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Discontinue Rituxan and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML. [*See Boxed Warning, Adverse Reactions (6).*]

5.5 Hepatitis B Virus (HBV) Reactivation

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death can occur in patients treated with Rituxan. The median time to the diagnosis of hepatitis among patients with hematologic malignancies was approximately 4 months after the initiation of Rituxan and approximately one month after the last dose.

Screen patients at high risk of HBV infection before initiation of Rituxan. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection for several months following Rituxan therapy. Discontinue Rituxan and any concomitant chemotherapy in patients who develop viral hepatitis, and institute appropriate treatment including antiviral therapy. Insufficient data exist regarding the safety of resuming Rituxan in patients who develop hepatitis subsequent to HBV reactivation. [*See Adverse Reactions (6.5).*]

5.6 Infections

Serious, including fatal, bacterial, fungal, and new or reactivated viral infections can occur during and following the completion of Rituxan-based therapy. Infections have been reported in some patients with prolonged hypogammaglobulinemia (defined as hypogammaglobulinemia >11 months after rituximab exposure). New or reactivated viral infections included cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis B and C. Discontinue Rituxan for serious infections and institute appropriate anti-infective therapy. [*See Adverse Reactions (6, 6.1).*]

5.7 Cardiovascular

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of Rituxan for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina. [*See Adverse Reactions (6).*]

5.8 Renal

Severe, including fatal, renal toxicity can occur after Rituxan administration in patients with NHL. Renal toxicity has occurred in patients who experience tumor lysis syndrome and in patients with NHL administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and Rituxan is not an approved treatment regimen. Monitor closely for signs of renal failure and discontinue Rituxan in patients with a rising serum creatinine or oliguria. [*See Warnings and Precautions (5.2).*]

5.9 Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, can occur in patients receiving Rituxan in combination with chemotherapy. In postmarketing reports, the mean time to documented gastrointestinal perforation was 6 (range 1–77) days in patients with NHL. Perform a thorough diagnostic evaluation and institute appropriate treatment for complaints of abdominal pain. [*See Adverse Reactions (6).*]

5.10 Immunization

The safety of immunization with live viral vaccines following Rituxan therapy has not been studied and vaccination with live virus vaccines is not recommended.

For RA patients, physicians should follow current immunization guidelines and administer non-live vaccines at least 4 weeks prior to a course of Rituxan.

The effect of Rituxan on immune responses was assessed in a randomized, controlled study in patients with RA treated with Rituxan and methotrexate (MTX) compared to patients treated with MTX alone.

A response to pneumococcal vaccination (a T-cell independent antigen) as measured by an increase in antibody titers to at least 6 of 12 serotypes was lower in patients treated with Rituxan plus MTX as compared to patients treated with MTX alone (19% vs. 61%). A lower proportion of patients in the Rituxan plus MTX group developed detectable levels of anti-keyhole limpet hemocyanin antibodies (a novel protein antigen) after vaccination compared to patients on MTX alone (47% vs. 93%).

A positive response to tetanus toxoid vaccine (a T-cell dependent antigen with existing immunity) was similar in patients treated with Rituxan plus MTX compared to patients on MTX alone (39% vs. 42%). The proportion of patients maintaining a positive Candida skin test (to evaluate delayed type hypersensitivity) was also similar (77% of patients on Rituxan plus MTX vs. 70% of patients on MTX alone).

Most patients in the Rituxan-treated group had B-cell counts below the lower limit of normal at the time of immunization. The clinical implications of these findings are not known.

5.11 Laboratory Monitoring

In patients with lymphoid malignancies, during treatment with Rituxan monotherapy, obtain complete blood counts (CBC) and platelet counts prior to each Rituxan course. During treatment with Rituxan and chemotherapy, obtain CBC and platelet counts at weekly to monthly intervals and more frequently in patients who develop cytopenias [*see Adverse Reactions (6.1)*]. In patients with RA, WG or MPA, obtain CBC and platelet counts at two to four month intervals during Rituxan therapy. The duration of cytopenias caused by Rituxan can extend months beyond the treatment period.

5.12 Concomitant Use with Biologic Agents and DMARDS other than Methotrexate in RA, WG and MPA

Limited data are available on the safety of the use of biologic agents or DMARDs other than methotrexate in RA patients exhibiting peripheral B-cell depletion following treatment with rituximab. Observe patients closely for signs of infection if biologic agents and/or DMARDs are used concomitantly. Use of concomitant immunosuppressants other than corticosteroids has not been studied in WG or MPA patients exhibiting peripheral B-cell depletion following treatment with Rituxan.

5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

While the efficacy of Rituxan was supported in four controlled trials in patients with RA with prior inadequate responses to non-biologic DMARDs, and in a controlled trial in MTX-naïve patients, a favorable risk-benefit relationship has not been established in these populations. The use of Rituxan in patients with RA who have not had prior inadequate response to one or more TNF antagonists is not recommended [*see Clinical Studies (14.5)*].

5.14 Retreatment in Patients with Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Limited data are available on the safety and efficacy of subsequent courses of Rituxan in patients with WG and MPA. The safety and efficacy of retreatment with Rituxan have not been established [*see Dosage and Administration (2.6), Adverse Reactions (6.3), and Clinical Studies (14.6)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

- Infusion reactions [*see Warnings and Precautions (5.1)*]
- Tumor lysis syndrome [*see Warnings and Precautions (5.2)*]
- Mucocutaneous reactions [*see Warnings and Precautions (5.3)*]
- Progressive multifocal leukoencephalopathy [*see Warnings and Precautions (5.4)*]
- Hepatitis B reactivation with fulminant hepatitis [*see Warnings and Precautions (5.5)*]
- Infections [*see Warnings and Precautions (5.6)*]
- Cardiac arrhythmias [*see Warnings and Precautions (5.7)*]
- Renal toxicity [*see Warnings and Precautions (5.8)*]
- Bowel obstruction and perforation [*see Warnings and Precautions (5.9)*]

The most common adverse reactions of Rituxan (incidence ≥25%) observed in clinical trials of patients with NHL were infusion reactions, fever, lymphopenia, chills, infection, and asthenia.

The most common adverse reactions of Rituxan (incidence≥25%) observed in clinical trials of patients with CLL were: infusion reactions and neutropenia.

6.1 Clinical Trials Experience in Lymphoid Malignancies

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to Rituxan in 2783 patients, with exposures ranging from a single infusion up to 2 years. Rituxan was studied in both single-arm and controlled trials (n=356 and n = 2427). The population included 1180 patients with low grade or follicular lymphoma, 927 patients with DLBCL, and 676 patients with CLL. Most NHL patients received Rituxan as an infusion of 375 mg/m^2 per infusion, given as a single agent weekly for up to 8 doses, in combination with chemotherapy for up to 8 doses, or following chemotherapy for up to 16 doses. CLL patients received Rituxan 375 mg/m^2 as an initial infusion followed by 500 mg/m^2 for up to 5 doses, in combination with fludarabine and cyclophosphamide. Seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

Infusion Reactions

In the majority of patients with NHL, infusion reactions consisting of fever, chills/rigors, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness, or hypertension occurred during the first Rituxan infusion. Infusion reactions typically occurred within 30 to 120 minutes of beginning the first infusion and resolved with slowing or interruption of the Rituxan infusion and with supportive care (diphenhydramine, acetaminophen, and intravenous saline). The incidence of infusion reactions was highest during the first infusion (77%)

and decreased with each subsequent infusion. [*See Boxed Warning, Warnings and Precautions (5.1).*]

Infections

Serious infections (NCI CTCAE Grade 3 or 4), including sepsis, occurred in less than 5% of patients with NHL in the single-arm studies. The overall incidence of infections was 31% (bacterial 19%, viral 10%, unknown 6%, and fungal 1%). [*See Warnings and Precautions (5.4), (5.5), (5.6).*]

In randomized, controlled studies where Rituxan was administered following chemotherapy for the treatment of follicular or low-grade NHL, the rate of infection was higher among patients who received Rituxan. In diffuse large B-cell lymphoma patients, viral infections occurred more frequently in those who received Rituxan.

Cytopenias and hypogammaglobulinemia

In patients with NHL receiving rituximab monotherapy, NCI-CTC Grade 3 and 4 cytopenias were reported in 48% of patients. These included lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1−588 days) and of neutropenia was 13 days (range, 2−116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following Rituxan therapy occurred during the single-arm studies.

In studies of monotherapy, Rituxan-induced B-cell depletion occurred in 70% to 80% of patients with NHL. Decreased IgM and IgG serum levels occurred in 14% of these patients.

Relapsed or Refractory, Low-Grade NHL

Adverse reactions in Table 1 occurred in 356 patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell NHL treated in single-arm studies of Rituxan administered as a single agent [*see Clinical Studies (14.1)*]. Most patients received Rituxan 375 mg/m^2 weekly for 4 doses.

Table 1

Incidence of Adverse Reactions in ≥5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent Rituxan (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Reactions	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Heme and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1
Respiratory System	38	4
Increased Cough	13	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1

Table 1 (cont'd)
Incidence of Adverse Reactions in ≥ 5% of
Patients with Relapsed or Refractory, Low-Grade or Follicular
NHL, Receiving Single-agent Rituxan (N=356)[a,b]

	All Grades (%)	Grade 3 and 4 (%)
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1

[a] Adverse reactions observed up to 12 months following Rituxan.

[b] Adverse reactions graded for severity by NCI-CTC criteria.

In these single-arm Rituxan studies, bronchiolitis obliterans occurred during and up to 6 months after Rituxan infusion.

