関節リウマチ (RA) 治療用リツキサン (Rituxan) リソースキット

リツキサン (Rituxan) の使用検討と治療開始のための完全ガイド

リツキサン (Rituxan) はわずか 1 コースの治療 (点滴 2 回) で症状を改善し、半年の緩和が得られます。

リツキサン (RITUXAN) とは? リツキサン (Rituxan) は成人用の処方薬で、他の腫瘍壊死因子 (TNF) 阻害薬1 種類以上を用いた治療の効果が芳しくなかった場合に、メトトレキサートというもうひとつの薬剤と併用して、中度から重度の活動性関節リウマチ (RA) の徴候と症状を軽減します。

重度の感染症がある方はリツキサン (Rituxan) を使用できません。

Rituxan® Rituximab
今日、そして6カ月先のために

重要な安全情報: **は注入反応、腫瘍崩壊症候群、重度の皮膚反応、および進行性多巣性白質脳症 (PML) を含む重度の感染症と関連が指摘されています。**詳細はこのパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

「リツキサン (Rituxan) のご紹介」

このたび弊社より、関節リウマチ (RA) の症状を長期間にわたって改善できる比類なく優れた治療薬、リツキサン (Rituxan®、一般名：リツキシマブ) をご紹介できる運びとなりました。リツキサン (Rituxan) は他の関節リウマチ治療薬とは異なる機能を持っています。他の治療薬が十分に功を奏しなかった方でも、リツキサン (Rituxan) が有効な場合があります。

以下の情報をお読みのうえ、リツキサン (Rituxan) について医師にご相談ください。大切なことができない毎日に「ストップ」をかけるための重要な第一歩となるかもしれません。

「リツキサン (Rituxan) 使用検討のための手引き

リツキサンが患者に適している理由

- 2 度の点滴静注から成る 1 コースによって 半年間関節リウマチ症状を改善 (P8)
- 便利な投与計画:年にわずか 4 回の点滴 (P10)
- 関節リウマチの進行を遅らせて関節を保護 (P16)
- 他の治療薬による成果が十分得られなかった場合でも期待できる効果 (P18)

治療の開始にあたり知っておくべきこと?

- 点滴に関する情報 (P23)
- リツキサン (Rituxan) の1回目の点滴で予想されること (P24)
- 2 回目以降の点滴について (P27)

医師と相談すべきこと?

- 医療提供者と患者の話し合いの手引き (P31)
- 起こりうる副作用をはじめとする重要な安全情報 (P40)
- 治療開始をお手伝いする Genentech Rheumatology Access Solutions® フォーム (P44)
- 経済的支援のリソース (P45)

治療を検討する際には、医療提供者と共に潜在的なリスクと利点を比べて考えることが重要です。リツキサン (Rituxan) に関連するリスクについては、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

このパンフレットに紹介されているリツキサン (Rituxan®、一般名：リツキシマブ) 使用者は、Genentech USA, Inc. と Biogen Idec Inc. が提供する RISE™ アンバサダー プログラムの会員です。会員の方々にはその経験談をお話しいただくにあたり、時間と費用に対して、Genentech から報酬をお渡ししています。

リツキサン(Rituxan)を選ぶ理由

この項の内容:

- リツキサン (Rituxan) 治療の 1 コース (2 回の点滴) で症状を半年間緩和できます。
- わずか 2 コース (4 回の点滴) で関節リウマチを 1 年間管理できます。
- リツキサン (Rituxan) は関節リウマチによる進行を遅らせて関節を保護できます。
- 他の治療薬で成果が得られなかった方でも、リツキサン (Rituxan) が効を奏する場合があることをご説明します。

重要な安全情報

ご自身のすべての病状、服用中の医薬品、受けているまたは受ける予定のある予防接種について医師とご相談ください。妊娠している方、妊娠を予定している方、授乳中の方は、その旨を医師に申し出てください。

楽しいひと時は持てていますか
No way, RA

中度から重度の活動性関節リウマチ (RA) にお悩みの方は、毎日直面する困難と自分への問いかけに心当たりがあることでしょう。

家族の集まりにどうしても参加できないことはありませんか?仕事を休んで自宅で過ごしていませんか?お友達と会って話す機会を逃していませんか?

リツキサン (Rituxan®、一般名：リツキシマブ)を治療に取り入れることで、他の治療薬が十分に功を奏しなかった方でも関節リウマチの症状を改善し、関節を保護することが可能です。

リツキサン (Rituxan) について医師にご相談ください。大切なことができない毎日に「ストップ」をかけるための、第一歩となるかもしれません。

重要な安全情報

リツキサン (Rituxan) への反応には個人差があることにご注意ください。場合によっては、リツキサン (Rituxan) 治療中またはその後に副作用を経験することがあります。

リツキサン (Rituxan) についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

リツキサン(Rituxan)
治療効果
の即効性と継続性?

リツキサン (Rituxan®、一般名：リツキシマブ) は、わずか 1 コースの治療 (2 週間ごとの 2 回の点滴) で 半年間症状を改善できる唯一の関節リウマチ治療薬です。

