

# KIT DE RECURSOS DE RITUXAN PARA LA AR

Su guía completa para considerar Rituxan y el tratamiento inicial

¿Perderme mi  
tiempo al aire libre?

PARA  
NADA,  
AR

Con Rituxan obtenga **6** meses  
de alivio de los síntomas de la AR.

Bobbi, recibe Rituxan desde 2007 >

Pregúntele a su médico sobre los efectos  
secundarios potenciales de Rituxan

Con solo 1 ciclo de tratamiento (2 infusiones), Rituxan puede proporcionar 6 meses de alivio al mejorar sus síntomas.

**¿QUÉ ES RITUXAN?** Rituxan es un medicamento recetado usado en adultos con otro medicamento llamado metotrexato para reducir los signos y síntomas de artritis reumatoide (AR) moderada a gravemente activa después de haber usado sin mucho éxito al menos otro medicamento dentro de los llamados antagonistas del factor de necrosis tumoral (TNF).

Las personas con infecciones graves no deberían recibir Rituxan.

**INFORMACIÓN IMPORTANTE SOBRE LA SEGURIDAD:** Rituxan ha estado asociado con reacciones a la infusión, síndrome de lisis tumoral, reacciones graves en la piel e infecciones graves, incluso con leucoencefalopatía multifocal progresiva (*progressive multifocal leukoencephalopathy, PML*). Para obtener más información, lea en esta sección "Hable con su médico", toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.

**Rituxan**  
Rituximab

Para hoy y hasta dentro de 6 meses

# Bienvenido a Rituxan

Nos complace compartir esta información sobre Rituxan® (rituximab), un tratamiento único que ha ayudado a muchas personas a encontrar una mejoría duradera de los síntomas de AR. Tenga en mente que Rituxan funciona de manera diferente a otros tratamientos para la AR. Aunque otros tratamientos no le hayan ayudado lo suficiente, Rituxan aún puede serle efectivo.

Revise la siguiente información y hable con su médico sobre Rituxan. Podría ser un paso importante para ayudarlo a decir “De ningún modo” a perderse las cosas que importan.

# Su guía para considerar Rituxan

## ¿Por qué podría ser Rituxan bueno para mí?

- Un ciclo de 2 infusiones puede proporcionar 6 meses de mejoría de los síntomas de la AR (página 8)
- Cronograma conveniente de dosificación: solo 4 infusiones por año (página 10)
- Ayuda a proteger las articulaciones retardando el daño de la AR (página 16)
- Puede funcionarle bien cuando otros tratamientos no le hayan ayudado lo suficiente (página 18)

## ¿Qué debería saber cuando inicio mi tratamiento?

- Información sobre infusiones (página 23)
- Qué esperar en su primera infusión de Rituxan (página 24)
- Su segunda infusión y después (página 27)

## ¿Cuáles son algunas de las cosas que debería hablar con mi médico?

- Guía para la conversación con el proveedor de atención médica (página 31)
- Información importante sobre la seguridad, que incluye los posibles efectos secundarios (página 40)
- Formulario de Genentech Rheumatology Access Solutions® para ayudarle a comenzar (página 44)
- Recursos para asistencia financiera (página 45)

Cuando considere cualquier tratamiento, es importante que compare los riesgos y los beneficios potenciales con su proveedor de atención médica. Para conocer los riesgos asociados con Rituxan, vea en este la sección “Hable con su médico”, toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.



Las personas destacadas en este folleto que toman Rituxan® (rituximab) son miembros del programa RISE™ Ambassador, patrocinado por Genentech USA, Inc. y Biogen Idec Inc. Genentech compensa a los Embajadores por su tiempo y gastos al presentar sus historias.

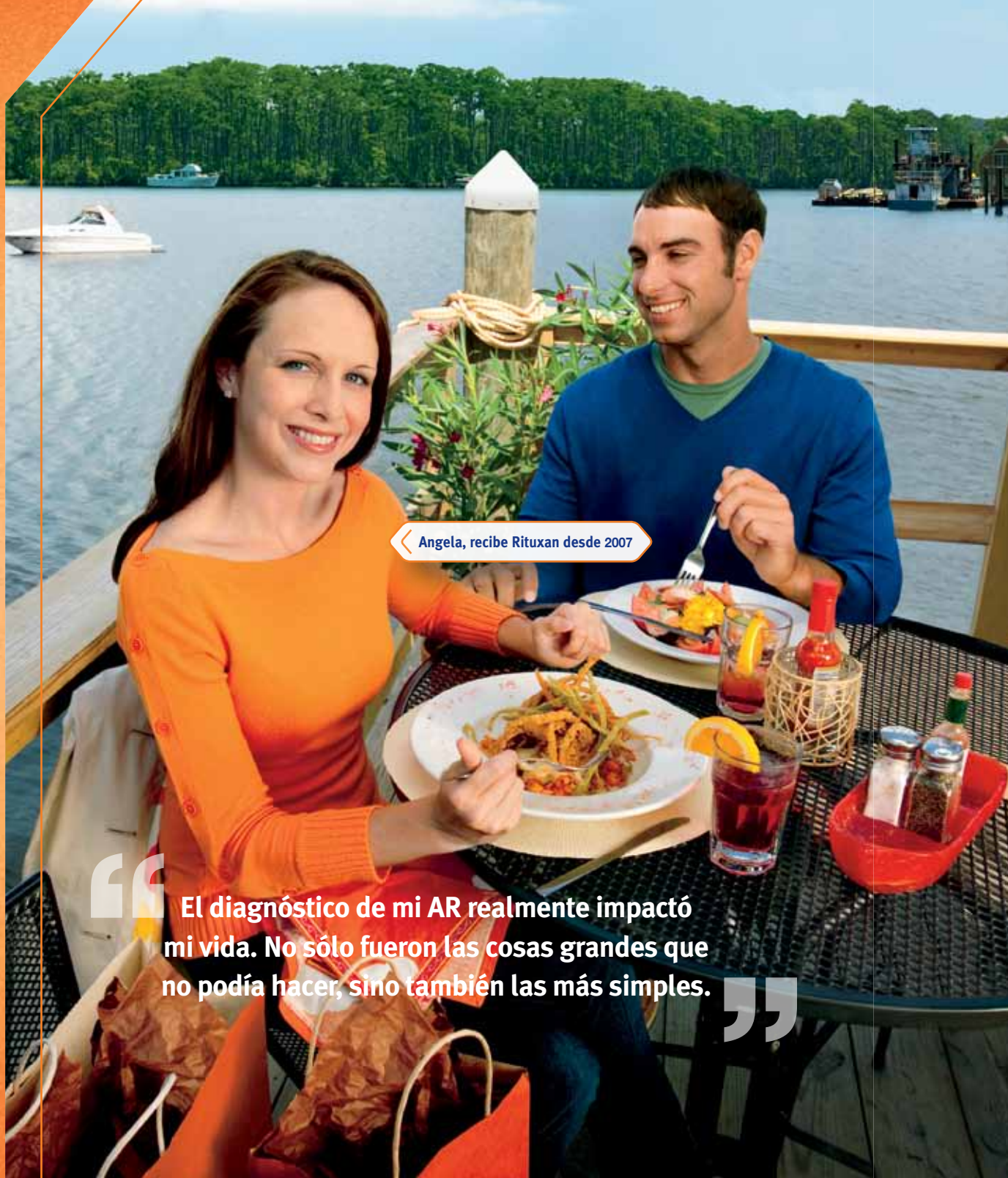
## Por qué Rituxan

### En esta sección:

- Un ciclo de tratamiento con Rituxan (2 infusiones) puede proporcionar alivio de los síntomas durante 6 meses
- Solo 2 ciclos (4 infusiones) pueden manejar su AR durante todo un año
- Rituxan puede ayudar a proteger sus articulaciones retardando el daño de la AR
- Por qué Rituxan puede funcionarle bien aunque otros tratamientos no le hayan funcionado

### Información importante sobre la seguridad

Hable con su médico sobre todas sus afecciones médicas, todos los medicamentos que esté tomando y cualquier vacuna que reciba o tenga programado recibir. Dígale a su médico si está embarazada, si planea quedar embarazada o si está amamantando.



« Angela, recibe Rituxan desde 2007 »

“ El diagnóstico de mi AR realmente impactó mi vida. No sólo fueron las cosas grandes que no podía hacer, sino también las más simples. ”

## ¿No poder ponerme al día con mis amigos? De ningún modo, AR.

Si tiene artritis reumatoide (AR) de moderada a gravemente activa, usted conoce los desafíos a los que se enfrenta y las preguntas que se hace todos los días.

¿Tendrá que perderse su reunión familiar? ¿Quedarse en casa en lugar de ir al trabajo? ¿No poder ponerse al día con amigos?