Previously Untreated, Low-Grade or Follicular, NHL

In Study 4, patients in the R-CVP arm experienced a higher incidence of infusional toxicity and neutropenia compared to patients in the CVP arm. The following adverse reactions occurred more frequently (≥5%) in patients receiving R-CVP compared to CVP alone: rash (17% vs. 5%), cough (15% vs. 6%), flushing (14% vs. 3%), rigors (10% vs. 2%), pruritus (10% vs. 1%), neutropenia (8% vs. 3%), and chest tightness (7% vs. 1%). [*See Clinical Studies (14.2).*]

In Study 5, detailed safety data collection was limited to serious adverse reactions, Grade ≥ 2 infections, and Grade ≥ 3 adverse reactions. In patients receiving Rituxan as single-agent maintenance therapy following Rituxan plus chemotherapy, infections were reported more frequently compared to the observation arm (37% vs. 22%). Grade 3-4 adverse reactions occurring at a higher incidence (≥ 2%) in the Rituxan group were infections (4% vs. 1%) and neutropenia (4% vs. <1%).

In Study 6, the following adverse reactions were reported more frequently (≥5%) in patients receiving Rituxan following CVP compared to patients who received no further therapy: fatigue (39% vs. 14%), anemia (35% vs. 20%), peripheral sensory neuropathy (30% vs. 18%), infections (19% vs. 9%), pulmonary toxicity (18% vs. 10%), hepato-biliary toxicity (17% vs. 7%), rash and/or pruritus (17% vs. 5%), arthralgia (12% vs. 3%), and weight gain (11% vs. 4%). Neutropenia was the only Grade 3 or 4 adverse reaction that occurred more frequently (≥2%) in the Rituxan arm compared with those who received no further therapy (4% vs. 1%). [*See Clinical Studies (14.3).*]

DLBCL

In Studies 7 and 8, [*see Clinical Studies (14.3)*], the following adverse reactions, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: pyrexia (56% vs. 46%), lung disorder (31% vs. 24%), cardiac disorder (29% vs. 21%), and chills (13% vs. 4%). Detailed safety data collection in these studies was primarily limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

In Study 8, a review of cardiac toxicity determined that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders (4.5% for R-CHOP vs. 1.0% for CHOP).

The following Grade 3 or 4 adverse reactions occurred more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other Grade 3 or 4 adverse reactions occurring more frequently among patients receiving R-CHOP were viral infection (Study 8), neutropenia (Studies 8 and 9), and anemia (Study 9).

CLL

The data below reflect exposure to Rituxan in combination with fludarabine and cyclophosphamide in 676 patients with CLL in Study 10 or Study 11 [*see Clinical Studies (14.4)*]. The age range was 30–83 years and 71% were men. Detailed safety data collection in Study 10 was limited to Grade 3 and 4 adverse reactions and serious adverse reactions.

Infusion-related adverse reactions were defined by any of the following adverse events occurring during or within 24 hours of the start of infusion: nausea, pyrexia, chills, hypotension, vomiting, and dyspnea.

In Study 10, the following Grade 3 and 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (9% in R-FC arm), neutropenia (30% vs. 19%), febrile neutropenia (9% vs. 6%), leukopenia (23% vs. 12%), and pancytopenia (3% vs. 1%).

In Study 11, the following Grade 3 or 4 adverse reactions occurred more frequently in R-FC-treated patients compared to FC-treated patients: infusion reactions (7% in R-FC arm), neutropenia (49% vs. 44%), febrile neutropenia (15% vs. 12%), thrombocytopenia (11% vs. 9%), hypotension (2% vs. 0%), and hepatitis B (2% vs.<1%). Fifty-nine percent of R-FC-treated patients experienced an infusion reaction of any severity.

6.2 Clinical Trials Experience in Rheumatoid Arthritis

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented below reflect the experience in 2578 RA patients treated with Rituxan in controlled and long-term studies with a total exposure of 5014 patient-years.

Among all exposed patients, adverse reactions reported in greater than 10% of patients include infusion-related reactions, upper respiratory tract infection, nasopharyngitis, urinary tract infection, and bronchitis.

In placebo-controlled studies, patients received 2 x 500 mg or 2 x 1000 mg intravenous infusions of Rituxan or placebo, in combination with methotrexate, during a 24-week period. From these studies, 938 patients treated with Rituxan (2 x 1000 mg) or placebo have been pooled (see Table 2). Adverse reactions reported in ≥ 5% of patients were hypertension, nausea, upper respiratory tract infection, arthralgia, pyrexia and pruritus (see Table 2). The rates and types of adverse reactions in patients who received Rituxan 2 x 500 mg were similar to those observed in patients who received Rituxan 2 x 1000 mg.

Table 2*

Incidence of All Adverse Reactions** Occurring in ≥2% and at Least 1% Greater than Placebo Among Rheumatoid Arthritis Patients in Clinical Studies Up to Week 24 (Pooled)

Preferred Term	Placebo + MTX N = 398 n (%)	Rituxan + MTX N = 540 n (%)
Hypertension	21 (5)	43 (8)
Nausea	19 (5)	41 (8)
Upper Respiratory Tract Infection	23 (6)	37 (7)
Arthralgia	14 (4)	31 (6)
Pyrexia	8 (2)	27 (5)
Pruritus	5 (1)	26 (5)
Chills	9 (2)	16 (3)
Dyspepsia	3 (<1)	16 (3)
Rhinitis	6 (2)	14 (3)
Paresthesia	3 (<1)	12 (2)
Urticaria	3 (<1)	12 (2)
Abdominal Pain Upper	4 (1)	11 (2)
Throat Irritation	0 (0)	11 (2)
Anxiety	5 (1)	9 (2)
Migraine	2 (<1)	9 (2)
Asthenia	1 (<1)	9 (2)

*These data are based on 938 patients treated in Phase 2 and 3 studies of Rituxan (2 × 1000 mg) or placebo administered in combination with methotrexate.

**Coded using MedDRA.

Infusion Reactions

In the Rituxan RA pooled placebo-controlled studies, 32% of Rituxan-treated patients experienced an adverse reaction during or within 24 hours following their first infusion, compared to 23% of placebo-treated patients receiving their first infusion. The incidence of adverse reactions during the 24-hour period following the second infusion, Rituxan or placebo, decreased to 11% and 13%, respectively. Acute infusion reactions (manifested by fever, chills, rigors, pruritus, urticaria/rash, angioedema, sneezing, throat irritation, cough, and/or bronchospasm, with or without associated hypotension or hypertension) were experienced by 27% of Rituxan-treated patients following their first infusion, compared to 19% of placebo-treated patients receiving their first placebo infusion. The incidence of these acute infusion reactions following the second infusion of Rituxan or placebo decreased to 9% and 11%, respectively. Serious acute infusion reactions were experienced by <1% of patients in either treatment group. Acute infusion reactions required dose modification (stopping, slowing, or interruption of the infusion) in 10% and 2% of patients receiving rituximab or placebo, respectively, after the first course. The proportion of patients experiencing acute infusion reactions decreased with subsequent courses of Rituxan. The administration of intravenous glucocorticoids prior to Rituxan infusions reduced the incidence and severity of such reactions, however, there was no clear benefit from the administration of oral glucocorticoids for the prevention of acute infusion

reactions. Patients in clinical studies also received antihistamines and acetaminophen prior to Rituxan infusions.

Infections

In the pooled, placebo-controlled studies, 39% of patients in the Rituxan group experienced an infection of any type compared to 34% of patients in the placebo group. The most common infections were nasopharyngitis, upper respiratory tract infections, urinary tract infections, bronchitis, and sinusitis.

The incidence of serious infections was 2% in the Rituxan-treated patients and 1% in the placebo group.

In the experience with Rituxan in 2578 RA patients, the rate of serious infections was 4.31 per 100 patient years. The most common serious infections ($\geq$0.5%) were pneumonia or lower respiratory tract infections, cellulitis and urinary tract infections. Fatal serious infections included pneumonia, sepsis and colitis. Rates of serious infection remained stable in patients receiving subsequent courses. In 185 Rituxan-treated RA patients with active disease, subsequent treatment with a biologic DMARD, the majority of which were TNF antagonists, did not appear to increase the rate of serious infection. Thirteen serious infections were observed in 186.1 patient years (6.99 per 100 patient years) prior to exposure and 10 were observed in 182.3 patient years (5.49 per 100 patient years) after exposure.

Cardiac Adverse Reactions

In the pooled, placebo-controlled studies, the proportion of patients with serious cardiovascular reactions was 1.7% and 1.3% in the Rituxan and placebo treatment groups, respectively. Three cardiovascular deaths occurred during the double-blind period of the RA studies including all rituximab regimens (3/769=0.4%) as compared to none in the placebo treatment group (0/389).

In the experience with Rituxan in 2578 RA patients, the rate of serious cardiac reactions was 1.93 per 100 patient years. The rate of myocardial infarction (MI) was 0.56 per 100 patient years (28 events in 26 patients), which is consistent with MI rates in the general RA population. These rates did not increase over three courses of Rituxan.

Since patients with RA are at increased risk for cardiovascular events compared with the general population, patients with RA should be monitored throughout the infusion and Rituxan should be discontinued in the event of a serious or life-threatening cardiac event.