治験では、リツキサン (Rituxan) を使用した初回のコース治療後わずか 2 週間で、症状の改善が認められた患者もありました。

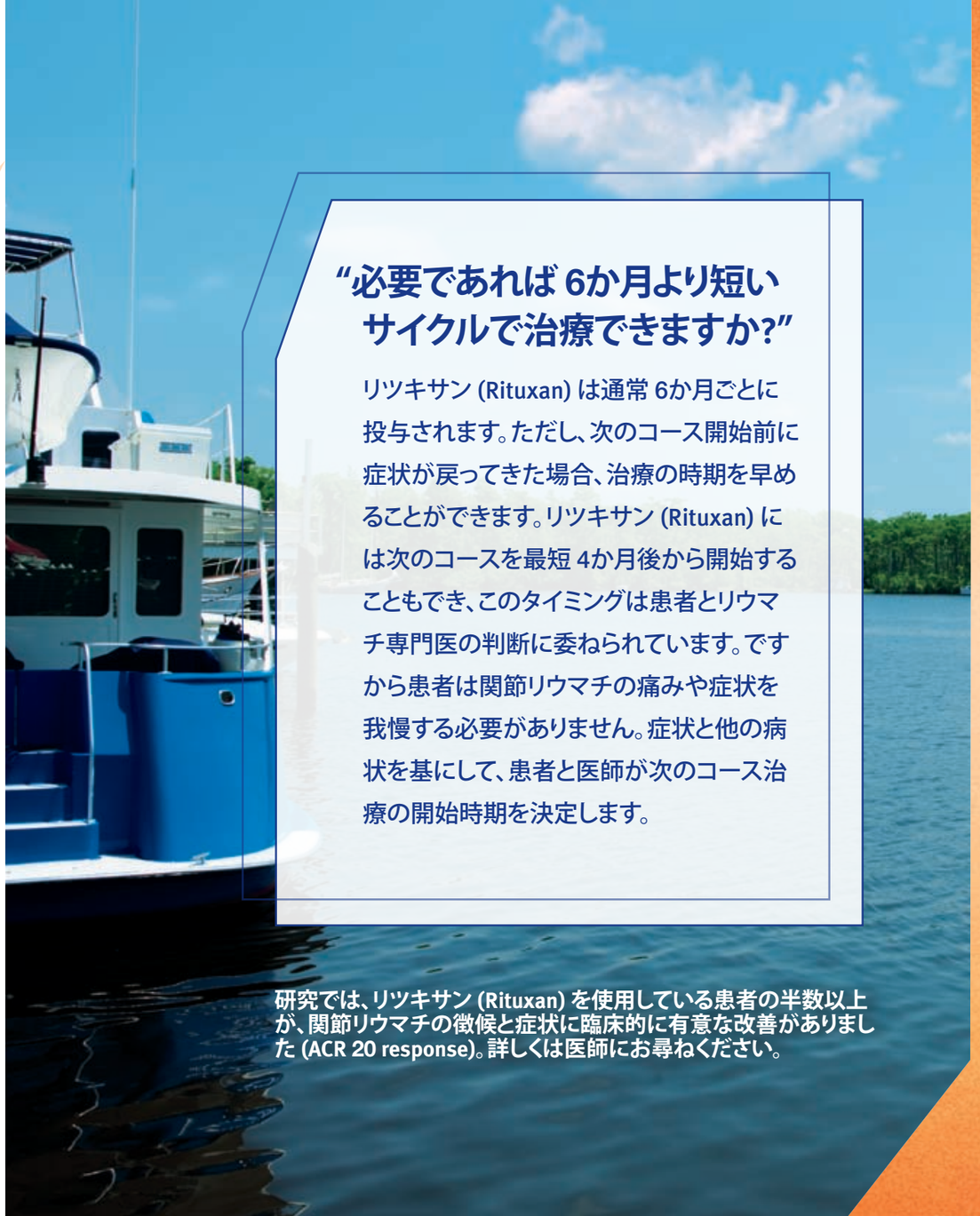
これらの患者は、注入の前にメトトレキサートとメチルプレドニゾロンも投与されているため、2 週間経過した時点での結果に影響を与えた可能性があります。しかし、リツキサン (Rituxan) 使用患者は未使用患者よりも 8 週間後の時点で、より良い症状の改善が見られました。

そして多くの患者同様、改善は 半年間継続しました。

その利点は 半年以上に延長される可能性があります。リツキサンの使用を継続した場合、同様の症状改善を半年間継続できることが研究で明らかにされています。

副作用についての重要な情報

リツキサン (Rituxan) は感染リスクを高めうることにご注意ください。しつこい咳、発熱、悪寒、うっ血、またはインフルエンザのような症状がある場合は、医療提供者に申し出てください。



“必要であれば 6か月より短いサイクルで治療できますか?”

リツキサン (Rituxan) は通常 6か月ごとに投与されます。ただし、次のコース開始前に症状が戻ってきた場合、治療の時期を早めることができます。リツキサン (Rituxan) には次のコースを最短 4か月後から開始することもでき、このタイミングは患者とリウマチ専門医の判断に委ねられています。ですから患者は関節リウマチの痛みや症状を我慢する必要がありません。症状と他の病状を基にして、患者と医師が次のコース治療の開始時期を決定します。

研究では、リツキサン (Rituxan) を使用している患者の半数以上が、関節リウマチの徴候と症状に臨床的に有意な改善がありました (ACR 20 response)。詳しくは医師にお尋ねください。

「必要な治療回数?」

リツキサン (Rituxan®、一般名：リツキシマブ) は、2 週間間隔で 2 回点滴する方法により、半年間症状を軽減することができます。ですから、年間わずか 4 回の点滴で関節リウマチを管理できます。

他の関節リウマチ治療薬 (右図を参照) の投薬スケジュールを見ると、リツキサン (Rituxan) の場合は経過時間に対する投薬回数が少ないことがわかります。

注入反応の可能性など、リツキサン (Rituxan) についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関するおよび「使用の手引き」をお読みください。