Al tratarse con Rituxan® (rituximab), usted podría mejorar los síntomas de la AR y ayudar a proteger sus articulaciones, aunque otros tratamientos no le hayan ayudado lo suficiente.

Hable con su médico sobre Rituxan. Podría ser su primer paso a ayudarlo a decir “De ningún modo” a perderse las cosas que importan.

### Información importante sobre la seguridad

Tenga en cuenta que no todos responden a Rituxan del mismo modo. Algunas personas han presentado efectos secundarios durante o después de su tratamiento con Rituxan.

Para obtener información importante sobre la seguridad de Rituxan, consulte en este la sección “Hable con su médico”, toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.

# ¿Qué tan pronto puedo esperar resultados con Rituxan y cuánto durarán?

Rituxan® (rituximab) es el único tratamiento para la AR que puede proporcionar 6 meses de mejoría de síntomas después de solo 1 ciclo de tratamiento (2 infusiones administradas con 2 semanas de diferencia).

En ensayos clínicos, algunos pacientes que recibieron Rituxan presentaron mejoría de los síntomas solo 2 semanas después de su primer ciclo de tratamiento.

Estos pacientes también fueron tratados con metotrexato y metilprednisolona antes de la infusión, lo cual puede haber influido en los resultados a las 2 semanas. Sin embargo, a las 8 semanas los pacientes que recibieron Rituxan demostraron una mayor mejoría de síntomas que los pacientes que no lo recibieron. Y para muchos, esa mejoría duró hasta 6 meses.

Los beneficios pueden extenderse más allá de los 6 meses. Los estudios han demostrado que si usted continúa recibiendo Rituxan, puede continuar proporcionándole 6 meses de mejoría de ese mismo síntoma.

## Información importante sobre efectos secundarios

Usted debería saber que Rituxan puede aumentar su riesgo de infección. Avise a su proveedor de atención médica si presenta tos persistente, fiebre, escalofríos, congestión o cualquier síntoma similar al de la gripe.

## “¿Puedo recibir tratamiento antes de los 6 meses si lo necesito?”

Generalmente, Rituxan se administra cada 6 meses. Pero es importante que sepa que si sus síntomas vuelven antes de que sea hora de su próximo ciclo, puede recibir tratamiento más pronto. Rituxan les ofrece a usted y a su reumatólogo la flexibilidad de que reciba su próximo ciclo de tratamiento en solo 4 meses. Así que no tiene que soportar el dolor ni los síntomas de la AR. Basándose en sus síntomas y en otras afecciones médicas, usted y su médico determinarán cuándo debería iniciar el próximo ciclo de tratamiento.

En los estudios, más de la mitad de las personas que recibieron Rituxan experimentaron una mejoría clínica significativa en los signos y síntomas de AR (respuesta ACR 20). Pídale más información a su médico.

# ¿Con qué frecuencia necesito el tratamiento?

Rituxan® (rituximab) puede proporcionar 6 meses de alivio de los síntomas con 2 infusiones administradas con 2 semanas de diferencia. De modo que en el transcurso de un año, usted puede manejar su AR con solo 4 infusiones.

Cuando considere los esquemas de dosificación de otros tratamientos para la AR (consulte el cuadro a la derecha), recibir Rituxan podría significar menos administraciones en el tiempo.

Para ver información importante sobre la seguridad de Rituxan, incluso las posibles reacciones a la infusión, consulte en este la sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta.

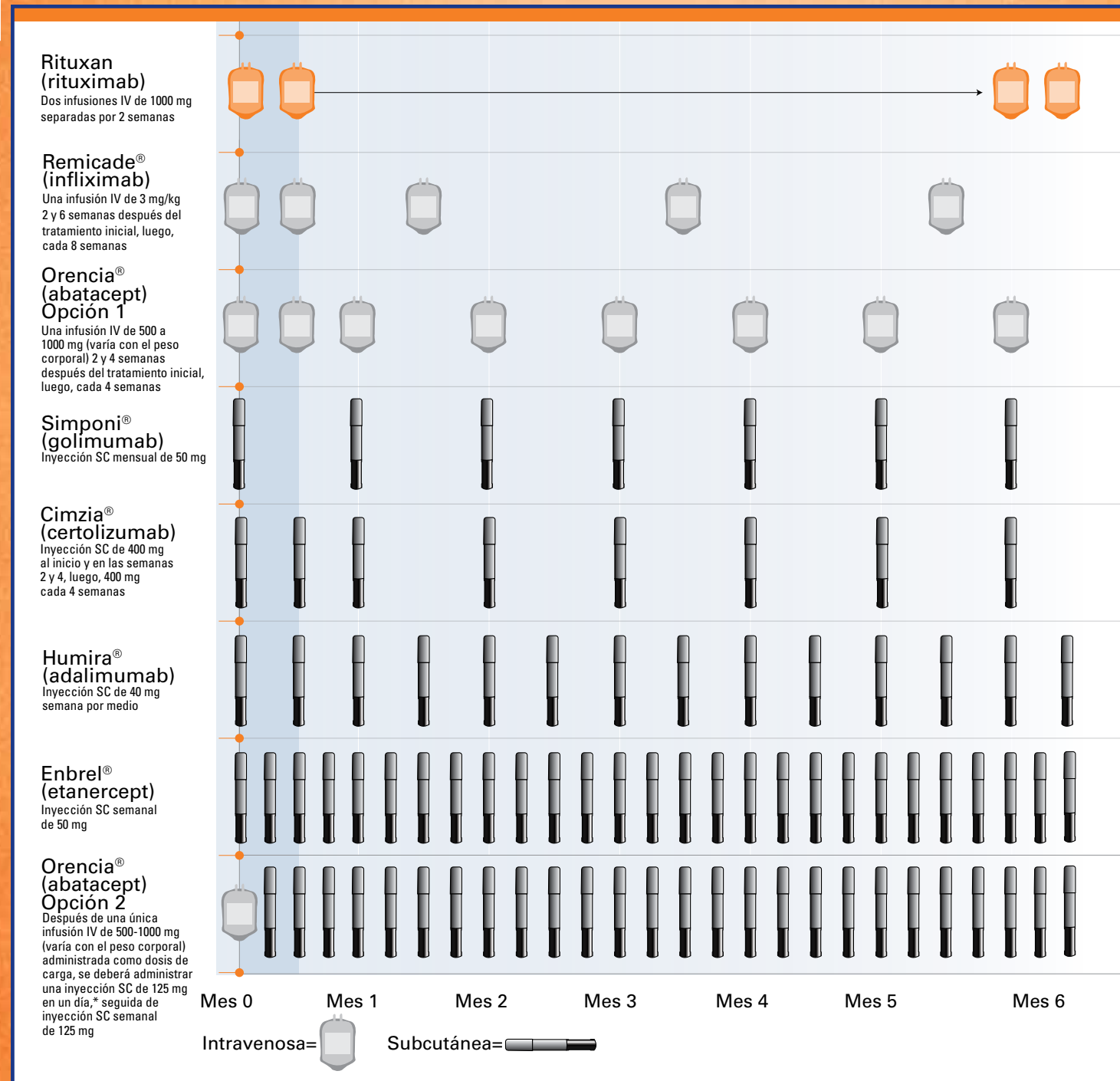
Rituxan en combinación con metotrexato está indicado para el tratamiento de pacientes adultos con artritis reumatoide moderada a gravemente activa que han presentado una respuesta insuficiente a una o más terapias con antagonistas del TNF.

“ Una de las cosas que más me gustan de Rituxan es la flexibilidad entre las infusiones. Cada 6 meses es maravilloso. ”