Hypophosphatemia and hyperuricemia

In the pooled, placebo-controlled studies, newly-occurring hypophosphatemia (<2.0 mg/dl) was observed in 12% (67/540) of patients on Rituxan versus 10% (39/398) of patients on placebo. Hypophosphatemia was more common in patients who received corticosteroids. Newly-occurring hyperuricemia (>10 mg/dl) was observed in 1.5% (8/540) of patients on Rituxan versus 0.3% (1/398) of patients on placebo.

In the experience with Rituxan in RA patients, newly-occurring hypophosphatemia was observed in 21% (528/2570) of patients and newly-occurring hyperuricemia was observed in 2% (56/2570) of patients. The majority of the observed hypophosphatemia occurred at the time of the infusions and was transient.

Retreatment in Patients with RA

In the experience with Rituxan in RA patients, 2578 patients have been exposed to Rituxan and have received up to 10 courses of Rituxan in RA clinical trials, with 1890, 1043, and 425 patients having received at least two, three, and four courses, respectively. Most of the patients who received additional courses did so 24 weeks or more after the previous course and none were retreated sooner than 16 weeks. The rates and types of adverse reactions reported for subsequent courses of Rituxan were similar to rates and types seen for a single course of Rituxan.

In RA Study 2, where all patients initially received Rituxan, the safety profile of patients who were retreated with Rituxan was similar to those who were retreated with placebo [*see Clinical Studies (14.5), and Dosage and Administration (2.5).*]

6.3 Clinical Trials Experience in Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data presented below reflect the experience in 197 patients with WG and MPA treated with Rituxan or cyclophosphamide in a single controlled study, which was conducted in two phases: a 6 month randomized, double-blind, double-dummy, active-controlled remission induction phase and an additional 12 month remission maintenance phase. In the 6-month remission induction phase, 197 patients with WG and MPA were randomized to either Rituxan 375 mg/ m^2 once weekly for 4 weeks plus glucocorticoids, or oral cyclophosphamide 2 mg/kg daily (adjusted for renal function, white blood cell count, and other factors) plus glucocorticoids to induce remission. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The primary analysis was at the end of the 6 month remission induction period and the safety results for this period are described below.

Adverse reactions presented below in Table 3 were adverse events which occurred at a rate of greater than or equal to 10% in the Rituxan group. This table reflects experience in 99 WG and MPA patients treated with Rituxan, with a total of 47.6 patient-years of observation and 98 WG and MPA patients treated with cyclophosphamide, with a total of 47.0 patient-years of observation. Infection was the most common category of adverse events reported (47-62%) and is discussed below.

Table 3
Incidence of All Adverse Reactions
Occurring in ≥ 10% of Rituxan-treated WG and MPA Patients
in the Clinical Study Up to Month 6*

Preferred Term	Rituxan N=99 n (%)	Cyclophosphamide N=98 n (%)
Nausea	18 (18%)	20 (20%)
Diarrhea	17 (17%)	12 (12%)
Headache	17 (17%)	19 (19%)
Muscle spasms	17 (17%)	15 (15%)
Anemia	16 (16%)	20 (20%)
Peripheral edema	16 (16%)	6 (6%)
Insomnia	14 (14%)	12 (12%)
Arthralgia	13 (13%)	9 (9%)
Cough	13 (13%)	11 (11%)
Fatigue	13 (13%)	21 (21%)
Increased ALT	13 (13%)	15 (15%)
Hypertension	12 (12%)	5 (5%)
Epistaxis	11 (11%)	6 (6%)
Dyspnea	10 (10%)	11 (11%)
Leukopenia	10 (10%)	26 (27%)
Rash	10 (10%)	17 (17%)

*The study design allowed for crossover or treatment by best medical judgment, and 13 patients in each treatment group received a second therapy during the 6 month study period.

Infusion Reactions

Infusion-related reactions in the active-controlled, double-blind study were defined as any adverse event occurring within 24 hours of an infusion and considered to be infusion-related by investigators. Among the 99 patients treated with Rituxan, 12% experienced at least one infusion related reaction, compared with 11% of the 98 patients in the cyclophosphamide group. Infusion-related reactions included cytokine release syndrome, flushing, throat irritation, and tremor. In the Rituxan group, the proportion of patients experiencing an infusion related reaction was 12%, 5%, 4%, and 1% following the first, second, third, and fourth infusions, respectively. Patients were pre-medicated with antihistamine and acetaminophen before each Rituxan infusion and were on background oral corticosteroids which may have mitigated or masked an infusion reaction; however, there is insufficient evidence to determine whether premedication diminishes the frequency or severity of infusion reactions.

Infections

In the active-controlled, double-blind study, 62% (61/99) of patients in the Rituxan group experienced an infection of any type compared to 47% (46/98) patients in the cyclophosphamide group by Month 6. The most common infections in the Rituxan group were upper respiratory tract infections, urinary tract infections, and herpes zoster.

The incidence of serious infections was 11% in the Rituxan-treated patients and 10% in the cyclophosphamide treated patients, with rates of approximately 25 and 28 per 100 patient-years, respectively. The most common serious infection was pneumonia.

Retreatment in Patients with WG and MPA

In the active-controlled, double-blind study, subsequent courses of Rituxan were allowed for patients experiencing a relapse of disease. The limited data preclude any conclusions regarding the safety of subsequent courses of Rituxan with WG and MPA [*see Dosage and Administration (2.6), and Warnings and Precautions (5.14)*].

6.4 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The observed incidence of antibody (including neutralizing antibody) positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Rituxan with the incidence of antibodies to other products may be misleading.

Using an ELISA assay, anti-human anti-chimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients with low-grade or follicular NHL receiving single-agent Rituxan. Three of the four patients had an objective clinical response.

A total of 273/2578 (11%) patients with RA tested positive for HACA at any time after receiving Rituxan. HACA positivity was not associated with increased infusion reactions or other adverse reactions. Upon further treatment, the proportions of patients with infusion reactions were similar between HACA positive and negative patients, and most reactions were mild to moderate. Four HACA positive patients had serious infusion reactions, and the temporal relationship between HACA positivity and infusion reaction was variable.

A total of 23/99 (23%) Rituxan-treated patients with WG and MPA tested positive for HACA by 18 months. The clinical relevance of HACA formation in Rituxan-treated patients is unclear.

6.5 Postmarketing Experience

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. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to Rituxan.

- Hematologic: prolonged pancytopenia, marrow hypoplasia, and late-onset neutropenia, hyperviscosity syndrome in Waldenstrom's macroglobulinemia, prolonged hypogammaglobulinemia [*see Warnings and Precautions (5.6)*].
- Cardiac: fatal cardiac failure.
- Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis, and vasculitis with rash.
- Infection: viral infections, including progressive multifocal leukoencephalopathy (PML), increase in fatal infections in HIV-associated lymphoma, and a reported increased incidence of Grade 3 and 4 infections [*see Warnings and Precautions (5.6)*].
- Neoplasia: disease progression of Kaposi's sarcoma.
- Skin: severe mucocutaneous reactions.
- Gastrointestinal: bowel obstruction and perforation.
- Pulmonary: fatal bronchiolitis obliterans and fatal interstitial lung disease.
- Nervous system: Posterior Reversible Encephalopathy Syndrome (PRES) / Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

7 DRUG INTERACTIONS

Formal drug interaction studies have not been performed with Rituxan. In patients with CLL, Rituxan did not alter systemic exposure to fludarabine or cyclophosphamide. In clinical trials of patients with RA, concomitant administration of methotrexate or cyclophosphamide did not alter the pharmacokinetics of rituximab.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Category C: There are no adequate and well-controlled studies of rituximab in pregnant women. Postmarketing data indicate that B-cell lymphocytopenia generally lasting less than six months can occur in infants exposed to rituximab in-utero. Rituximab was detected postnatally in the serum of infants exposed in-utero.

Non-Hodgkin's lymphoma, moderate-severe rheumatoid arthritis, Wegener's Granulomatosis and Microscopic Polyangiitis are serious conditions that require treatment. Rituximab should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Reproduction studies in cynomolgus monkeys at maternal exposures similar to human therapeutic exposures showed no evidence of teratogenic effects. However, B-cell lymphoid tissue was reduced in the offspring of treated dams. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months of birth [*see Non-Clinical Toxicology (13.2)*].

8.3 Nursing Mothers

It is not known whether Rituxan is secreted into human milk. However, Rituxan is secreted in the milk of lactating cynomolgus monkeys, and IgG is excreted in human milk. Published data suggest that antibodies in breast milk do not enter the neonatal and infant circulations in substantial amounts. The unknown risks to the infant from oral ingestion of Rituxan should be weighed against the known benefits of breastfeeding.

8.4 Pediatric Use

FDA has not required pediatric studies in polyarticular juvenile idiopathic arthritis (PJIA) patients ages 0 to 16 due to concerns regarding the potential for prolonged immunosuppression as a result of B-cell depletion in the developing juvenile immune system.

The safety and effectiveness of Rituxan in pediatric patients have not been established.

8.5 Geriatric Use

Diffuse Large B-Cell NHL

Among patients with DLBCL evaluated in three randomized, active-controlled trials, 927 patients received Rituxan in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse reactions, mostly supraventricular arrhythmias, occurred more frequently among elderly patients. Serious pulmonary adverse reactions were also more common among the elderly, including pneumonia and pneumonitis.

Low-Grade or Follicular Non-Hodgkin's Lymphoma

Patients with previously untreated follicular NHL evaluated in Study 5 were randomized to Rituxan as single-agent maintenance therapy (n = 505) or observation (n = 513) after achieving a response to Rituxan in combination with chemotherapy. Of these, 123 (24%) patients in the Rituxan arm were age 65 or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other clinical studies of Rituxan in low-grade or follicular, CD20-positive, B-cell NHL did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

Chronic Lymphocytic Leukemia

Among patients with CLL evaluated in two randomized active-controlled trials, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older; of these, 100 Rituxan-treated patients (15%) were 70 years of age or older.