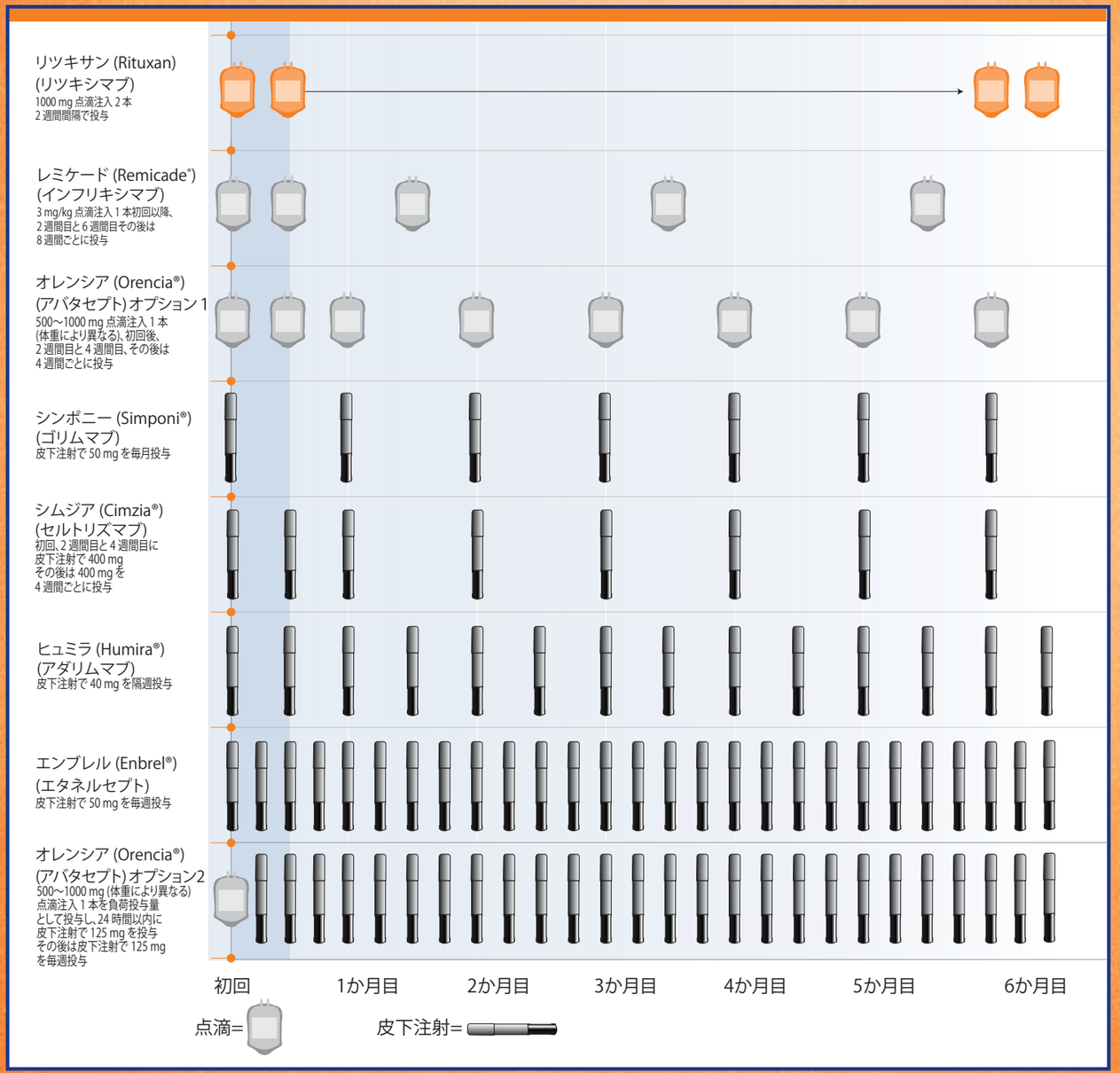
リツキサン (Rituxan) のメトトレキサートとの併用は、中度から重度の活動性関節リウマチを患い、1 種類以上の腫瘍壊死因子 (TNF) 阻害薬療法で適切な改善が見られなかった成人患者の治療に適応されます。

「リツキサン (Rituxan) で特に気に入っているのは、点滴の間の柔軟性です。6か月おきというのは素晴らしいことです。」

—キャシィさん、2006年からリツキサン使用

一部の生物学的製剤の投薬スケジュール

各治療薬の相対的な安全性や効能について、投薬スケジュールの比較から結論を導くことはできません。



各製品の用量の考察については、それぞれの処方情報を参照してください。すべての商標は各所有者に帰属します。データはリツキサン (Rituxan)、レミケード (Remicade)、オレンシア(Orencia)、シンポニー (Simponi®)、シムジア (Cimzia)、ヒュミラ (Humira)、エンブレル (Enbrel) の完全な処方情報から得ています。

*点滴注入を受けられない患者は、負荷投与量なしで毎週の皮下注射を開始することができます。

「大切な時間を取り戻したいですか? No way, RA」

アモスさんは 1996 年に関節リウマチと診断され、病気が進行するに従って、体の多くの関節に影響を受けてきました。「この病気のせいで膝を痛めてしまい、人工股関節全置換術を受けなければなりませんでした。

2005 年、アモスさんはリツキサン (Rituxan®、一般名:リツキシマブ) の治験に参加しました。「リツキサン (Rituxan) を使用し始めてから、調子が良くなり始めました」とアモスさんは言います。「ついに症状が改善され、こぶしを握ることができるようになりました。」

リツキサン (Rituxan) の使用はアモスさんと同様の結果を保証するものではない点にご注意ください。一般的な副作用として感染症と注入反応があります。リツキサン (Rituxan) についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

最近、アモスさんは趣味として絵画を始めました。また、散歩や夫人と一緒に買い物も楽しんでいます。リツキサン (Rituxan) を使用する今では、アモスさんは自分に大切なことをあきらめずにいられます。

“今では妻と一緒に行動しています。一緒に買い物に出かけますし、私自身は絵画も学びました。”

リツキサン（Rituxan®、一般名：リツキシマブ）に対する反応には個人差があることにご注意ください。リツキサン（Rituxan）についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

「どのようにリツキサン(Rituxan)は関節を保護するのですか?」

リツキサン (Rituxan®、一般名：リツキシマブ) は症状を半年間改善するだけでなく、関節リウマチの進行を遅らせて関節を保護します。

関節リウマチの症状発現により、関節に硬化、痛み、腫れを引き起こすことがあります。関節リウマチはやがて周囲の骨と軟骨も弱くすることがあります。

関節リウマチは、たとえその症状を感じていなくても、関節に永久損傷を与える原因となる場合があります。関節を保護するために、リツキサン (Rituxan) による関節リウマチの治療について医師とご相談ください。

研究では、リツキサン (Rituxan) の使用継続により関節が継続的に保護できることが示されています。

副作用についての重要な情報

リツキサン (Rituxan) の副作用には B 型肝炎の再活性化、心臓の問題、感染症などが含まれます。
詳しくは、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

他の治療が功を奏しなくてもリツキサン (Rituxan) が効く場合がある理由?