— Kathy, recibe Rituxan desde 2006

## Esquemas de dosificación de tratamientos biológicos seleccionados

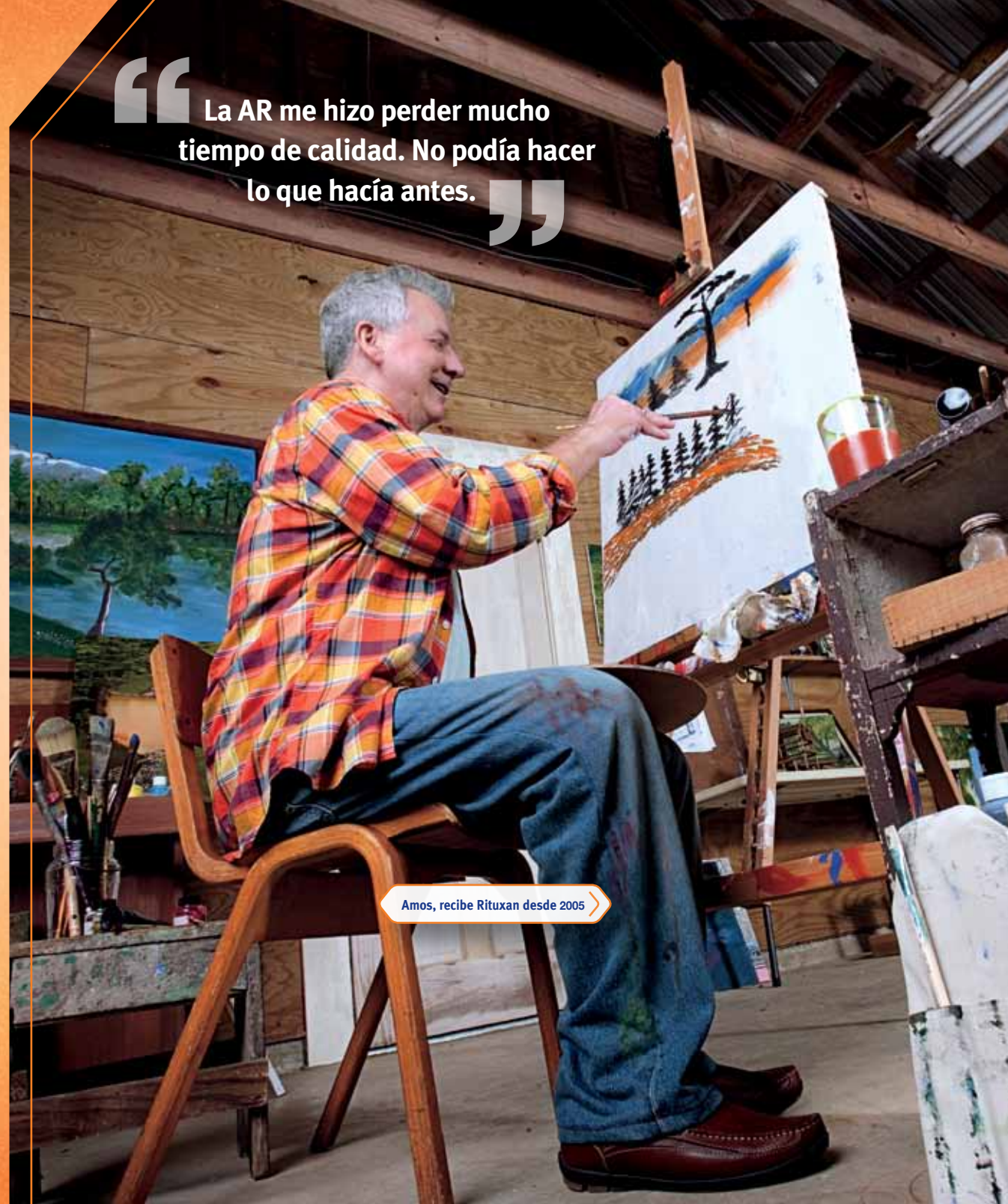
No se pueden sacar conclusiones en relación con la seguridad o la eficacia comparativa entre tratamientos comparando sus esquemas de dosificación.



Consultar información de prescripción respectiva para consideraciones de dosificación de cada producto. Todas las marcas registradas son de propiedad de sus respectivos dueños. Datos obtenidos de la información completa de prescripción de Rituxan, Remicade, Orencia, Simponi, Cimzia, Humira y Enbrel.

\*Los pacientes que no puedan recibir una infusión IV pueden iniciar inyecciones SC semanales sin una dosis de infusión IV de carga.

“ La AR me hizo perder mucho tiempo de calidad. No podía hacer lo que hacía antes. ”



Amos, recibe Rituxan desde 2005 >>

## ¿Perder mi tiempo de calidad? De ningún modo, AR.

A Amos le diagnosticaron AR en 1996. A medida que la enfermedad avanzaba, le afectó muchas de las articulaciones de su cuerpo. “Me arruinó las rodillas. Tuvieron que reemplazarme ambas caderas.”

En 2005, Amos se inscribió en un ensayo clínico de Rituxan® (rituximab). “Después de que comencé a recibir Rituxan, las cosas comenzaron a mejorar,” dice Amos. “Eventualmente, mis síntomas mejoraron. Pude cerrar el puño.”

Tenga en cuenta que sus resultados con Rituxan pueden no ser los mismos que los de Amos. Los efectos secundarios comunes incluyen infecciones y reacciones a la infusión. Para leer información importante sobre la seguridad de Rituxan, consulte en este la sección “Hable con su médico”, toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.

En cuando a Amos, hoy se dedica a la pintura para pasar el tiempo. Disfruta salir a caminar y de compras con su esposa. Con Rituxan, Amos ha encontrado una forma de no perderse las cosas que más le importan.

“ Ahora mi esposa y yo hacemos cosas juntos. Salimos de compras y hasta he aprendido a pintar. ”

Tenga en cuenta que su respuesta a Rituxan® (rituximab) puede ser diferente. Para leer información importante sobre la seguridad de Rituxan, consulte en este la sección “Hable con su médico”, toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.



## ¿Cómo puede Rituxan proteger mis articulaciones?

Además de proporcionar 6 meses de mejoría de síntomas, Rituxan® (rituximab) también protege las articulaciones retardando el daño de la AR.

El ataque de AR a las articulaciones del cuerpo puede hacer que las sienta rígidas, doloridas e inflamadas. La AR también puede debilitar el hueso y el cartílago circundante con el tiempo.

**Aunque no presente los síntomas de AR, aún puede estar causando daños permanentes en sus articulaciones. Hable con su médico sobre el tratamiento de su AR con Rituxan para proteger sus articulaciones.**

Los estudios hasta han demostrado que si continúa recibiendo Rituxan, puede continuar protegiendo sus articulaciones.

### **Información importante sobre los efectos secundarios**

Los efectos secundarios de Rituxan incluyen reactivación del virus de la hepatitis B, problemas cardíacos e infecciones. Para obtener más información, consulte en este folleto la sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicación adjunta.

“ Para mí personalmente, es muy importante tener un tratamiento que retrase el daño a las articulaciones. ”



◀ Maria, recibe Rituxan desde 2006

## ¿Por qué podría Rituxan funcionar cuando otros tratamientos no lo han hecho?

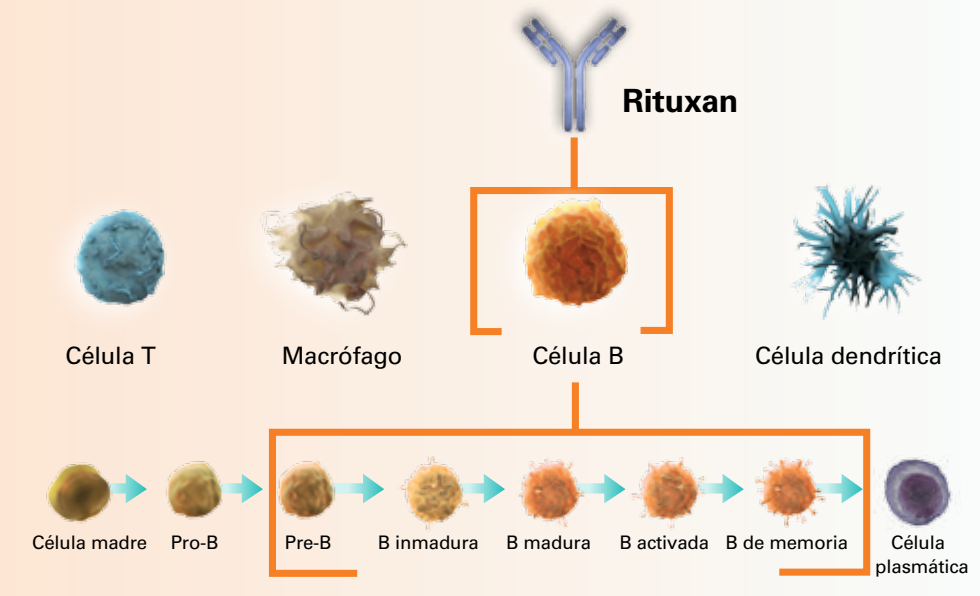
Rituxan® (rituximab) afecta a un tipo específico de célula del sistema inmunitario que otros tratamientos para la AR no afectan. Porque funciona de una forma diferente, Rituxan puede funcionarle aunque otros tratamientos no lo hayan hecho.

Aunque Rituxan funciona de un modo diferente al de otros tratamientos para la AR, se lo ha probado y usado ampliamente. De hecho, por más de una década, Rituxan se ha utilizado para tratar diversas afecciones en más de 1 millón de pacientes.

Infórmele a su médico sobre todas sus afecciones médicas, esto incluye si tiene programado recibir vacunas. No debe recibir vacunas vivas después de recibir Rituxan.

Rituxan afecta a células específicas del sistema inmunitario para tratar la AR.

A diferencia de otros tratamientos, Rituxan afecta selectivamente a las células B, las cuales se cree que juegan un papel clave en el ataque del sistema inmunitario a las articulaciones.