In exploratory analyses defined by age, there was no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 70 years of age or older in Study 10 or in Study 11; there was also no observed benefit from the addition of Rituxan to fludarabine and cyclophosphamide among patients 65 years of age or older in Study 11 [*see Clinical Studies (14.4)*]. Patients 70 years or older received lower dose intensity of fludarabine and cyclophosphamide compared to younger patients, regardless of the addition of Rituxan. In Study 10, the dose intensity of Rituxan was similar in older and younger patients, however in Study 11 older patients received a lower dose intensity of Rituxan.

The incidence of Grade 3 and 4 adverse reactions was higher among patients receiving R-FC who were 70 years or older compared to younger patients for neutropenia [44% vs. 31% (Study 10); 56% vs. 39% (Study 11)], febrile neutropenia [16% vs. 6% (Study 10)], anemia [5% vs. 2% (Study 10); 21% vs. 10% (Study 11)], thrombocytopenia [19% vs. 8% (Study 11)], pancytopenia [7% vs. 2% (Study 10); 7% vs. 2% (Study 11)] and infections [30% vs. 14% (Study 11)].

Rheumatoid Arthritis

Among the 2578 patients in global RA studies completed to date, 12% were 65−75 years old and 2% were 75 years old and older. The incidences of adverse reactions were similar between older and younger patients. The rates of serious adverse reactions, including serious infections, malignancies, and cardiovascular events were higher in older patients.

Wegener's Granulomatosis and Microscopic Polyangiitis

Of the 99 Rituxan-treated WG and MPA patients, 36 (36%) were 65 years old and over, while 8 (8%) were 75 years and over. No overall differences in efficacy were observed between patients that were 65 years old and over and younger patients. The overall incidence and rate of all serious adverse events was higher in patients 65 years old and over. The clinical study did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger subjects.

10 OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m^2 have been administered in clinical trials.

11 DESCRIPTION

Rituxan® (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG_1 kappa antibody directed against the CD20 antigen. Rituximab has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. Rituxan is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous administration. Rituxan is supplied at a concentration of 10 mg/mL in either 100 mg/10 mL or 500 mg/50 mL single-use vials. The product is formulated in polysorbate 80 (0.7 mg/mL), sodium citrate dihydrate (7.35 mg/mL), sodium chloride (9 mg/mL) and Water for Injection. The pH is 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes. The antigen is expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL), but the antigen is not found on hematopoietic stem cells, pro-B-cells, normal plasma cells or other normal tissues. CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation, and possibly functions as a calcium ion channel. CD20 is not shed from the cell surface and does not internalize upon antibody binding. Free CD20 antigen is not found in the circulation.

B cells are believed to play a role in the pathogenesis of rheumatoid arthritis (RA) and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor (RF) and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

Mechanism of Action: The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC) and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

12.2 Pharmacodynamics

Non-Hodgkins Lymphoma (NHL)

In NHL patients, administration of Rituxan resulted in depletion of circulating and tissue-based B cells. Among 166 patients in Study 1, circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range.

Rheumatoid Arthritis

In RA patients, treatment with Rituxan induced depletion of peripheral B lymphocytes, with the majority of patients demonstrating near complete depletion (CD19 counts below the lower limit of quantification, 20 cells/μl) within 2 weeks after receiving the first dose of Rituxan. The majority of patients showed peripheral B-cell depletion for at least 6 months. A small proportion of patients (~4%) had prolonged peripheral B-cell depletion lasting more than 3 years after a single course of treatment.

Total serum immunoglobulin levels, IgM, IgG, and IgA were reduced at 6 months with the greatest change observed in IgM. At Week 24 of the first course of Rituxan treatment, small proportions of patients experienced decreases in IgM (10%), IgG (2.8%), and IgA (0.8%) levels below the lower limit of normal (LLN). In the experience with Rituxan in RA patients during repeated Rituxan treatment, 23.3%, 5.5%, and 0.5% of patients experienced decreases in IgM, IgG, and IgA concentrations below LLN at any time after receiving Rituxan, respectively. The clinical consequences of decreases in immunoglobulin levels in RA patients treated with Rituxan are unclear.

Treatment with rituximab in patients with RA was associated with reduction of certain biologic markers of inflammation such as interleukin-6 (IL-6), C-reactive protein (CRP), serum amyloid protein (SAA), S100 A8/S100 A9 heterodimer complex (S100 A8/9), anti-citrullinated peptide (anti-CCP), and RF.

Wegener's Granulomatosis and Microscopic Polyangiitis

In WG and MPA patients, peripheral blood CD19 B-cells depleted to less than 10 cells/μl following the first two infusions of Rituxan, and remained at that level in most (84%) patients through Month 6. By Month 12, the majority of patients (81%) showed signs of B-cell return with counts >10 cells/μL. By Month 18, most patients (87%) had counts >10 cells/μL.

12.3 Pharmacokinetics

Non-Hodgkins Lymphoma (NHL)

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m^2 Rituxan weekly by intravenous infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

The pharmacokinetic profile of rituximab when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with rituximab alone.

Based on a population pharmacokinetic analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median terminal elimination half-life was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher clearance. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the pharmacokinetics of rituximab.

Pharmacokinetics were characterized in 21 patients with CLL receiving rituximab according to the recommended dose and schedule. The estimated median terminal half-life of rituximab was 32 days (range, 14 to 62 days).

Rheumatoid Arthritis

Following administration of 2 doses of Rituxan in patients with RA, the mean (± S.D.; % CV) concentrations after the first infusion (Cmax first) and second infusion (Cmax second) were 157 (± 46; 29%) and 183 (± 55; 30%) mcg/mL, and 318 (± 86; 27%) and 381 (± 98; 26%) mcg/mL for the 2 × 500 mg and 2 × 1000 mg doses, respectively.

Based on a population pharmacokinetic analysis of data from 2005 RA patients who received Rituxan, the estimated clearance of rituximab was 0.335 L/day; volume of distribution was 3.1 L and mean terminal elimination half-life was 18.0 days (range, 5.17 to 77.5 days). Age, weight and gender had no effect on the pharmacokinetics of rituximab in RA patients.

Wegener's Granulomatosis and Microscopic Polyangiitis

Based on the population pharmacokinetic analysis of data in 97 WG and MPA patients who received 375 mg/m^2 rituximab once weekly by intravenous infusion for four weeks, the estimated median terminal elimination half-life was 23 days (range, 9 to 49 days). Rituximab mean clearance and volume of distribution were 0. 312 L/day (range, 0.115 to 0.728 L/day) and 4.50 L (range, 2.21 to 7.52 L) respectively. Male patients and patients with higher BSA or positive HACA levels have higher clearance. However, further dose adjustment based on gender or HACA status is not necessary.

The pharmacokinetics of rituximab have not been studied in children and adolescents. No formal studies were conducted to examine the effects of either renal or hepatic impairment on the pharmacokinetics of rituximab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of Rituxan or to determine potential effects on fertility in males or females.

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

An embryo-fetal developmental toxicity study was performed on pregnant cynomolgus monkeys. Pregnant animals received rituximab via the intravenous route during early gestation (organogenesis period; post-coitum days 20 through 50). Rituximab was administered as loading doses on post-coitum (PC) days 20, 21 and 22, at 15, 37.5 or 75 mg/kg/day, and then weekly on PC Days 29, 36, 43 and 50, at 20, 50 or 100 mg/kg/week. The 100 mg/kg/week dose resulted in 80% of the exposure (based on AUC) of those achieved following a dose of 2 grams in humans. Rituximab crosses the

monkey placenta. Exposed offspring did not exhibit any teratogenic effects but did have decreased lymphoid tissue B cells.

A subsequent pre- and postnatal reproductive toxicity study in cynomolgus monkeys was completed to assess developmental effects including the recovery of B cells and immune function in infants exposed to rituximab in utero. Animals were treated with a loading dose of 0, 15, or 75 mg/kg every day for 3 days, followed by weekly dosing with 0, 20, or 100 mg/kg dose. Subsets of pregnant females were treated from PC Day 20 through postpartum Day 78, PC Day 76 through PC Day 134, and from PC Day 132 through delivery and postpartum Day 28. Regardless of the timing of treatment, decreased B cells and immunosuppression were noted in the offspring of rituximab-treated pregnant animals. The B-cell counts returned to normal levels, and immunologic function was restored within 6 months postpartum.

14 CLINICAL STUDIES

14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in relapsed, refractory CD20+ NHL were demonstrated in 3 single-arm studies enrolling 296 patients.

Study 1

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory, low-grade or follicular, B-cell NHL who received 375 mg/m^2 of Rituxan given as an intravenous infusion weekly for 4 doses. Patients with tumor masses > 10 cm or with > 5000 lymphocytes/μL in the peripheral blood were excluded from the study.

Results are summarized in Table 4. The median time to onset of response was 50 days. Disease-related signs and symptoms (including B-symptoms) resolved in 64% (25/39) of those patients with such symptoms at study entry.

Study 2

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of Rituxan weekly for 8 doses. Results are summarized in Table 4.