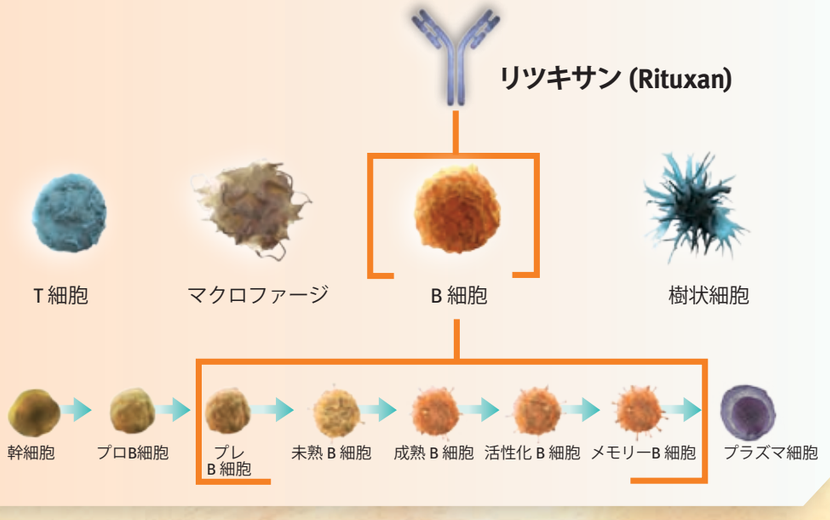
リツキサン (Rituxan®、一般名：リツキシマブ) は、他の関節リウマチ治療薬が標的にしていない免疫システムの特定の種類の細胞を標的にしています。リツキサン (Rituxan) は他の治療薬と異なる方法で機能するため、他の治療薬が効果を上げなかった患者にも有効な場合があります。

リツキサンは他の関節リウマチ治療薬と異なる方法で機能しますが、広範囲にわたり試験され使用されています。事実、過去 10 年以上にわたり、リツキサン (Rituxan) は 100 万人以上の様々な病状の患者の治療に用いられてきました。

予防接種の予定も含め、すべての病状について医師にお伝えください。リツキサン (Rituxan) の投与後は、生ワクチンの接種を受けることができません。

リツキサン (Rituxan) は免疫システム内の特定の細胞を標的にして関節リウマチを治療します。

他の治療薬と異なり、リツキサン (Rituxan) は選択的に B 細胞を標的とします。B 細胞は免疫システムによる関節攻撃に主要な役割を果たすと考えられています。



攻撃を制限することにより、リツキサン (Rituxan) は関節リウマチによる痛みや、症状、関節の損傷を抑えます。

リツキサン(Rituxan)治療について

この項の内容:

- 点滴に関する重要な事実
- 初回のコース治療 (点滴 2 回) とその後についての説明

リツキサン (Rituxan®、一般名：リツキシマブ) についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

点滴について知っておくべきこと?

リツキサン (Rituxan®、一般名:リツキシマブ) は点滴 で投与されます。点滴についてよくご存知ない方は、以下にご留意ください。

- 点滴は様々な疾患に使用される治療法です。
- 他の治療法よりも時間を要する場合がありますが、関節リウマチ治療には通常あまり頻繁に使用されません。
- 他の治療法と異なり、点滴は研修を積んだ医療専門家が行い、患者の近くでプロセスの管理を手伝い、副作用を監視します。
- リツキサン (Rituxan) で発生しうる注入反応には、発熱、悪寒と震え、かゆみ、咳などがあります。そのほとんどが軽度で管理可能であり、重度のものは 1% 未満であることが研究で明らかになっています。

リツキサン (Rituxan) についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

「初回のリツキサン (Rituxan) 点滴にあたっての知識?」

- リツキサン (Rituxan®、一般名：リツキシマブ) を 2 回点滴する初めてのコース治療にあたり、かかりつけの医院は同医院や点滴センター、病院などで 2 回分の予約を入れます。
- 1 回の点滴には 4〜6 時間かかることにご注意ください。時間をやり過ごすために本や音楽などをお持ちになると良いでしょう。
- 点滴の前にリツキサン (Rituxan) の「使用の手引き」をお読みになり、医療提供者とご相談ください。
- 副作用のリスクを軽くするために、点滴の前に別の薬剤が投与される場合があります。治療中に不快感があった場合、直ちに処置を求めてください。
- 注入反応が起きるのは、通常、初回の点滴から 24 時間以内です。起こりうる反応の一覧は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」にありますのでご覧ください。

2 回目の点滴にあたっての知識

2 回目の点滴時間は初回よりもいくらか短くなるかもしれませんが、それでも数時間はかかります。初回の点滴で副作用がみられなかった方は、2 回目も同じように順調に進むかもしれません。その場合でも、点滴中はどのように感じるかに注意を払うようにしてください。

初回に副作用のあった方は、そのことを必ず医師にお伝えください。

2 回目の点滴後、症状の改善がみられ始め、次のコース治療まで半年間の効果継続が見込まれます。

副作用についての重要な情報

注入反応はリツキサン (Rituxan®、一般名：リツキシマブ) で起きやすい副作用のひとつです。このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

リツキサン（Rituxan®、一般名：リツキシマブ）に対する反応には個人差があることにご注意ください。リツキサン（Rituxan）についての重要な安全情報は、このパンフレットの「医師にご相談ください」の項、添付の処方に関する詳細および「使用の手引き」をお読みください。

リツキサン (Rituxan) について医師にご相談ください

この項の内容:

- リツキサン (Rituxan®、一般名：リツキシマブ) について医療提供者と話し合うための手引き
- リツキサン (Rituxan) の安全情報を理解するために
- 使用開始にあたり、負担費用援助および保険の支援を申請する必要がある方のための Genentech Rheumatology Access Solutions®
- 費用援助のリソース

リツキサン (Rituxan) について
医師にご相談ください

リツキサン (Rituxan®、一般名：リツキシマブ) の使用をお考えの方やリツキサン (Rituxan) 治療を始める方は、医療提供者との話し合いにこの項をお役立てください。この項を最大限にご活用いただくためのヒントを以下に示しています。

- 診察時にこのリソースキットを忘れずにお持ちください。
- このキットの他の項に記載されている適切な情報をお読みいただき話し合いにご利用ください。可能性のある副作用など、リツキサン (Rituxan) の安全情報を理解するには、この項の P42～44が役立ちます。そこに掲載されている情報と共に、添付の処方に関する詳細および「使用の手引き」も医療提供者と一緒にご検討ください。
- 話し合いで得た重要な情報は、「メモ」欄に書き込むことができます。