Al limitar este ataque, Rituxan puede limitar el dolor, los síntomas y el daño en las articulaciones que produce la AR.



## Su tratamiento con Rituxan

### En esta sección:

- Conozca datos importantes sobre las infusiones.
- Sepa lo que debe esperar de su primer ciclo de tratamiento (2 infusiones) y después.

Para obtener información importante sobre la seguridad de Rituxan® (rituximab), consulte en este folleto la sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta.



Julie, recibe Rituxan desde 2007 >

“ Durante las infusiones, las enfermeras me monitorean continuamente y se aseguran de que me sienta cómoda. ”

## ¿Qué debería saber sobre las infusiones?

Rituxan® (rituximab) se administra como infusión. Si no está familiarizado con las infusiones, aquí hay algunas cosas que debería saber:

- Las infusiones son una forma de tratamiento utilizada para una diversidad de afecciones.
- Pueden llevar más tiempo que otras formas de tratamiento, pero en la AR habitualmente se administran con menor frecuencia.
- A diferencia de otras formas de tratamiento, las infusiones son administradas por un profesional de atención médica capacitado que está allí con usted para ayudarle a manejar el proceso y monitorear los efectos secundarios.
- Pueden ocurrir reacciones a la infusión de Rituxan, y pueden incluir fiebre, escalofríos y temblores, picazón y tos. En los estudios, la mayoría fue leve y manejable, y menos del 1% fue grave.

Para obtener información importante sobre la seguridad de Rituxan, consulte en este folleto la sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta.

# ¿Qué debería esperar en mi primera infusión de Rituxan?

- El consultorio de su médico programará citas para su primer ciclo de 2 infusiones de Rituxan® (rituximab), las cuales se pueden administrar en el consultorio de su médico, en un centro de infusión o en un hospital.
- Cada infusión podría llevar de 4 a 6 horas, así que planifique de manera acorde. Lleve algo con usted que le ayude a pasar el tiempo, como un libro o algo de música.
- Revise la Guía de medicamentos de Rituxan antes de su infusión y analícela con su proveedor de atención médica.
- Es posible que se le administre un medicamento adicional antes de cada infusión para reducir el riesgo de efectos secundarios. Si sufre alguna incomodidad durante el tratamiento, busque atención médica inmediata.
- Si ocurren reacciones a la infusión, normalmente lo hacen dentro de las 24 horas posteriores a la primera infusión. Revise la sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta para obtener una lista de las reacciones posibles.



“ Para mí, mi tiempo de infusión pasó muy rápido. No me molesta pasar el tiempo con juegos o lectura, o simplemente conversando. ”

“ Tener que ir solo a 4 infusiones por año ha sido genial para mí. Con mis tratamientos anteriores, me tenía que inyectar con mucha mayor frecuencia. ”

◀ Bobbi, toma Rituxan desde 2007

## ¿Qué debería esperar en mi segunda infusión?

Su segunda infusión puede llevar menos tiempo que la primera, pero también durará varias horas. Si no tuvo efectos secundarios de su primera infusión, la segunda saldrá igual de bien. Pero de todos modos debe estar atento a cómo se siente durante la infusión.

Si presentó efectos secundarios la primera vez, asegúrese de hablar de ellos con su médico.

Después de su segunda infusión, puede comenzar a ver una mejoría en los síntomas que podría durar 6 meses antes de que sea tiempo de su próximo ciclo de tratamiento.

### Información importante sobre los efectos secundarios

Las reacciones a la infusión están entre los efectos secundarios comunes que pueden ocurrir con Rituxan® (rituximab). Vea en esta sección “Hable con su médico”, toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta.

“ No hay nada que disfrutemos más que cocinar, recibir y estar en el jardín. Simplemente es una alegría. ”

Tenga en cuenta que su respuesta a Rituxan® (rituximab) puede ser diferente. Para leer información importante sobre la seguridad de Rituxan, consulte en este la sección “Hable con su médico”, toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.





## Hable con su médico sobre Rituxan

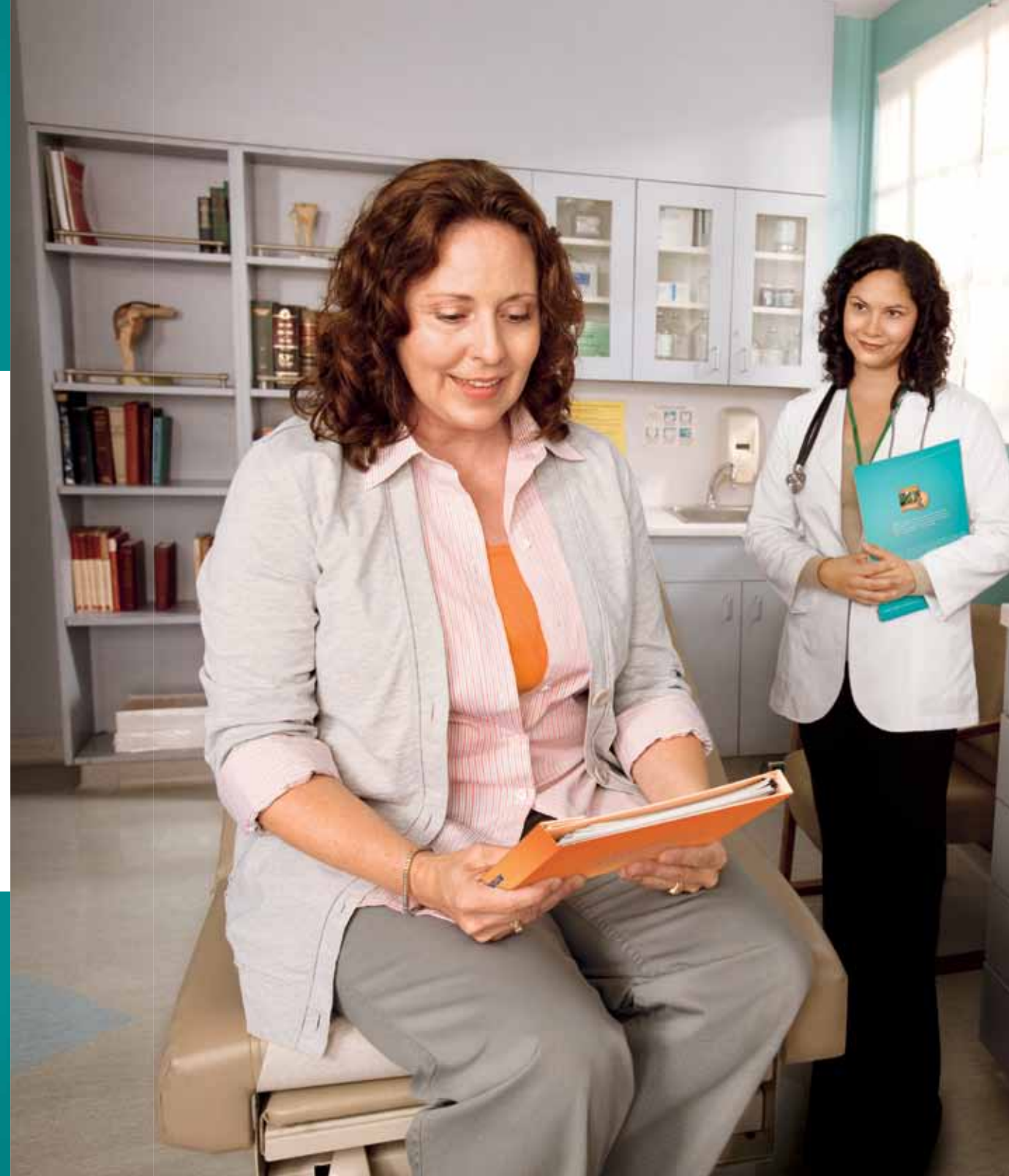
### En esta sección:

- Una guía de conversación para que hable sobre el Rituxan® (rituximab) con su proveedor de atención médica.
- Ayuda para entender la información sobre la seguridad de Rituxan.
- Un formulario de Genentech Rheumatology Access Solutions® para comenzar si necesita solicitar copago y asistencia en el seguro.
- Recursos para asistencia financiera.

# Hable con su médico sobre Rituxan

Ya sea que esté considerando al Rituxan® (rituximab) o que esté iniciando su tratamiento con Rituxan, use esta sección para que le ayude de guía para hablar con su proveedor de atención médica. A continuación encontrará algunos consejos para ayudarle a sacar el mayor provecho de esta sección.

- Recuerde llevar este Kit de recursos a la cita con su médico.
- Revise la información apropiada en las otras secciones de este kit para ayudarle a informar su conversación. Para obtener ayuda para entender la información sobre la seguridad de Rituxan, que incluye los efectos secundarios posibles, revise las páginas 42 a 44 de esta sección. Asegúrese de revisar esta información, así como toda la Información de prescripción que la acompaña y la Guía de medicamentos adjunta, con su proveedor de atención médica.
- Puede escribir la información importante de su conversación en las secciones de Notas que la acompañan.