Study 3

In a multicenter, single-arm study, 60 patients received 375 mg/m^2 of Rituxan weekly for 4 doses. All patients had relapsed or refractory, low-grade or follicular, B-cell NHL and had achieved an objective clinical response to Rituxan administered 3.8–35.6 months (median 14.5 months) prior to retreatment with Rituxan. Of these 60 patients, 5 received more than one additional course of Rituxan. Results are summarized in Table 4.

Bulky Disease

In pooled data from studies 1 and 3, 39 patients with bulky (single lesion > 10 cm in diameter) and relapsed or refractory, low-grade NHL received Rituxan 375 mg/m^2 weekly for 4 doses. Results are summarized in Table 4.

Table 4
Summary of Rituxan Efficacy Data by Schedule and Clinical Setting

	Study 1 Weekly×4 N=166	Study 2 Weekly×8 N=37	Study 1 and Study 3 Bulky disease, Weekly×4 N=39[a]	Study 3 Retreatment, Weekly×4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b, c, d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

[a] Six of these patients are included in the first column. Thus, data from 296 intent-to-treat patients are provided in this table.

[b] Kaplan-Meier projected with observed range.

[c] "+" indicates an ongoing response.

[d] Duration of response: interval from the onset of response to disease progression.

14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL

The safety and effectiveness of Rituxan in previously untreated, low-grade or follicular, CD20+ NHL were demonstrated in 3 randomized, controlled trials enrolling 1,662 patients.

Study 4

A total of 322 patients with previously untreated follicular NHL were randomized (1:1) to receive up to eight 3-week cycles of CVP chemotherapy alone (CVP) or in combination with Rituxan 375 mg/m^2 on Day 1 of each cycle (R-CVP) in an open-label, multicenter study. The main outcome measure of the study was progression-free survival (PFS) defined as the time from randomization to the first of progression, relapse, or death.

Twenty-six percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 50% had an International Prognostic Index (IPI) score ≥2. The results for PFS as determined by a blinded, independent assessment of progression are presented in Table 5. The point estimates may be influenced by the presence of informative censoring. The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Table 5
Efficacy Results in Study 4

	Study Arm	
	R-CVP N=162	CVP N=160
Median PFS (years)[a]	2.4	1.4
Hazard ratio (95% CI)[b]	0.44 (0.29, 0.65)	

[a] $p < 0.0001$, two-sided stratified log-rank test.

[b] Estimates of Cox regression stratified by center.

Study 5

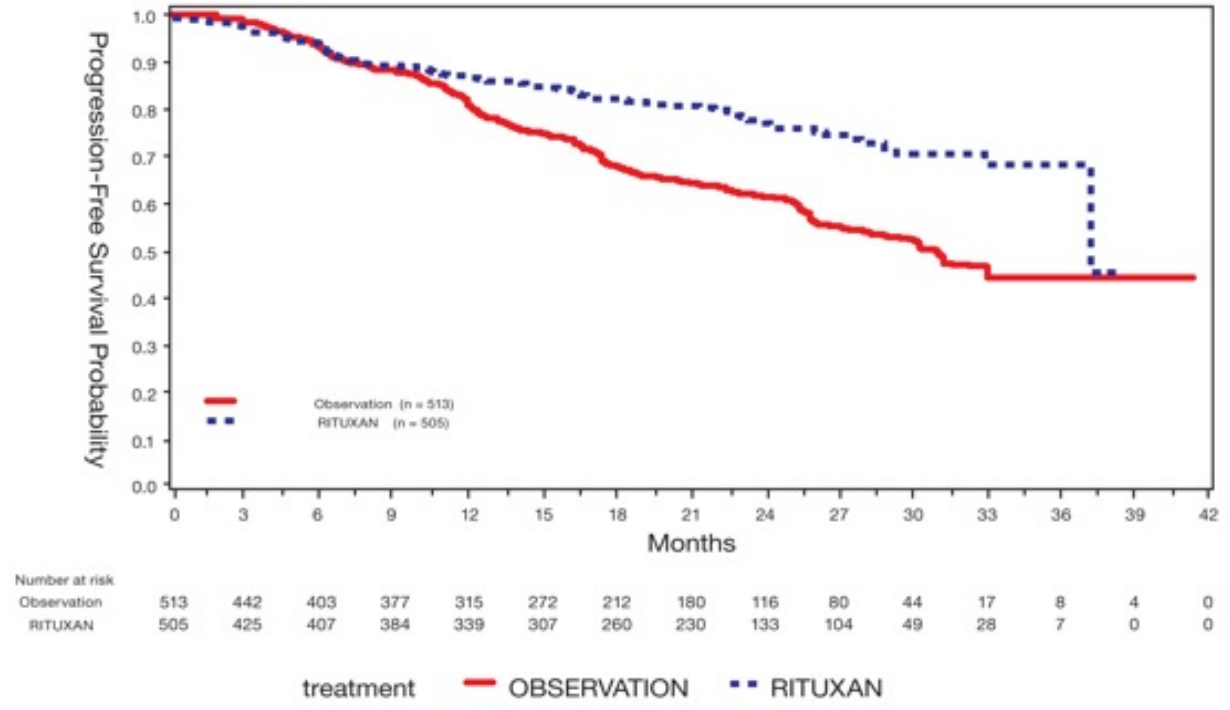
An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

375 mg/m^2 every 8 weeks for up to 12 doses or to observation. Rituxan was initiated at 8 weeks following completion of chemotherapy. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization in the maintenance/observation phase to progression, relapse, or death, as determined by independent review.

Of the randomized patients, 40% were ≥60 years of age, 70% had Stage IV disease, 96% had ECOG performance status (PS) 0–1, and 42% had FLIPI scores of 3–5. Prior to randomization to maintenance therapy, patients had received R-CHOP (75%), R-CVP (22%), or R-FCM (3%); 71% had a complete or unconfirmed complete response and 28% had a partial response.

PFS was longer in patients randomized to Rituxan as single agent maintenance therapy (HR: 0.54, 95% CI: 0.42, 0.70). The PFS results based on investigator assessment of progression were similar to those obtained by the independent review assessment.

Figure 1
Kaplan-Meier Plot of IRC Assessed PFS



Study 6

A total of 322 patients with previously untreated low-grade, B-cell NHL who did not progress after 6 or 8 cycles of CVP chemotherapy were enrolled in an open-label, multicenter, randomized trial. Patients were randomized (1:1) to receive Rituxan, 375 mg/m^2 intravenous infusion, once weekly for 4 doses every 6 months for up to 16 doses or no further therapeutic intervention. The main outcome measure of the study was progression-free survival defined as the time from randomization to progression, relapse, or death. Thirty-seven percent of the study population was >60 years of age, 99% had Stage III or IV disease, and 63% had an IPI score ≥2.

There was a reduction in the risk of progression, relapse, or death (hazard ratio estimate in the range of 0.36 to 0.49) for patients randomized to Rituxan as compared to those who received no additional treatment.

14.3 Diffuse Large B-Cell NHL (DLBCL)

The safety and effectiveness of Rituxan were evaluated in three randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse large B-cell NHL received Rituxan in combination with

cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 7

A total of 632 patients age ≥ 60 years with DLBCL (including primary mediastinal B-cell lymphoma) were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients received 6 or 8 cycles of CHOP, each cycle lasting 21 days. All patients in the R-CHOP arm received 4 doses of Rituxan 375 mg/m^2 on Days −7 and −3 (prior to Cycle 1) and 48−72 hours prior to Cycles 3 and 5. Patients who received 8 cycles of CHOP also received Rituxan prior to Cycle 7. The main outcome measure of the study was progression-free survival, defined as the time from randomization to the first of progression, relapse, or death. Responding patients underwent a second randomization to receive Rituxan or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III–IV disease, 56% had IPI scores ≥ 2, 86% had ECOG performance status of < 2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 6. These results reflect a statistical approach which allows for an evaluation of Rituxan administered in the induction setting that excludes any potential impact of Rituxan given after the second randomization.

Analysis of results after the second randomization in Study 7 demonstrates that for patients randomized to R-CHOP, additional Rituxan exposure beyond induction was not associated with further improvements in progression-free survival or overall survival.

Study 8

A total of 399 patients with DLBCL, age ≥ 60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP. All patients received up to eight 3-week cycles of CHOP induction; patients in the R-CHOP arm received Rituxan 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event-free survival, defined as the time from randomization to relapse, progression, change in therapy, or death from any cause. Among all enrolled patients, 80% had Stage III or IV disease, 60% of patients had an age-adjusted IPI ≥ 2, 80% had ECOG performance status scores < 2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 6.

Study 9

A total of 823 patients with DLBCL, aged 18−60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy regimen alone or in combination with Rituxan. The main outcome measure of the study was time to treatment failure, defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse, or death. Among all enrolled patients, 28% had Stage III–IV disease, 100% had IPI scores of ≤ 1, 99% had ECOG performance status of < 2, 29% had elevated LDH levels, 49% had bulky disease, and 34% had extranodal involvement. Efficacy results are presented in Table 6.

Table 6
Efficacy Results in Studies 7, 8, and 9

	Study 7 (n=632)		Study 8 (n=399)		Study 9 (n=823)	
	R-CHOP	CHOP	R-CHOP	CHOP	R-Chemo	Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	3.1	1.6	2.9	1.1	NE[b]	NE[b]
Hazard ratio[d]	0.69[a]		0.60[a]		0.45[a]	
Overall survival at 2 years[c]	74%	63%	69%	58%	95%	86%
Hazard ratio[d]	0.72[a]		0.68[a]		0.40[a]	

[a] Significant at $p < 0.05$, 2-sided.

[b] NE = Not reliably estimable.