「リツキサン (Rituxan) を検討」

現在の治療を評価する

以下の質問を考えて医療提供者と話し合い、リツキサン (Rituxan®、一般名：リツキシマブ) がご自分に適した選択かどうかをお確かめください。

- 関節リウマチは毎日の活動にどれだけ影響していますか?仕事を休まざるを得なかったことがありますか?ご家族での行事や社交行事についてはどうですか?
- 最近、以前よりも関節リウマチの病状再燃が悪化していますか?
- 関節の腫れや硬化が毎日起きていますか?
- 関節リウマチのために現在使用している処方薬、市販薬、ビタミン剤、ハーブサプリメントについて医師に伝えましたか?そのなかで関節リウマチに効果を上げたものがありますか。
- 現在の関節リウマチの治療の使いやすさに満足していますか?
- これまでにどのような薬を使用しましたか? またその中で関節リウマチによく効いたものはありますか?

メモ

リツキサン(Rituxan)はあなたに合っていますか?

以下の質問を考えて医療提供者とお話し合いください。右側はメモ用にご利用ください。

- これまでに使用した治療薬や使用できるその他の治療薬とリツキサン(Rituxan®、一般名:リツキシマブ) はどのように違いますか? (詳しくは P11とP18をご覧ください。)
- B 細胞を標的にした療法はどのように作用しますか? (P19をご覧ください。)
- リツキサン (Rituxan) 治療のリスクと利点は何ですか?それはあなたとどのように関係するのですか? (P40〜43 P40〜43 をご覧ください。)
- リツキサン (Rituxan) を使用すると何が期待できますか (症状の改善、改善が見られるまでの時間、起こりうる副作用など) ? (P8とP40〜43 をご覧ください。)

以下の場合は医療提供者に申し出てください:

- 解消されないまたは再発を繰り返す感染症のある方
- 手術または予防接種の予定のある方
- 心臓や肺に障害のある方
- 授乳中の方または妊娠の予定のある方
- B 型肝炎にかかった方または B 型肝炎ウイルス持続感染者の方。リツキサン (Rituxan) での治療中および治療後数か月間、医師が肝炎への感染徴候を注意深く調べます。
- 過去に注入反応が起きたことのある方

メモ

「治療開始」

リツキサン (Rituxan) の点滴

以下の項目に目を通し、医療従事者と話し合ってください。右側はメモ用にご利用ください。(点滴に関する詳細は P26〜29をご覧ください。)

- 点滴を受ける前の準備
- リツキサン (Rituxan®、一般名：リツキシマブ) の各点滴治療の間に感じることの記録方法
- 降圧剤や抗生剤の服用、予防接種など、点滴前に医療提供者から受ける指示について
- 点滴中と点滴後に起こりうる副作用の記録をつけること関して、医療提供者から受ける指示について

メモ

リツキサン (Rituxan) の安全情報を理解する

治療を考慮する際には、潜在的なリスクと利点を医療提供者と一緒に比較検討することが重要です。治療の安全情報は「使用の手引き」に記載されており、潜在的なリスクについてご説明しています。

リツキサン (Rituxan®、一般名：リツキシマブ) に関連するリスクの中には、重大かつ生命にかかわりうる以下の副作用が含まれます。

- 進行性多巣性白質脳症 (PML) などの重大な感染症
- 重度の注入反応
- 腫瘍崩壊症候群 (TLS)
- 重度の皮膚反応

これらはいずれも関節リウマチ治療のリスクと見なされていますが、非ホジキンリンパ腫 (NHL) の患者のみに起きた副作用もあります。

> **どの薬を使用するにしても使用の手引きを必ず読むことが重要だと思います**
>
> キャシーさん、2006年からリツキサン (Rituxan) を使用

PML などの重篤な感染症

リツキサン (Rituxan) は感染症にかかる可能性を高めることがあります。臨床研究では、リツキサン (Rituxan) を使用する患者の 2% に重度の感染症が発生しました。その感染症の中で最も一般的だったのは肺炎でした。

進行性多巣性白質脳症 (PML) と呼ばれる稀な脳への感染が、リツキサン (Rituxan) 使用患者に発生しています。PML は関節リウマチの治療にリツキサン (Rituxan) を使用する患者には稀ですが、リスクであることに変わりはありませんので、この点について医師と話し合ってください。PML の治療、予防、治癒の方法はまだ確立されていません。PML はリツキサン (Rituxan) での治療中または治療終了後に発生することがあります。

重度の注入反応

注入反応はリツキサン (Rituxan) で最もよく起こる副作用です。点滴中または点滴後 24 時間以内に、生命にかかわりうる重大な反応が起きる場合があることを知っておくことは重要です。研究ではすべての反応のうち 1% 未満が重度のものでした。医療提供者は点滴の前に、重篤な注入反応を起こす可能性を抑える薬を提供してもらってください。そして患者は、これらの反応について医師と話し合いってください。

TLS と重度の皮膚反応

TLS と重度の皮膚反応は、非ホジキンリンパ腫 (NHL) の治療にリツキサン (Rituxan) を使用する患者に発生していますが、関節リウマチに使用する患者については報告されていません。TLS は腎不全を招き、透析療法が必要になることのある疾患です。

ご質問のある方は医療提供者にご相談ください。個人の健康状態に基づく具体的な助言を得られるかもしれません。

潜在的なその他の重大な副作用

- **B 型肝炎ウイルス (HBV) の再活性化。** B 型肝炎にかかった方または B 型肝炎ウイルス持続感染者の方は、リツキサンの投与によってウイルスが再活性化して活動性感染症となる場合があります。B 型肝炎ウイルス再活性化は、そ、重大な肝臓の障害を引き起こして肝不全や死などに至ることがあります。活動性 B 型肝炎の方は、リツキサンの投与を受けないでください。リツキサンの投与中及び投与後数カ月は、医師がB 型肝炎感染症の経過観察を行います。