# Entender la información sobre la seguridad de Rituxan

Cuando considere cualquier tratamiento, es importante que entienda los riesgos y beneficios potenciales y que los compare con su proveedor de atención médica. Para informarle los riesgos potenciales, puede hallar información sobre la seguridad del tratamiento, la cual se puede encontrar en la Guía de medicamentos.

Entre los riesgos asociados al Rituxan® (rituximab) hay algunos efectos secundarios que son graves y potencialmente fatales, entre ellos:

- Infecciones graves, incluso leucoencefalopatía multifocal progresiva (PML).
- Reacciones graves a la infusión.
- Síndrome de lisis tumoral (TLS)
- Reacciones cutáneas graves.

Es importante que sepa que aunque todos son riesgos considerados en el tratamiento de la AR, algunos de estos efectos secundarios solo han ocurrido en pacientes con linfoma no Hodgkin (NHL).

**“ Pienso que es importante revisar siempre la Guía de medicamentos con cualquier medicamento que esté tomando. ”**

—Kathy, recibe Rituxan desde 2006

## Infecciones graves que incluyen PML

Rituxan puede incrementar las probabilidades de contraer infecciones. En estudios clínicos, las infecciones graves ocurrieron en el 2% de los pacientes que recibieron Rituxan. Y la más común de estas infecciones fue la neumonía.

Ha ocurrido una infección cerebral poco frecuente llamada leucoencefalopatía multifocal progresiva o PML en pacientes que reciben Rituxan. Aunque la PML es poco frecuente en los pacientes que reciben Rituxan para la AR, aún es un riesgo y usted debería analizarlo con su médico. No existe ningún tratamiento, prevención o cura conocidos para la PML. La PML puede ocurrir durante el tratamiento con Rituxan o después de que el tratamiento ha terminado.

## Reacciones graves a la infusión

Las reacciones a la infusión son el efecto secundario más común de Rituxan y es importante saber que podrían ocurrir reacciones graves, potencialmente fatales, durante su infusión o dentro de las 24 horas posteriores. En los estudios, menos del 1% de todas las reacciones fueron graves. Su proveedor de atención médica debería darle medicamentos antes de su infusión para disminuir la probabilidad de una reacción grave a la infusión. Y usted debería analizar con su médico el riesgo de estas reacciones.

## TLS y reacciones cutáneas graves

Han ocurrido TLS y reacciones cutáneas graves en pacientes que reciben Rituxan para NHL, pero no se las ha informado en pacientes con AR. La TLS es una enfermedad que puede conducir a la insuficiencia renal y la necesidad de diálisis.

**Si tiene alguna pregunta, hable con su proveedor de atención médica ya que puede tener consejos específicos basándose en su salud personal.**

## Otros efectos secundarios graves potenciales

- **Reactivación del virus de la hepatitis B (HBV).** Si usted ha tenido hepatitis B o es portador del virus de la hepatitis B, recibir Rituxan podría causar que el virus vuelva a convertirse en infección activa. La reactivación de la hepatitis B podría causar graves problemas hepáticos que incluyen la insuficiencia hepática y la muerte. Usted no debería recibir Rituxan si tiene la enfermedad hepática de hepatitis B activa. Su médico debería vigilarle la infección por hepatitis B durante y varios meses después de dejar de recibir Rituxan.
- **Infecciones graves.** Infecciones graves que pueden ocurrir durante y después del tratamiento con Rituxan pueden conducir a la muerte. Rituxan puede disminuir la capacidad de su sistema inmune para luchar contra las infecciones. Los tipos de infecciones graves que pueden ocurrir con Rituxan incluyen infecciones bacterianas, micóticas y virales. Después de recibir Rituxan, algunos pacientes han desarrollado niveles bajos de ciertos anticuerpos en sangre durante un lapso prolongado (más de 11 meses). Algunos de estos pacientes con niveles bajos de anticuerpos desarrollaron infecciones. Llame inmediatamente a su médico si tiene algún síntoma de infección:
  - fiebre
  - síntomas de resfrío, tal como goteo nasal o dolor de garganta que no desaparecen
  - síntomas de gripe, tales como tos, cansancio y dolores corporales
  - dolor de oídos o dolor de cabeza
  - dolor al orinar
  - parches blancos en la boca o en la garganta
  - cortes, rasguños o incisiones que estén rojas, tibias, inflamadas o dolorosas
- **Problemas cardíacos.** Rituxan puede causar dolor de pecho y latidos cardíacos irregulares que pueden necesitar tratamiento, o su médico puede decidir detener su tratamiento con Rituxan.
- **Problemas renales,** especialmente si recibe Rituxan para NHL. Su médico debería hacer análisis de sangre para verificar qué tan bien trabajan sus riñones.
- **Estómago y problemas intestinales graves que, a veces, pueden conducir a la muerte.** Pueden ocurrir problemas intestinales, que incluyen taponamiento o desgarros en el intestino, si usted recibe Rituxan con medicamentos quimioterapéuticos para tratar el linfoma no Hodgkin. Avísele inmediatamente a su médico si tiene algún dolor en el área del estómago durante el tratamiento con Rituxan.

- **Bajos recuentos de células sanguíneas.** Su médico puede hacerle análisis de sangre durante el tratamiento con Rituxan para revisar sus recuentos de células sanguíneas.
  - **Glóbulos blancos.** Los glóbulos blancos luchan contra las infecciones bacterianas. Un bajo recuento de glóbulos blancos puede causar que contraiga infecciones, lo que puede ser grave. Vea “Riesgo aumentado de infecciones” arriba para obtener una lista de síntomas de infección.
  - **Glóbulos rojos.** Los glóbulos rojos llevan el oxígeno a los tejidos y órganos de su cuerpo.
  - **Plaquetas.** Las plaquetas son células sanguíneas que ayudan a la coagulación de su sangre.

## Efectos secundarios comunes

La información sobre seguridad de Rituxan también incluye el riesgo de algunos efectos secundarios menos graves pero más comunes tales como reacciones graves a la infusión con síntomas que incluyen fiebre, escalofríos y temblores, picazón, ronchas, estornudos, irritación u opresión en la garganta, dolor de cabeza, náuseas y tos. Si estos ocurren, habitualmente lo hacen en las 24 horas posteriores a la primera infusión.

Otros efectos secundarios incluyen dolor articular, respiración de vías aéreas superiores, recuentos disminuidos de las células sanguíneas y problemas pulmonares.

Aunque estos síntomas pueden no ocurrir como resultado de su tratamiento con Rituxan, es importante que le diga a su proveedor de atención médica si experimenta alguno de ellos.

Para obtener más información sobre seguridad de Rituxan, consulte toda la Información de prescripción que lo acompaña y la Guía de medicamentos adjunta.

“ Mi médico y yo hablamos mucho de los riesgos y beneficios de Rituxan. ”

— María, recibe Rituxan desde 2006

## Formularios para ayudarle a comenzar

Si usted y su médico deciden que Rituxan® (rituximab) es apropiado para usted, el programa Genentech Rheumatology Access Solutions® puede jugar un papel importante para ayudarle a obtener el tratamiento que necesita.

Complete el formulario de la página siguiente con su proveedor de atención médica para hacer la solicitud a Genentech Rheumatology Access Solutions hoy.

## Genentech Access Solutions es un programa gratis de Genentech.

Trabajamos para ayudarle a pagar el Rituxan® (rituximab) o ACTEMRA® (tocilizumab). Podemos ayudar de muchas formas diferentes. Ayudamos a las personas que cuentan con un plan de atención médica así como a aquellas que no tienen uno.

Si usted no tiene un plan de atención médica o si su plan no pagará los productos Genentech, tal vez podríamos ayudarle. Si cumple ciertos requisitos financieros y médicos, podemos suministrarle medicamentos gratis. Esto se hace a través de la Genentech® Access to Care Foundation (GATCF).

Para ayudarle, necesitamos mirar, usar y revelar su información personal de salud (personal health information, PHI). Su médico y el plan de atención médica pueden revelarnos su PHI únicamente con su consentimiento escrito. Una vez que usted firme este formulario y nos lo envíe, podemos comenzar a prestar estos servicios. Podemos proporcionarle una copia de esta Divulgación. Usted nos la tiene que pedir antes de que podamos enviarle la copia.

**Usted no tiene que estar de acuerdo con esta Divulgación**, pero no podemos prestar nuestros servicios sin ella. Esto significa que tal vez usted deba pagar ciertos medicamentos por su cuenta.