[c] Kaplan-Meier estimates.

[d] R-CHOP vs. CHOP.

In Study 8, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

14.4 Chronic Lymphocytic Leukemia (CLL)

The safety and effectiveness of Rituxan were evaluated in two randomized (1:1) multicenter open-label studies comparing FC alone or in combination with Rituxan for up to 6 cycles in patients with previously untreated CLL [Study 10 (n = 817)] or previously treated CLL [Study 11 (n = 552)]. Patients received fludarabine 25 mg/m^2/day and cyclophosphamide 250 mg/m^2/day on days 1, 2 and 3 of each cycle, with or without Rituxan. In both studies, seventy-one percent of CLL patients received 6 cycles and 90% received at least 3 cycles of Rituxan-based therapy.

In Study 10, 30% of patients were 65 years or older, 31% were Binet stage C, 45% had B symptoms, more than 99% had ECOG performance status (PS) 0–1, 74% were male, and 100% were White. In Study 11, 44% of patients were 65 years or older, 28% had B symptoms, 82% received a prior alkylating drug, 18% received prior fludarabine, 100% had ECOG PS 0–1, 67% were male and 98% were White.

The main outcome measure in both studies was progression-free survival (PFS), defined as the time from randomization to progression, relapse, or death, as determined by investigators (Study 10) or an independent review committee (Study 11). The investigator assessed results in Study 11 were supportive of those obtained by the independent review committee. Efficacy results are presented in Table 7.

Table 7
Efficacy Results in Studies 10 and 11

	Study 10* (Previously untreated)		Study 11* (Previously treated)	
	R-FC N=408	FC N=409	R-FC N=276	FC N=276
Median PFS (months)	39.8	31.5	26.7	21.7
Hazard ratio (95% CI)	0.56 (0.43, 0.71)		0.76 (0.6, 0.96)	
P value (Log-Rank test)	<0.01		0.02	
Response rate (95% CI)	86% (82, 89)	73% (68, 77)	54% (48, 60)	45% (37, 51)

*As defined in 1996 National Cancer Institute Working Group guidelines.

Across both studies, 243 of 676 Rituxan-treated patients (36%) were 65 years of age or older and 100 Rituxan-treated patients (15%) were 70 years of age or older. The results of exploratory subset analyses in elderly patients are presented in Table 8.

Table 8
Efficacy Results in Studies 10 and 11 in Subgroups Defined by Age[a]

	Study 10		Study 11	
Age subgroup	Number of Patients	Hazard Ratio for PFS (95% CI)	Number of Patients	Hazard Ratio for PFS (95% CI)
Age < 65 yrs	572	0.52 (0.39, 0.70)	313	0.61 (0.45, 0.84)
Age ≥ 65 yrs	245	0.62 (0.39, 0.99)	233	0.99 (0.70, 1.40)
Age < 70 yrs	736	0.51 (0.39, 0.67)	438	0.67 (0.51, 0.87)
Age ≥ 70 yrs	81	1.17 (0.51, 2.66)	108	1.22 (0.73, 2.04)

[a] From exploratory analyses.

14.5 Rheumatoid Arthritis (RA)

Reducing the Signs and Symptoms: Initial and Re-Treatment Courses

The efficacy and safety of Rituxan were evaluated in two randomized, double-blind, placebo-controlled studies of adult patients with moderately to severely active RA who had a prior inadequate response to at least one TNF inhibitor. Patients were 18 years of age or older, diagnosed with active RA according to American College of Rheumatology (ACR) criteria, and had at least 8 swollen and 8 tender joints.

In RA Study 1, patients were randomized to receive either Rituxan 2×1000 mg+MTX or placebo+MTX for 24 weeks. Further courses of Rituxan 2×1000 mg+MTX were administered in an open label extension study at a frequency determined by clinical evaluation, but no sooner than 16 weeks after the preceding course of Rituxan. In addition to the intravenous premedication, glucocorticoids were administered orally on a tapering schedule from baseline through Day 14. The proportions of patients achieving ACR 20, 50, and 70 responses at Week 24 of the placebo-controlled period are shown in Table 9.

In RA Study 2, all patients received the first course of Rituxan 2 × 1000 mg + MTX. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 × 1000 mg + MTX or placebo + MTX, the majority between Weeks 24–28. The proportions of

patients achieving ACR 20, 50, and 70 responses at Week 24, before the re-treatment course, and at Week 48, after retreatment, are shown in Table 9.

Table 9
ACR Responses in Study 1 and Study 2 (Percent of Patients)
(Modified Intent-to-Treat Population)

Inadequate Response to TNF Antagonists							
Study 1 24 Week Placebo-Controlled (Week 24)				Study 2 Placebo-Controlled Retreatment (Week 24 and Week 48)			
Response	Placebo + MTX n = 201	Rituxan + MTX n = 298	Treatment Difference (Rituxan – Placebo)[c] (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo)[a,b,c] (95% CI)
ACR20				ACR20			
Week 24	18%	51%	33% (26%, 41%)	Week 24	48%	45%	NA
				Week 48	45%	54%	11% (2%, 20%)
ACR50				ACR50			
Week 24	5%	27%	21% (15%, 27%)	Week 24	27%	21%	NA
				Week 48	26%	29%	4% (-4%, 13%)
ACR70				ACR70			
Week 24	1%	12%	11% (7%, 15%)	Week 24	11%	8%	NA
				Week 48	13%	14%	1% (-5%, 8%)

[a] In Study 2, all patients received a first course of Rituxan 2 x 1000 mg. Patients who experienced ongoing disease activity were randomized to receive a second course of either Rituxan 2 x 1000 mg + MTX or placebo + MTX at or after Week 24.

[b] Since all patients received a first course of Rituxan, no comparison between Placebo + MTX and Rituxan + MTX is made at Week 24.

[c] For Study 1, weighted difference stratified by region (US, rest of the world) and Rheumatoid Factor (RF) status (positive >20 IU/mL, negative <20 IU/mL) at baseline; For Study 2, weighted difference stratified by RF status at baseline and ≥20% improvement from baseline in both SJC and TJC at Week 24 (Yes/No).

Improvement was also noted for all components of ACR response following treatment with Rituxan, as shown in Table 10.

Table 10
Components of ACR Response at Week 24 in Study 1
(Modified Intent-to-Treat Population)

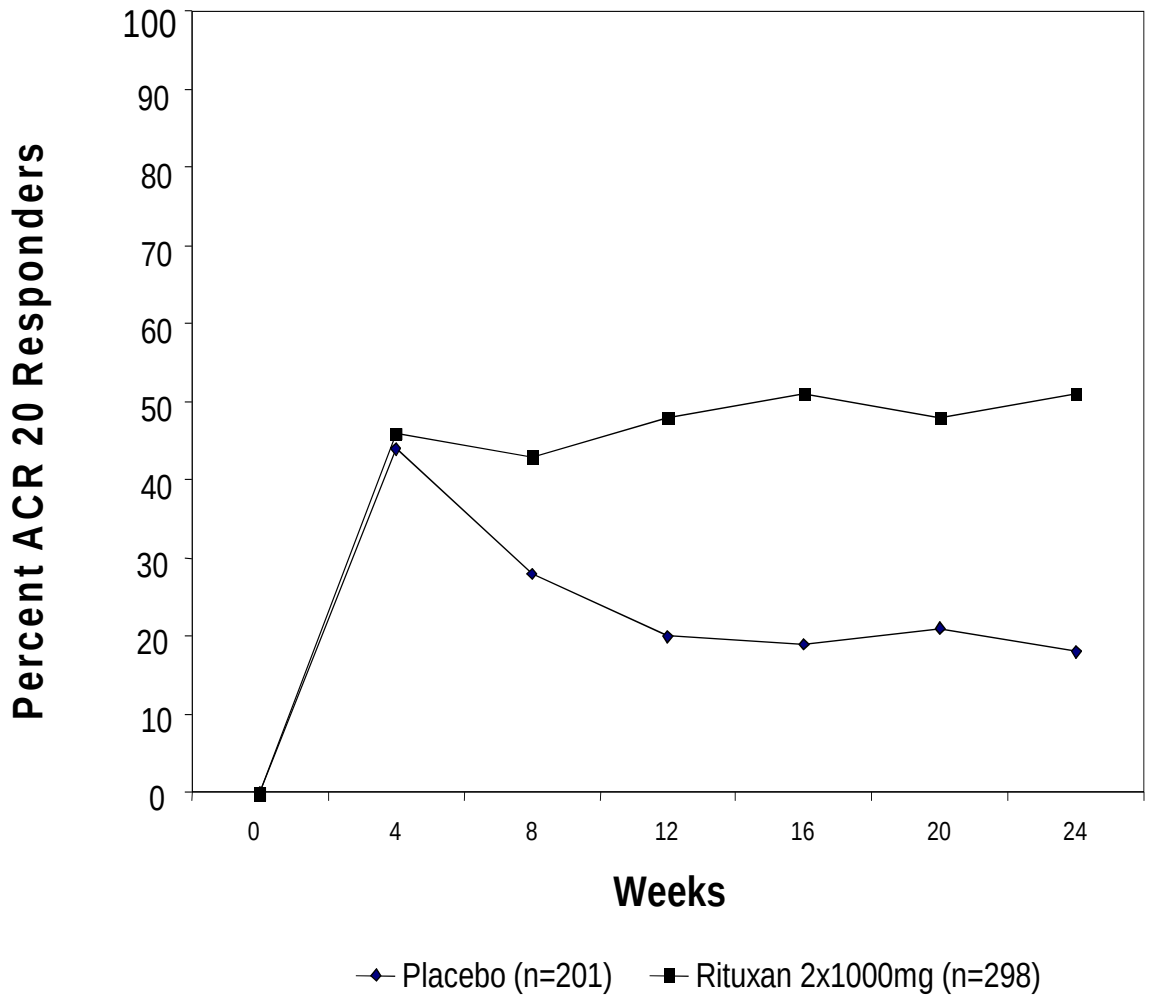
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	73.0	68.0	71.0	41.0
Pain[a]	68.0	68.0	67.0	38.5
Disability Index (HAQ)[b]	2.0	1.9	1.9	1.5
CRP (mg/dL)	2.4	2.5	2.6	0.9

[a] Visual Analogue Scale: 0 = best, 100 = worst.