- **重大な感染症。** リツキサンを用いた治療中及び治療後に重大な感染症を起こし、死に至る場合があります。リツキサンは感染症に対する免疫力を低下させることがあります。リツキサンで発生しうる重大な感染症には細菌性、真菌性、ウィルス感染が含まれます。一部の患者は、リツキサン投与後、長期間（11か月以上）にわたり低い血中抗体価が続きました。血中抗体価の低い患者の一部で感染症が起こりました。次のような感染症状がある場合は、直ちに医師にご連絡ください。
  - 発熱
  - 風邪の症状 - 鼻水やのどの痛みなどが続く
  - インフルエンザの症状 - 咳、けん怠感、体の痛みなど
  - 耳の痛みや頭痛
  - 排尿時の痛み
  - 口や喉にできた白斑
  - 赤く、熱または腫れまたは痛みを伴う切り傷、擦り傷、切開部

- **心臓障害。** リツキサンは治療の要する胸の痛みや治療を要する不整脈を引き起こすことがあり、医師がリツキサンでの治療を中止する場合があります。

- **腎臓障害。** 特に非ホジキンリンパ腫 (HNL) でリツキサン (Rituxan) を使用している場合。医師は患者の腎臓機能を調べるための血液検査を実施すべきです。

- **胃と重大な腸の障害により、時として死に至る場合があります。** 非ホジキンリンパ腫の治療を目的としてリツキサン (Rituxan) と抗がん剤を投与した場合、腸の閉塞や裂傷など、腸の問題が起きることがあります。リツキサン (Rituxan) での治療中に腹部の痛みを感じた場合は、直ちに医師にご連絡ください。

- **低血球数。** リツキサン (Rituxan) での治療中、医師が血球数を調べるための血液検査を行う場合があります。

- **白血球。** 白血球は細菌性感染症と戦います。白血球数が低いことは感染症にかかる原因となり、重大な状況にもなりえます。感染症の症状の一覧は、前ページの「重大な感染症」を参照してください。

- **赤血球。** 赤血球は体内の組織と器官に酸素を運びます。

- **血小板。** 赤血球は体内の組織と器官に酸素を運びます。

一般的な副作用

リツキサン (Rituxan) の安全情報には、あまり重大でないより一般的ないくつかの副作用、つまり発熱、悪寒、震え、かゆみ、じんましん、くしゃみ、喉の炎症やつかえ、頭痛、吐き気、咳などの症状を伴う重度の注入反応のリスクも含まれています。これらは通常、初回の点滴後 24 時間以内に起きるものです。

その他の副作用としては、関節の痛み、上気道感染症、血球数の減少、肺の問題などがあります。

その他の副作用としては、関節の痛み、上気道感染症、血球数の減少、肺の問題などがあります。

これらの症状はリツキサン (Rituxan) の使用が原因で起きるとは限りませんが、起きた場合には医療提供者に申し出ることが重要です。

リツキサン (Rituxan) についての重要な安全情報の詳細は、添付の処方に関する詳細および「使用の手引き」をお読みください。

“医師と私はリツキサン (Rituxan) のリスクと利点についてしっかり話し合いました。”

—マリアさん、2006 年からリツキサン (Rituxan) 使用

使用開始に役立つ書類

リツキサン (Rituxan®、一般名：リツキシマブ) が適しているとご本人と医師が判断なさった場合は、Genentech Rheumatology Access Solutions® プログラムをご利用ください。このプログラムは、必要な治療を受けるための重要なお手伝いを提供します。

医療提供者と一緒に次のページの書類に必要事項をご記入いただき、Genentech Rheumatology Access Solutions にお申し込みください。

情報公開に関する患者の承諾および通知

Tel: (866) 681-3261 **Fax:** (866) 681-3288 **GenentechAccessSolutions.com**

Genentech Access Solutions は Genentechが提供する無料プログラムです。

弊社ではリツキサン (Rituxan®、一般名：リツキシマブ) またはアクテムラ (ACTEMRA®、一般名：トシリズマブ) に関して、患者の皆様に経済的支援を行っております。弊社では各種サポートをご用意し、健康保険制度への加入・未加入にかかわらず援助を提供しております。

弊社は、健康保険制度に未加入の方や加入している保険が Genentech 製品を保障の対象としていない方をお手伝いできることがあります。一定の経済的条件と医療条件を満たしている方には、弊社が薬剤を無料提供できます。このプログラムは Genentech® Access to Care Foundation (GATCF) を通して実施されています。

支援にあたり、弊社では、患者の個人健康情報を確認、使用および公開する必要があります。患者の個人健康情報を弊社に公開するにあたり、医師と健康保険会社はいずれも、患者の書面による同意を必要とします。本承諾書にご署名のうえ弊社に返送していただいた時点から、弊社は前述のサービスを提供することが可能となります。本情報公開承諾書は、複製を申請者である患者に提供することが可能です。複製をご希望の方は、あらかじめ弊社にその旨をお伝えいただく必要があります。

患者の皆様は本情報公開に同意する必要はありません。ただしその場合、弊社では同サービスを提供できませんので、特定の薬剤についてご自身で負担いただく必要がありうることをご了承ください。

本承諾書の内容を注意深くお読みください。何かご不明な点があれば、かかりつけの医師の病院・診療所にお尋ねになるか、弊社まで、このページ上部に記載の電話番号にお問い合わせください。

1. 公開または使用される情報

本署名済み承諾書により、私は、私の医師ならびに加入している健康保険会社が私の個人健康情報を Genentech Access Solutions および GATCF に送付することを承諾するものです。これには以下が含まれます。

- 私の治療に関連するカルテのすべて
- 加入健康保険の医療給付についての情報
- 加入健康保険が負担する生涯給付金額の内の未使用ドル残高(該当する場合)
- 私の健康または私が忠実に治療に取り組んでいることに関連するあらゆる情報

上記はいずれも私の個人健康情報の一部として見なされ、私はこれに以下についての情報が含まれる場合があることを認識しています。

- 性感染症
- 精神疾患
- 遺伝子検査の結果

弊社ではこれらの情報を求めていませんが、弊社に送付されるカルテに含まれている可能性があります。

2. 個人健康情報を閲覧しうる個人および組織

Genentech Access Solutions と GATCF は私の個人健康情報を閲覧することができます。これらは Genentech が提供するプログラムです。Genentech の所在地は米国の 1 DNA Way, Mail Stop #858a, South San Francisco, CA 94080-4990 です。私の個人健康情報は Genentech の従業員ならびに Genentech のパートナーなど、Genentech Access Solutions が提供するサービスの実施にかかわる個人であれば誰でも閲覧することができます。