**LEA CUIDADOSAMENTE ESTE FORMULARIO. SI TIENE ALGUNA PREGUNTA, LLAME AL CONSULTORIO DE SU MÉDICO O LLÁMENOS AL NÚMERO INDICADO EN LA PARTE SUPERIOR DE ESTA PÁGINA.**

### 1. Información que será revelada o utilizada

Este formulario firmado permite que mis médicos y planes de atención médica envíen mi PHI a Genentech Access Solutions y/o a GATCF. Esta incluye:

- Todos mis registros de salud relacionados con mi tratamiento.
- Información sobre los beneficios de mi plan de atención médica.
- El saldo restante en dólares en el total de los pagos de por vida cubiertos por la póliza de mi plan de atención médica (si esto se aplica a mi plan).
- Toda información que influya en mi salud o mi adherencia al tratamiento.

Todo lo anterior se considera parte de mi PHI. Sé que esto puede incluir información sobre:

- Enfermedades de transmisión sexual.
- Trastornos de salud mental.
- Resultados de pruebas genéticas.

No estamos buscando esta información. Podría formar parte del registro médico que nos envían.

## 2. Quién puede ver y usar mi PHI (información personal de salud)

Genentech Access Solutions y/o GATCF pueden ver mi PHI. Estos son programas patrocinados por Genentech. Su dirección es 1 DNA Way, Mail Stop #858a, South San Francisco, CA 94080-4990. Toda persona que ayude a Genentech Access Solutions a prestar servicios también puede ver mi información de salud, incluyendo los empleados de Genentech y cualquiera de los asociados de Genentech.

Solo se puede usar mi PHI de estas formas:

- Ayudar con la cobertura para Rituxan o ACTEMRA de mi plan de atención médica
- Hacer la solicitud a GATCF
- Rastrear mi uso de Rituxan o ACTEMRA
- Para tareas administrativas de Genentech

## 3. Fecha de vencimiento

Esta Divulgación está en vigencia por 1 año a partir de la fecha en que la firme. También puedo retirarla por escrito en cualquier momento.

## 4. Avisos

Una vez que firme este formulario, sé que mi PHI podría no estar cubierta por ninguna ley federal sobre el uso de mi PHI o cómo se la divulga. No existe garantía de que mi PHI no pueda ser divulgada a un tercero. Este tercero tal vez no tenga que seguir las condiciones de esta Divulgación.

Sé que me puedo negar a firmar este formulario. Puedo retirarme en cualquier momento y por cualquier motivo. Esto no afectará el inicio ni la continuidad de mi tratamiento. No tendrá ningún efecto sobre la calidad de mi tratamiento.

Sé que esta Divulgación se mantiene vigente durante 1 año o hasta que la retire por escrito. Para retirarla, debo enviar una nota escrita a Genentech. Se la puede enviar por fax o por correo a la dirección que figura al pie de esta página. Este retiro entra en efecto una vez que Genentech lo reciba. No tendrá ningún impacto en el tratamiento que me proporcione mi médico.

Si no firmo este formulario o si lo retiro, yo puedo ser responsable de los costos de mi tratamiento.

## 5. Aceptación de distribución

Si acepto el producto gratis de GATCF, usaré Rituxan o ACTEMRA según mi médico me lo haya recetado. No venderé ni distribuiré Rituxan o ACTEMRA. Entiendo que es ilegal hacerlo. Soy responsable de garantizar el envío de Rituxan o ACTEMRA a una dirección segura cuando me los envíen a mí. Sé que es mi deber controlar el Rituxan o ACTEMRA mientras se encuentren en mi posesión.

### LA SECCIÓN 6 EN LA PRÓXIMA PÁGINA ES REQUERIDA.

Este aviso escrito se deberá firmar, fechar y enviar por correo o fax a:

**Genentech Access Solutions**

1 DNA Way, Mail Stop #858a

South San Francisco, CA 94080-4990

**Fax: (866) 681-3288**

## 6. Firma y fecha (REQUERIDAS)

He leído y entiendo los términos de este formulario de Divulgación. He tenido la oportunidad de hacer preguntas sobre el uso de mi información personal de salud (PHI) y quién la puede ver. Al firmar este formulario a continuación, sé que estoy divulgando mi PHI como se indicó en él. **(Complete toda la información de abajo. Asegúrese de firmar y fechar este formulario. Si no lo hace, podría detener el proceso para ayudarle).**

Debe firmar y fechar aquí

Debe escribir su nombre en letra de imprenta aquí

\_\_\_\_\_  
Firma del paciente o tutor\* Descripción de la autoridad Fecha

\_\_\_\_\_  
Nombre del paciente en letra de imprenta

\_\_\_\_\_  
Dirección del paciente/tutor

\*Si el paciente es un menor no emancipado o está incapacitado de algún otro modo (física o mentalmente).

## 7. Información financiera

Complete esta sección solo si desea solicitar ayuda de GATCF.

**Ingresos brutos ajustados del hogar:**  \$0-\$25.000/año  \$25.001-\$50.000/año  
 \$50.001-\$75.000/año  \$75.001-\$100.000/año  Otro: \_\_\_\_\_

Sé que para calificar para medicamentos gratis, los ingresos brutos ajustados de mi hogar no deben superar \$100.000 por año. Certifico que la declaración anterior sobre mis ingresos para el último año es verdadera. Certifico que no tengo cobertura de plan de salud para Rituxan o ACTEMRA. Esto incluye Medicare, Medicaid u otros programas públicos. No tengo los recursos financieros para pagar Rituxan o ACTEMRA. Accedo a darle a GATCF prueba de mis ingresos. Esta puede ser una copia de mi formulario IRS 1040 del año pasado. También puede ser otra prueba de mis ingresos. Enviaré esto a GATCF dentro de los 45 días posteriores a la fecha de presentación de este formulario. Sé que si no lo hago, GATCF no podrá continuar ayudándome.

Debe firmar y fechar aquí (si es necesario)

\_\_\_\_\_  
Firma del paciente o tutor Fecha

## 8. Un programa opcional y sin cargo de apoyo para pacientes

Deseo inscribirme en un programa de Genentech opcional y sin cargo de apoyo para pacientes. Entiendo que se necesita mi PHI para que yo forme parte de este programa. También sé que mi PHI se compartirá con Genentech Access Solutions y con el programa de apoyo para pacientes. Puedo elegir que me contacten por correo, correo electrónico o por teléfono. Entiendo que mi PHI no se compartirá fuera de Genentech ni por sus agentes. Accedo a permitir que Genentech o sus agentes me contacten en el futuro en relación con este programa. La política de privacidad de Genentech se puede encontrar en [GenentechAccessSolutions.com](http://GenentechAccessSolutions.com). Entiendo que no tengo que firmar esta parte del formulario. No juega ningún papel para obtener mi medicamento. No forma parte de la ayuda que se recibe de Genentech Access Solutions. También sé que puedo cancelar esta inscripción en el programa de apoyo para pacientes en cualquier momento. Para cancelar, puedo escribir a Genentech, a través de su agente al 5901B Peachtree Dunwoody Rd., Suite 380, Atlanta, GA 30328.

**Forma preferida para contactarme** (Marque las casillas que corresponda y complete su información. Puede marcar más de una casilla.):

Correo electrónico: \_\_\_\_\_  Número de teléfono: \_\_\_\_\_ ¿Se puede dejar mensaje?  Sí  No  
 Dirección: \_\_\_\_\_

Elija inscribirse firmando aquí

\_\_\_\_\_  
Firma del paciente (debe firmar aquí para inscribirse en el programa de apoyo para pacientes). Fecha

El logotipo de Access Solutions es una marca comercial registrada de Genentech, Inc.

# Recursos para asistencia financiera

Hay 3 programas importantes que pueden jugar un papel fundamental para ayudarle a obtener el tratamiento Rituxan® (rituximab) que necesita:



**RITUXAN EXPERIENCE Program™** — Le proporciona a los pacientes elegibles hasta \$4000 por año para ayudarle a cubrir sus gastos de copago. Y si aún es elegible en el futuro, puede continuar cargando su tarjeta cada 12 meses durante el tiempo durante el tiempo que se ofrece el programa. Para obtener más información y todos los requisitos de elegibilidad, llame al (888) MY-RITUXAN, o visite <http://Rituxan.TMGcard.com>.\*



**Genentech Rheumatology Access Solutions** — Si tiene seguro público (por ejemplo, Medicare) o privado y le preocupa su copago de Rituxan, Genentech Rheumatology Access Solutions puede ayudarle. Podemos remitirlo a una organización independiente sin fines de lucro (*independent non-profit organization*, INO) para ayudarle con su copago. Ver el formulario de inscripción en la página 44.