[b] Disability Index of the Health Assessment Questionnaire: 0 = best, 3 = worst.

The time course of ACR 20 response for Study 1 is shown in Figure 2. Although both treatment groups received a brief course of intravenous and oral glucocorticoids, resulting in similar benefits at Week 4, higher ACR 20 responses were observed for the Rituxan group by Week 8. A similar proportion of patients achieved these responses through Week 24 after a single course of treatment (2 infusions) with Rituxan. Similar patterns were demonstrated for ACR 50 and 70 responses.

Figure 2
Percent of Patients Achieving ACR 20 Response by Visit*
Study 1 (Inadequate Response to TNF Antagonists)



*The same patients may not have responded at each time point.

Radiographic Response

In RA Study 1, structural joint damage was assessed radiographically and expressed as changes in Genant-modified Total Sharp Score (TSS) and its components, the erosion score (ES) and the joint space narrowing (JSN) score. Rituxan +MTX slowed the progression of structural damage compared to placebo +MTX after 1 year as shown in Table 11.

Table 11
Mean Radiographic Change From Baseline to 104 Weeks

Inadequate Response to TNF Antagonists				
Parameter	Rituxan 2 × 1000 mg + MTX[b]	Placebo + MTX[c]	Treatment Difference (Placebo – Rituxan)	95% CI
Change during First Year				
TSS	0.66	1.77	1.11	(0.47, 1.75)
ES	0.44	1.19	0.75	(0.32, 1.19)
JSN Score	0.22	0.58	0.36	(0.10, 0.62)
Change during Second Year[a]				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

[a] Based on radiographic scoring following 104 weeks of observation.

[b] Patients received up to 2 years of treatment with Rituxan + MTX.

[c] Patients receiving Placebo + MTX. Patients receiving Placebo + MTX could have received retreatment with Rituxan + MTX from Week 16 onward.

In RA Study 1 and its open-label extension, 70% of patients initially randomized to Rituxan + MTX and 72% of patients initially randomized to placebo + MTX were evaluated radiographically at Year 2. As shown in Table 11 progression of structural damage in Rituxan + MTX patients was further reduced in the second year of treatment.

Following 2 years of treatment with Rituxan + MTX, 57% of patients had no progression of structural damage. During the first year, 60% of Rituxan + MTX treated patients had no progression, defined as a change in TSS of zero or less compared to baseline, compared to 46% of placebo + MTX treated patients. In their second year of treatment with Rituxan + MTX, more patients had no progression than in the first year (68% vs. 60%), and 87% of the Rituxan + MTX treated patients who had no progression in the first year also had no progression in the second year.

Lesser Efficacy of 500 Vs. 1000 mg Treatment Courses for Radiographic Outcomes

RA Study 3 is a randomized, double-blind, placebo-controlled study which evaluated the effect of placebo + MTX compared to Rituxan 2 x 500 mg + MTX and Rituxan 2 × 1000 mg + MTX treatment courses in MTX-naïve RA patients with moderately to severely active disease. Patients received a first course of two infusions of rituximab or placebo on Days 1 and 15. MTX was initiated at 7.5 mg/week and escalated up to 20 mg/week by Week 8 in all three treatment arms. After a minimum of 24 weeks, patients with ongoing disease activity were eligible to receive re-treatment with additional courses of their assigned treatment. After one year of treatment, the proportion of patients achieving ACR 20/50/70 responses were similar in both Rituxan dose groups and were higher than in the placebo group. However, with respect to radiographic scores, only the Rituxan 1000 mg treatment group demonstrated a statistically significant reduction in TSS: a change of 0.36 units compared to 1.08 units for the placebo group, a 67% reduction.

Physical Function Response

RA Study 4 is a randomized, double-blind, placebo-controlled study in adult RA patients with moderately to severely active disease with inadequate response to MTX. Patients were randomized to receive an initial course of Rituxan 500 mg, Rituxan 1000 mg, or placebo in addition to background MTX.

Physical function was assessed at Weeks 24 and 48 using the Health Assessment Questionnaire Disability Index (HAQ-DI). From baseline to Week 24, a greater proportion of Rituxan-treated patients had an improvement in HAQ-DI of at least 0.22 (a minimal clinically important difference) and a greater mean HAQ-DI improvement compared to placebo, as shown in Table 12. HAQ-DI results for the Rituxan 500 mg treatment group were similar to the Rituxan 1000 mg treatment group; however radiographic responses were not assessed (see Dosing Precaution in the Radiographic Responses section above). These improvements were maintained at 48 weeks.

Table 12
Improvement from Baseline in Health Assessment
Questionnaire Disability Index (HAQ-DI) at Week 24 in Study 4

	Placebo + MTX n = 172	Rituxan 2 × 1000 mg + MTX n = 170	Treatment Difference (Rituxan – Placebo)[b] (95% CI)
Mean Improvement from Baseline	0.19	0.42	0.23 (0.11, 0.34)
Percent of patients with "Improved" score (Change from Baseline ≥ MCID)[a]	48%	58%	11% (0%, 21%)

[a] Minimal Clinically Important Difference: MCID for HAQ = 0.22.

[b] Adjusted difference stratified by region (US, rest of the world) and rheumatoid factor (RF) status (positive ≥ 20 IU/mL, negative < 20 IU/mL) at baseline.

14.6 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

A total of 197 patients with active, severe WG and MPA (two forms of ANCA Associated Vasculidities) were treated in a randomized, double-blind, active-controlled multicenter, non-inferiority study, conducted in two phases – a 6 month remission induction phase and a 12 month remission maintenance phase. Patients were 15 years of age or older, diagnosed with WG (75% of patients) or MPA (24% of patients) according to the Chapel Hill Consensus conference criteria (1% of the patients had unknown vasculitis type). All patients had active disease, with a Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG) ≥ 3, and their disease was severe, with at least one major item on the BVAS/WG. Ninety-six (49%) of patients had new disease and 101 (51%) of patients had relapsing disease.

Patients in both arms received 1000 mg of pulse intravenous methylprednisolone per day for 1 to 3 days within 14 days prior to initial infusion. Patients were randomized in a 1:1 ratio to receive either Rituxan 375 mg/m^2 once weekly for 4 weeks or oral cyclophosphamide 2 mg/kg daily for 3 to 6 months in the remission induction phase. Patients were pre-medicated with antihistamine and acetaminophen prior to Rituxan infusion. Following intravenous corticosteroid administration, all patients received oral prednisone (1 mg/kg/day, not exceeding 80 mg/day) with pre-specified tapering. Once remission was achieved or at the end of the 6 month remission induction period, the cyclophosphamide group received azathioprine to maintain remission. The Rituxan group did not receive additional therapy to maintain remission. The main outcome measure for both WG and MPA patients was achievement of complete remission at 6 months defined as a BVAS/WGof 0, and off glucocorticoid therapy. The pre-specified non-inferiority margin was a treatment difference of 20%. As shown in Table 13, the study demonstrated non-inferiority of Rituxan to cyclophosphamide for complete remission at 6 months.

Table 13
Percentage of Patients Who Achieved
Complete Remission at 6 Months (Intent-to-Treat Population)

	Rituxan (n=99)	Cyclophosphamide (n=98)	Treatment Difference (Rituxan – Cyclophosphamide)
Rate	64%	53%	11%
95.1%[b] CI	(54%, 73%)	(43%, 63%)	(–3%, 24%)[a]

[a] non-inferiority was demonstrated because the lower bound was higher than the prespecified non-inferiority margin (–3%>–20%).

[b] The 95.1% confidence level reflects an additional 0.001 alpha to account for an interim efficacy analysis.

Complete Remission (CR) at 12 and 18 months

In the Rituxan group, 44% of patients achieved CR at 6 and 12 months, and 38% of patients achieved CR at 6, 12, and 18 months. In patients treated with cyclophosphamide (followed by azathioprine for maintenance of CR), 38% of patients achieved CR at 6 and 12 months, and 31% of patients achieved CR at 6, 12, and 18 months.

Retreatment with Rituxan

Based upon investigator judgment, 15 patients received a second course of Rituxan therapy for treatment of relapse of disease activity which occurred between 8 and 17 months after the first course of Rituxan. The limited data preclude any conclusions regarding the efficacy of subsequent courses of Rituxan in patients with WG and MPA [*see Warnings and Precautions (5.14)*].

16 HOW SUPPLIED/STORAGE AND HANDLING

Rituxan vials [100 mg/10 mL single-use vials (NDC 50242-051-21) and 500 mg/50 mL single-use vials (NDC 50242-053-06)] are stable at 2°C–8°C (36°F–46°F). Do not use beyond expiration date stamped on carton. Rituxan vials should be protected from direct sunlight. Do not freeze or shake.