私の個人健康情報は以下の方法でのみ使用することができます。

- リツキサン (Rituxan) またはアクテムラ (ACTEMRA) の費用負担に関して、私が加入している健康保険を補う
- GATCF に申し込む
- 私のリツキサン (Rituxan) またはアクテムラ (ACTEMRA) の使用を追跡する
- Genentech の管理上の目的で使用する

3. 有効期限

本情報公開は私が署名をした日から一年間有効です。私は書面にていつでも承諾を取り消すことができます。

4. 通知

本承諾書に署名することによって、私は、私の個人健康情報が、個人健康情報の使用やその公開方法を定めた連邦法によって保障されない可能性があることを認識しています。私の個人健康情報が第三者に公開されないことの保証はなく、当該の第三者は本情報公開の条件に従う必要がないかもしれません。

私は本承諾書への署名を拒否できることを認識しています。私は、いつでも、理由を問わず情報公開の承諾を取り消すことができます。承諾取り消しが私の治療の開始や継続に影響を及ぼすことはなく、治療の質にも一切影響しません。

私は、書面によって取り消さない限り、本情報公開が一年間有効であることを認識しています。情報公開の承諾を取り消すには私は書面による通知をGenentech に送付しなければなりません。承諾取り消し通知はこのページの一番下に記載されている番号・住所へファックスにて送信または郵送することができます。承諾取り消しは Genentech が受領次第有効となります。これは医師が行う私の治療に一切影響を与えません。

本承諾書に署名しない場合、または情報公開の承諾を取り消した場合は、私は治療費用を負担する責任を負う可能性があります。

5. 流通に関する同意

GATCF から無料で製品提供を受ける場合は、私は医師の処方に従いリツキサン (Rituxan) またはアクテムラ (ACTEMRA) を使用します。私はリツキサン(Rituxan) またはアクテムラ (ACTEMRA) を販売または配布しません。私はそのような行為が違法であることを理解しています。リツキサン (Rituxan) またはアクテムラ (ACTEMRA) が私宛に安全な住所に発送されるようにする責任は私にあります。私はリツキサン (Rituxan) またはアクテムラ (ACTEMRA) を所有する間、その管理は私の義務であることを認識しています。

次のページの第 6 項へのご記入は必須です。
この書面通知にご署名のうえ、日付を記入して以下へ郵送またはファックスにて送信してください。

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

Fax: (866) 681-3288

6. 署名と日付 (必須)

私は本情報公開承諾書の条件を読んで理解いたしました。私は、私の個人健康情報の使用およびこれを閲覧しうる個人・組織について質問する機会がありました。本承諾書に署名をすることにより、私は、本承諾書の記載の通り、私の個人健康情報を公開するものであることを認識するものです。**(以下に漏れなく記入し、承諾書へのご署名と日付の記入を忘れずしてください。記入不備があった場合には支援手続きに遅れが生じることがあります。)**

署名
日付

保護者または後見人の署名* 続柄 日付

氏名

患者氏名

保護者/後見人住所

*患者が親権の保護・管理下にある未成年か、(肉体的または精神的) 障害がある場合。

7. 経済的情報

この項はGATCFの支援を申請する方のみが記入してください。

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署名・日付
(必要な場合)

患者または後見人の署名 日付

8. 任意の患者サポート無料プログラム

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希望する連絡方法 (該当するボックスに印を付け、あなたの情報を記入してください。ボックスは複数選ぶことができます。)

☐ Email: _____ ☐ Tel: _____ メッセージを残してもよろしいですか? ☐ はい ☐ いいえ
☐ 住所: _____

署名により
参加します

患者の署名 (患者サポートプログラムに参加するには、ここに署名する必要があります)。 日付

「経済的支援のリソース」

患者の皆様が必要とするリツキサン (Rituxan®、一般名：リツキシマブ) 治療を受けるための重要なお手伝いをするプログラムが3 つあります。

RITUXAN EXPERIENCE Program™— 対象患者に年間最大 $4000 を支給し、これは自己負担費用に充てることができます。その患者が将来的にも支給対象であれば、プログラムの実施中は 12 か月ごとに更新される限度額まで、継続してカードで自己負担額を支払うことができます。詳細との受給要件については、お電話 (888) MY-RITUXAN またはウェブサイト http://Rituxan.TMGcard.com でご確認ください。*

Access Solutions®

Genentech Rheumatology Access Solutions—政府 (メディケア) または民間の保険への加入者で、リツキサン (Rituxan) の自己負担費用に不安をお持ちの方は、Genentech Rheumatology Access Solutions をご利用ください。自己負担費用の援助を行っている独立非営利団体 (INO) をご紹介することができます。P44の申請書をご覧ください。

Genentech Access to Care Foundation—The Genentech Access to Care Foundation (GATCF) では、リツキサン (Rituxan) の費用が健康保険の対象になっていない患者の皆様を支援します。受給対象となった方は GATCF により薬剤を無料で受け取ることができます。詳しくは、お電話 (866) 681-3261 でお問い合わせになるか、ウェブサイトwww.RheumatologyAccessSolutions.com.*をご覧ください。

*このウェブサイトは英語のみの表示となっています。他の言語でのご理解が必要な方は、翻訳のできる方の協力をお求めください。詳しくは医師にもお尋ねいただけます。

Genentech | biogen idec

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*

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*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