**Genentech Access to Care Foundation** — La fundación Genentech Access to Care Foundation (GATCF) ayuda a los pacientes que no tienen un plan de atención médica para Rituxan. GATCF ayuda a que los pacientes calificados reciban su medicamento sin cargo. Para obtener más información, llame al (866) 681-3261 o visite [www.RheumatologyAccessSolutions.com](http://www.RheumatologyAccessSolutions.com).\*

\*Los sitios web mencionados están disponibles únicamente en inglés. Si desea visitarlos, piense en pedirle ayuda a alguien que se los pueda traducir. También puede pedirle más información a su médico.

**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<sup>2</sup> (2.2).
- The dose for CLL is 375 mg/m<sup>2</sup> in the first cycle and 500 mg/m<sup>2</sup> 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<sup>2</sup> (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<sup>2</sup> 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\***

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

**1 INDICATIONS AND USAGE**

- 1.1 Non-Hodgkin's Lymphoma (NHL)
- 1.2 Chronic Lymphocytic Leukemia (CLL)
- 1.3 Rheumatoid Arthritis (RA)
- 1.4 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 1.5 Limitations of Use

**2 DOSAGE AND ADMINISTRATION**

- 2.1 Administration
- 2.2 Recommended Dose for Non-Hodgkin's Lymphoma (NHL)
- 2.3 Recommended Dose for Chronic Lymphocytic Leukemia (CLL)
- 2.4 Recommended Dose as a Component of Zevalin®
- 2.5 Recommended Dose for Rheumatoid Arthritis (RA)
- 2.6 Recommended Dose for Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 2.7 Recommended Concomitant Medications
- 2.8 Preparation for Administration

**3 DOSAGE FORMS AND STRENGTHS**

**4 CONTRAINDICATIONS**

**5 WARNINGS AND PRECAUTIONS**

- 5.1 Infusion Reactions
- 5.2 Tumor Lysis Syndrome (TLS)
- 5.3 Severe Mucocutaneous Reactions
- 5.4 Progressive Multifocal Leukoencephalopathy (PML)
- 5.5 Hepatitis B Virus (HBV) Reactivation
- 5.6 Infections
- 5.7 Cardiovascular
- 5.8 Renal
- 5.9 Bowel Obstruction and Perforation
- 5.10 Immunization
- 5.11 Laboratory Monitoring
- 5.12 Concomitant Use with Biologic Agents and DMARDs other than Methotrexate in RA, WG and MPA
- 5.13 Use in RA Patients Who Have Not Had Prior Inadequate Response to Tumor Necrosis Factor (TNF) Antagonists

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

**6 ADVERSE REACTIONS**

- 6.1 Clinical Trials Experience in Lymphoid Malignancies
- 6.2 Clinical Trials Experience in Rheumatoid Arthritis
- 6.3 Clinical Trials Experience in Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)
- 6.4 Immunogenicity
- 6.5 Postmarketing Experience

**7 DRUG INTERACTIONS**

**8 USE IN SPECIFIC POPULATIONS**

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

**10 OVERDOSAGE**

**11 DESCRIPTION**

**12 CLINICAL PHARMACOLOGY**

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics

**13 NONCLINICAL TOXICOLOGY**

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
- 13.2 Animal Toxicology and/or Pharmacology

**14 CLINICAL STUDIES**

- 14.1 Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.2 Previously Untreated, Low-Grade or Follicular, CD20-Positive, B-Cell NHL
- 14.3 Diffuse Large B-Cell NHL (DLBCL)
- 14.4 Chronic Lymphocytic Leukemia (CLL)
- 14.5 Rheumatoid Arthritis (RA)
- 14.6 Wegener's Granulomatosis (WG) and Microscopic Polyangiitis (MPA)

**16 HOW SUPPLIED/STORAGE AND HANDLING**

**17 PATIENT COUNSELING INFORMATION**

\*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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (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<sup>®</sup> (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<sup>2</sup> 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<sup>2</sup> the day prior to the initiation of FC chemotherapy, then 500 mg/m<sup>2</sup> on Day 1 of cycles 2–6 (every 28 days).

## 2.4 Recommended Dose as a Component of Zevalin®

- Infuse rituximab 250 mg/m<sup>2</sup> 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<sup>2</sup> 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 ( $\geq 25,000/\text{mm}^3$ ). [*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 ( $\geq 25,000/\text{mm}^3$ ) 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  $\geq 25\%$ ) 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  $\geq 25\%$ ) 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  $375 \text{ mg/m}^2$  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  $375 \text{ mg/m}^2$  as an initial infusion followed by  $500 \text{ mg/m}^2$  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<sup>2</sup> weekly for 4 doses.

**Table 1**  
Incidence of Adverse Reactions in  $\geq 5\%$  of  
Patients with Relapsed or Refractory, Low-Grade or Follicular  
NHL, Receiving Single-agent Rituxan (N=356)<sup>a,b</sup>

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

**Table 1 (cont'd)**  
 Incidence of Adverse Reactions in  $\geq 5\%$  of  
 Patients with Relapsed or Refractory, Low-Grade or Follicular  
 NHL, Receiving Single-agent Rituxan (N=356)<sup>a,b</sup>

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

<sup>a</sup> Adverse reactions observed up to 12 months following Rituxan.

<sup>b</sup> 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 ( $\geq 5\%$ ) 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  $\geq 2$  infections, and Grade  $\geq 3$  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 ( $\geq 2\%$ ) 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 ( $\geq 5\%$ ) 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 ( $\geq 2\%$ ) 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 ( $\geq 5\%$ ) in patients age  $\geq 60$  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  $\geq 5\%$  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  $\geq 2\%$   
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<sup>2</sup> 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  $\geq 10\%$  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<sup>2</sup> have been administered in clinical trials.

## **11 DESCRIPTION**

Rituxan<sup>®</sup> (rituximab) is a genetically engineered chimeric murine/human monoclonal IgG<sub>1</sub> 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/ $\mu$ l) 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/ $\mu$ l 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/ $\mu$ L. By Month 18, most patients (87%) had counts >10 cells/ $\mu$ L.

## 12.3 Pharmacokinetics

### *Non-Hodgkins Lymphoma (NHL)*

Pharmacokinetics were characterized in 203 NHL patients receiving 375 mg/m<sup>2</sup> 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<sup>2</sup> 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 ( $\pm$  S.D.; % CV) concentrations after the first infusion (C<sub>max</sub> first) and second infusion (C<sub>max</sub> second) were 157 ( $\pm$  46; 29%) and 183 ( $\pm$  55; 30%) mcg/mL, and 318 ( $\pm$  86; 27%) and 381 ( $\pm$  98; 26%) mcg/mL for the 2  $\times$  500 mg and 2  $\times$  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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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<sup>2</sup> 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 <sup>a</sup>	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 <sup>b, c,</sup> <sup>d</sup> (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+]

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

<sup>b</sup> Kaplan-Meier projected with observed range.

<sup>c</sup> “+” indicates an ongoing response.

<sup>d</sup> 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<sup>2</sup> 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) <sup>a</sup>	2.4	1.4
Hazard ratio (95% CI) <sup>b</sup>	0.44 (0.29, 0.65)	

<sup>a</sup> p<0.0001, two-sided stratified log-rank test.

<sup>b</sup> Estimates of Cox regression stratified by center.

##### Study 5

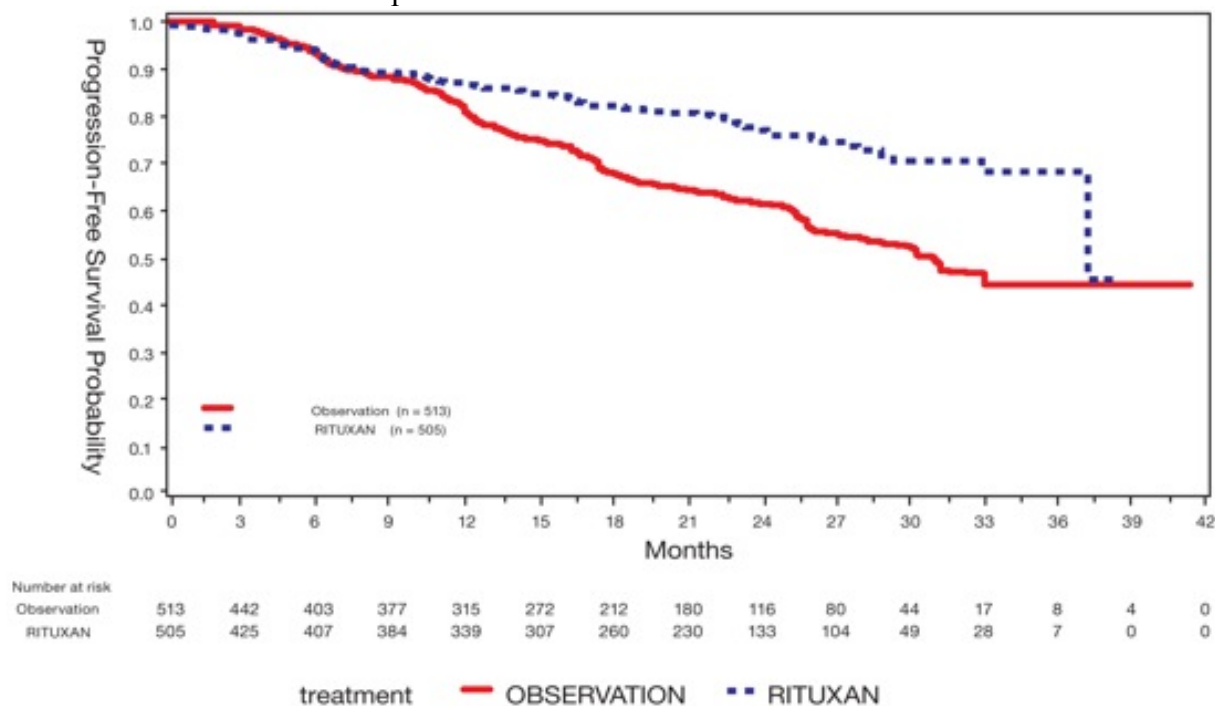
An open-label, multicenter, randomized (1:1) study was conducted in 1,018 patients with previously untreated follicular NHL who achieved a response (CR or PR) to Rituxan in combination with chemotherapy. Patients were randomized to Rituxan as single-agent maintenance therapy,