Rituxan solutions for infusion may be stored at 2°C–8°C (36°F–46°F) for 24 hours. Rituxan solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituxan solutions do not contain a preservative, diluted solutions should be stored refrigerated (2°C–8°C). No incompatibilities between Rituxan and polyvinylchloride or polyethylene bags have been observed.

17 PATIENT COUNSELING INFORMATION

Patients should be provided the Rituxan Medication Guide and provided an opportunity to read prior to each treatment session. It is important that the patient's overall health be assessed at each visit and the risks of Rituxan therapy and any questions resulting from the patient's reading of the Medication Guide be discussed.

Rituxan is detectable in serum for up to six months following completion of therapy. Individuals of childbearing potential should use effective contraception during treatment and for 12 months after Rituxan therapy.

RITUXAN® [rituximab]
Manufactured by: 10134808
Genentech, Inc. Initial US Approval: November 1997
A Member of the Roche Group PI Revision Date 02 2012
1 DNA Way Rituxan® is a registered trademark of Biogen Idec, Inc.
South San Francisco, CA 94080-4990

MEDICATION GUIDE
Rituxan® (ri-tuk-san)
(rituximab)
for injection

Read this Medication Guide before you start Rituxan and before each Rituxan infusion. There may be new information. This Medication Guide does not take the place of talking to your doctor about your medical condition or your treatment.

What is the most important information I should know about Rituxan?

Rituxan can cause serious side effects that can lead to death, including:

1. **Infusion reactions.** Infusion reactions are the most common side effect of Rituxan treatment. Serious infusion reactions can happen during your infusion or within 24 hours after your infusion of Rituxan. Your doctor should give you medicines before your infusion of Rituxan to decrease your chance of having a severe infusion reaction.

   Tell your doctor or get medical help right away if you get any of these symptoms during or after an infusion of Rituxan:

   - hives (red itchy welts) or rash
   - itching
   - swelling of your lips, tongue, throat or face
   - sudden cough
   - shortness of breath, difficulty breathing, or wheezing
   - weakness
   - dizziness or feel faint
   - palpitations (feel like your heart is racing or fluttering)
   - chest pain

2. **Progressive Multifocal Leukoencephalopathy (PML).** PML is a rare, serious brain infection caused by a virus. People with weakened immune systems can get PML. Your chance of getting PML may be higher if you are treated with Rituxan alone or with other medicines that weaken your immune system. PML can result in death or severe disability. There is no known treatment, prevention, or cure for PML.

   Tell your doctor right away if you have any of the following symptoms or if anyone close to you notices these symptoms:

   - confusion or problems thinking
   - loss of balance
   - change in the way you walk or talk
   - decreased strength or weakness on one side of your body
   - blurred vision or loss of vision

3. **Tumor Lysis Syndrome (TLS).** TLS is caused by the fast breakdown of cancer cells. TLS can cause you to have:

   - kidney failure and the need for dialysis treatment
   - abnormal heart rhythm

Your doctor may do blood tests to check you for TLS. Your doctor may give you medicine to help prevent TLS.

4. **Severe skin and mouth reactions.** Tell your doctor or get medical help right away if you get any of these symptoms at anytime during your treatment with Rituxan:
    - painful sores or ulcers on your skin, lips or in your mouth
    - blisters
    - peeling skin
    - rash
    - pustules

See "**What are possible side effects of Rituxan?"** for more information about side effects.

What is Rituxan?

Rituxan is a prescription medicine used to treat:

- **Non-Hodgkin's Lymphoma (NHL):** alone or with other chemotherapy medicines.
- **Chronic Lymphocytic Leukemia (CLL):** with the chemotherapy medicines fludarabine and cyclophosphamide.
- **Rheumatoid Arthritis (RA):** with another prescription medicine called methotrexate, to reduce the signs and symptoms of moderate to severe active RA in adults, after treatment with at least one other medicine called a Tumor Necrosis Factor (TNF) antagonist has been used and did not work well enough.
- **Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA):** with glucocorticoids, to treat WG and MPA.

People with serious infections should not receive Rituxan.
It is not known if Rituxan is safe or effective in children.

What should I tell my doctor before receiving Rituxan?
Before receiving Rituxan, tell your doctor if you:

- have had a severe infusion reaction to Rituxan in the past
- have a history of heart problems, irregular heart beat or chest pain
- have lung or kidney problems
- have an infection or weakened immune system.
- have or have had any severe infections including:
    - Hepatitis B virus (HBV)
    - Hepatitis C virus (HCV)
    - Cytomegalovirus (CMV)
    - Herpes simplex virus (HSV)
    - Parvovirus B19
    - Varicella zoster virus (chickenpox or shingles)
    - West Nile Virus

- have had a recent vaccination or are scheduled to receive vaccinations. You should not receive certain vaccines before or after you receive Rituxan. Tell your doctor if anyone in your household is scheduled to receive a vaccination. Some types of vaccines can spread to people with a weakened immune system, and cause serious problems.
- have taken Rituxan for WG or MPA in the past.
- have any other medical conditions
- are pregnant or planning to become pregnant. Rituxan may affect the white blood cell counts of your unborn baby. It is not known if Rituxan may harm your unborn baby in other ways.

  Women who are able to become pregnant should use effective birth-control (contraception) while using Rituxan and for 12 months after you finish treatment. Talk to your doctor about effective birth control.
- are breast-feeding or plan to breast-feed. It is not known if Rituxan passes into your breast milk. You and your doctor should decide the best way to feed your baby if you receive Rituxan.

Tell your doctor about all the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. Especially tell your doctor if you take or have taken:

- a Tumor Necrosis Factor (TNF) inhibitor medicine
- a Disease Modifying Anti-Rheumatic Drug (DMARD)

If you are not sure if your medicine is one listed above, ask your doctor or pharmacist.

Know the medicines you take. Keep a list of them to show to your doctor and pharmacist when you get a new medicine. Do not take any new medicine without talking with your doctor.

How will I receive Rituxan?

- Rituxan is given by infusion through a needle placed in a vein (intravenous infusion), in your arm. Talk to your doctor about how you will receive Rituxan.
- Your doctor may prescribe medicines before each infusion of Rituxan to reduce side effects of infusions such as fever and chills.
- Your doctor should do regular blood tests to check for side effects to Rituxan.

Before each Rituxan treatment, your doctor or nurse will ask you questions about your general health. Tell your doctor or nurse about any new symptoms.

What are the possible side effects of Rituxan?

Rituxan can cause serious and life-threatening side effects, including:

See **"What is the most important information I should know about Rituxan?"**

- **Hepatitis B virus (HBV) reactivation.** If you have had hepatitis B or are a carrier of hepatitis B virus, receiving Rituxan could cause the virus to become an active infection again. Hepatitis B reactivation may cause serious liver problems including liver failure, and death. You should not receive Rituxan if you have active hepatitis B liver disease. Your doctor should monitor you for hepatitis B infection during and for several months after you stop receiving Rituxan.

- **Serious infections.** Serious infections can happen during and after treatment with Rituxan, and can lead to death. Rituxan can lower the ability of your immune system to fight infections. Types of serious infections that can happen with Rituxan include bacterial, fungal, and viral infections. After receiving Rituxan, some patients have developed low levels of certain antibodies in their blood for a long period of time (longer than 11 months). Some of these

patients with low antibody levels developed infections. Call your doctor right away if you have any symptoms of infection:

- fever
- cold symptoms, such as runny nose or sore throat that do not go away
- flu symptoms, such as cough, tiredness, and body aches
- earache or headache
- pain during urination
- white patches in the mouth or throat
- cuts, scrapes or incisions that are red, warm, swollen or painful

- **Heart problems.** Rituxan may cause chest pain and irregular heart beats which may need treatment, or your doctor may decide to stop your treatment with Rituxan.
- **Kidney problems,** especially if you are receiving Rituxan for NHL. Your doctor should do blood tests to check how well your kidneys are working.
- **Stomach and Serious bowel problems that can sometimes lead to death.** Bowel problems, including blockage or tears in the bowel can happen if you receive Rituxan with chemotherapy medicines to treat non-Hodgkin's lymphoma. Tell your doctor right away if you have any stomach area pain during treatment with Rituxan.
- **Low blood cell counts.** Your doctor may do blood tests during treatment with Rituxan to check your blood cell counts.
  - **White blood cells.** White blood cells fight against bacterial infections. Low white blood cells can cause you to get infections, which may be serious. See "Increased risk of infections" above for a list of symptoms of infection.
  - **Red blood cells.** Red blood cells carry oxygen to your body tissues and organs.
  - **Platelets.** Platelets are blood cells that help your blood to clot.

Common side effects during Rituxan treatment include:

- infusion reactions (see What is the most important information I should know about Rituxan?)
- chills
- infections
- body aches
- tiredness
- low white blood cells

Other side effects with Rituxan include:

- aching joints during or within hours of receiving an infusion
- more frequent upper respiratory tract infection

Tell your doctor about any side effect that bothers you or that does not go away.
These are not all of the possible side effects with Rituxan. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about Rituxan

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. This Medication Guide provides a summary of the most important information about Rituxan. If you would like more information, talk with your doctor. You can ask your doctor for information about Rituxan that is written for healthcare professionals.

For more information, go to www.Rituxan.com or call 1-877-474-8892.

What are the ingredients in Rituxan?

Active ingredient: rituximab

Inactive ingredients: sodium chloride, sodium citrate dihydrate, polysorbate 80, and water for injection.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Jointly Marketed by: Biogen Idec Inc. and Genentech USA, Inc.

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