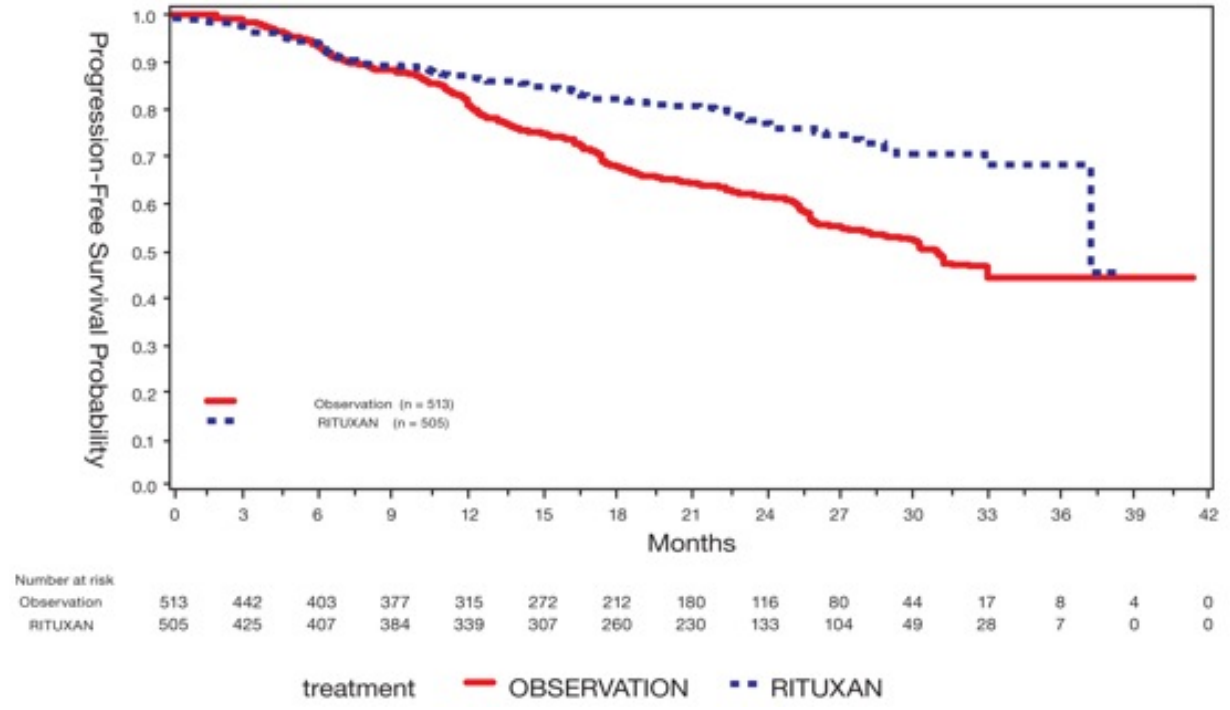
An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

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)

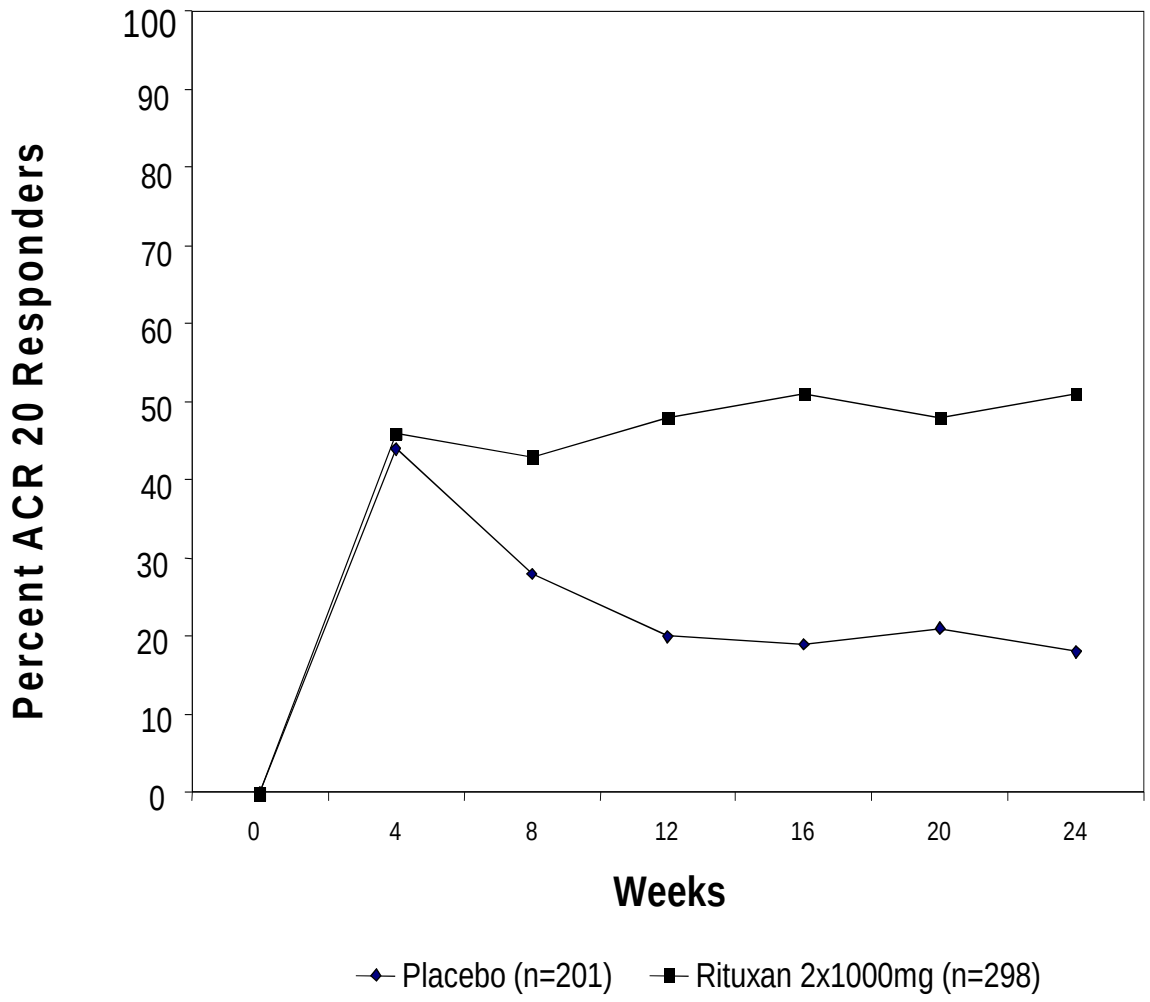
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo + MTX (n = 201)		Rituxan + MTX (n = 298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment[a]	71.0	69.0	71.0	36.0
Patient Global Assessment[a]	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.

RITUXAN® [rituximab]

Manufactured by:
Genentech, Inc.
A Member of the Roche Group
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