375 mg/m<sup>2</sup> 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<sup>2</sup> 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  $\geq 60$  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<sup>2</sup> 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  $\geq 2$ , 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  $\geq 60$  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<sup>2</sup> 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  $\geq 2$ , 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  $\leq 1$ , 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 <sup>b</sup>	NE <sup>b</sup>
Hazard ratio <sup>d</sup>	0.69 <sup>a</sup>		0.60 <sup>a</sup>		0.45 <sup>a</sup>	
Overall survival at 2 years <sup>c</sup>	74%	63%	69%	58%	95%	86%
Hazard ratio <sup>d</sup>	0.72 <sup>a</sup>		0.68 <sup>a</sup>		0.40 <sup>a</sup>	

<sup>a</sup> Significant at p<0.05, 2-sided.

<sup>b</sup> NE=Not reliably estimable.

<sup>c</sup> Kaplan-Meier estimates.

<sup>d</sup> 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<sup>2</sup>/day and cyclophosphamide 250 mg/m<sup>2</sup>/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*		Study 11*	
	(Previously untreated)		(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<sup>a</sup>

Age subgroup	Study 10		Study 11	
	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)

<sup>a</sup> 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) <sup>c</sup> (95% CI)	Response	Placebo + MTX Retreatment n = 157	Rituxan + MTX Retreatment n = 318	Treatment Difference (Rituxan – Placebo) <sup>a,b,c</sup> (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%)

<sup>a</sup> 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.

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

<sup>c</sup> 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)**

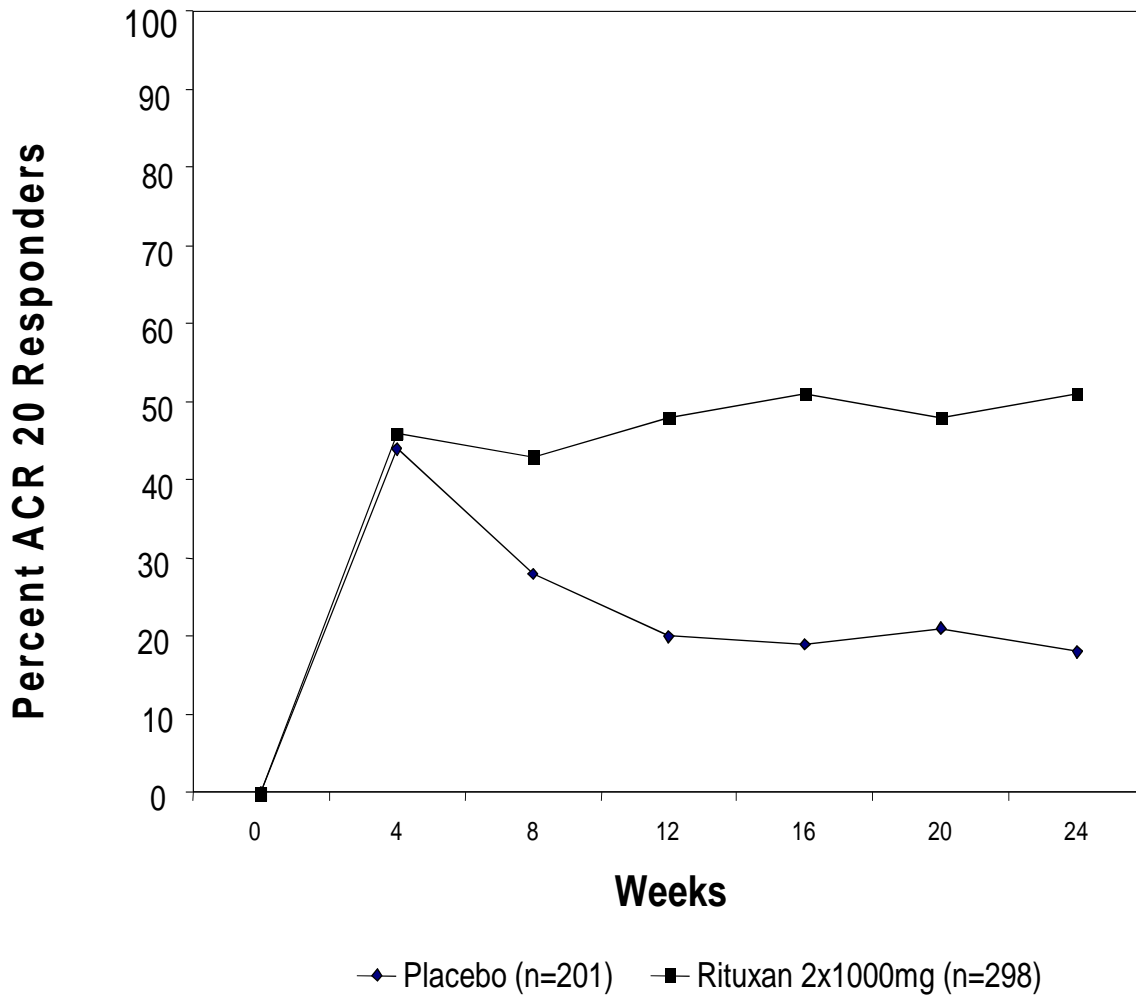
Inadequate Response to TNF Antagonists				
Parameter (median)	Placebo+MTX (n=201)		Rituxan+MTX (n=298)	
	Baseline	Wk 24	Baseline	Wk 24
Tender Joint Count	31.0	27.0	33.0	13.0
Swollen Joint Count	20.0	19.0	21.0	9.5
Physician Global Assessment <sup>a</sup>	71.0	69.0	71.0	36.0
Patient Global Assessment 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

<sup>a</sup> Visual Analogue Scale: 0=best, 100=worst.

<sup>b</sup> 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 <sup>b</sup>	Placebo + MTX <sup>c</sup>	Treatment Difference (Placebo – Rituxan)	95% CI
<u>Change during First Year</u>				
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)
<u>Change during Second Year<sup>a</sup></u>				
TSS	0.48	1.04	—	—
ES	0.28	0.62	—	—
JSN Score	0.20	0.42	—	—

<sup>a</sup> Based on radiographic scoring following 104 weeks of observation.

<sup>b</sup> Patients received up to 2 years of treatment with Rituxan + MTX.

<sup>c</sup> 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 × 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) <sup>b</sup> (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) <sup>a</sup>	48%	58%	11% (0%, 21%)

<sup>a</sup> Minimal Clinically Important Difference: MCID for HAQ=0.22.

<sup>b</sup> 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<sup>2</sup> 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/WG of 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% <sup>b</sup> CI	(54%, 73%)	(43%, 63%)	(–3%, 24%) <sup>a</sup>

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

<sup>b</sup> 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.

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#### **RITUXAN<sup>®</sup> [rituximab]**

Manufactured by:

**Genentech, Inc.**

A Member of the Roche Group

1 DNA Way

South San Francisco, CA 94080-4990

10134808

Initial US Approval: November 1997

PI Revision Date 02 2012

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**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](http://www.Rituxan.com) or call 1-877-474-8892.

## What are the ingredients in Rituxan?

Active ingredient: rituximab

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

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

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

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### **RITUXAN<sup>®</sup> [rituximab]**

Manufactured by:

10134808

**Genentech, Inc.**

Initial US Approval: November 1997

A Member of the Roche Group

Med Guide Revision Date: February 2012

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Rituxan<sup>®</sup> is a registered trademark of Biogen Idec, Inc.

South San Francisco, CA 94080-4990

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