



No. 11-065408- -00006-0000

Fecha: 2014-03-12 16:57:30

Dep. 2020 DIR.NUEVASCR

Tra. 11 PATENTEIYII

Eve: 378 FASENACIONALI

Act. 523 RESPUESTA

Folios: 63

Señor Director

DIRECCIÓN DE NUEVAS CREACIONES

Superintendencia de Industria y Comercio

E. S. D.

Trámite : 011

Evento : 378

Actuación : 523

Referencia : Expediente No. **11.065.408**

Asunto : Solicitud de patente para: **"COMBINACIONES
ANTITUMORALES QUE CONTIENEN ANTICUERPOS
QUE RECONOCEN ESPECÍFICAMENTE CD38 Y
VINCRISTINA"**

Solicitante : **SANOFI**

Fecha de solicitud : 26 de mayo de 2011.

1. Yo, Luz Clemencia DE PÁEZ, en mi condición de apoderada de la sociedad solicitante de la patente de la referencia, me refiero al oficio No. **22873** notificado por fijación en lista el 17 de diciembre de 2013.

2. Mediante oficio No. **22873** se puso en conocimiento del solicitante el informe que contiene las observaciones hechas por su Despacho sobre la presente solicitud de patente. Las observaciones realizadas en el oficio se refieren a que las reivindicaciones 6-10 se refieren a un uso y por ende no son patentables, a la claridad del pliego reivindicatorio, a la falta de unidad de invención y al nivel inventivo de las reivindicaciones 1-5 en vista de los documentos D1: EP 1914242A y D2: WO 9962526.

3. **Respuesta a las objeciones**

De este modo y con el objeto de atender las objeciones arriba mencionadas, se desea presentar las siguientes modificaciones, aclaraciones y argumentos:

"EXCELENCIA LEGAL EN UN MUNDO SIN FRONTERAS"

BOGOTÁ - Edificio Siski - Carrera 4 No. 72 - 35 - Tel. (57-1) 347 3611 - Fax (57-1) 211 8650 - Fax In U.S.A: (1-305) 675 7743 - COLOMBIA
MEDELLÍN - San Fernando Plaza - Carrera 43 A No. 1 - 50 - Torre Protección Oficina 652 - Tel: (57-4) 604 4794 Ext. 6729 / 6731 - Fax: (57-4) 604 4731- COLOMBIA

www.cavelier.com
cavelier@cavelier.com

3.1 Modificación de una solicitud en trámite

De acuerdo con el artículo 34 de la Decisión 486 de la Comisión de la Comunidad Andina, donde se establece que la modificación de una solicitud es posible en cualquier momento del trámite mientras no implique una ampliación de la solicitud inicial, me permito presentar un nuevo pliego reivindicatorio conformado por 8 reivindicaciones.

Se han introducido las siguientes modificaciones al capítulo reivindicatorio:

Se modificó la reivindicación 1 para especificar los CDRs del anticuerpo humanizado anti-CD38 descrito en la descripción de la presente solicitud. El soporte para dicha modificación se encuentra desde la página 2, línea 11 hasta la página 3, línea 16 de la descripción de la presente solicitud y la previa reivindicación 3. La definición de los CDRs de huSB3819 (reivindicación 1(iii)) ha sido más completada al referirse a tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID NOs: 13, 15 y posiciones 50 a 66 de SEQ ID NO: 66. El soporte para dicha modificación se encuentra en la página 5, líneas 16 a 20 y página 6, líneas 8 a 15 de la descripción de la presente solicitud. Las posiciones 50 a 66 de SEQ ID NO: 66 representan V_H CDR 2 del anticuerpo huSB3819. La posición del CDR es clara a partir de la inspección de SEQ ID NO: 66 (la región V_H de huSB3819) y comparación con SEQ ID NO: 14, que representa V_H CDR 2 del anticuerpo huSB3819 murino parental (página 2, líneas 25 a 31).

La reivindicación 2 ha sido modificada para agregar la referencia a anticuerpos quiméricos. El soporte para dicha modificación se encuentra en la página 3, línea 24 de la descripción. La reivindicación 3 ha sido eliminada. Las reivindicaciones 4 y 5 (nuevas reivindicaciones 3 y 4) fueron modificadas para eliminar las características que ahora se presentan en la nueva reivindicación 1. Las reivindicaciones también han sido modificadas para además aclarar que las cadenas pesadas y ligeras comprenden la secuencia de SEQ ID Nos 66, 62, 64, 72, 68 o 70. Es claro a partir de la descripción en la página 6, líneas 8 a 23 que estas secuencias representan solamente la región variable de las cadenas pesada y ligera y no las secuencias completas de las cadenas pesadas y ligeras.

Se agregó nueva reivindicación 5 que corresponde a la limitación de la reivindicación 1 (iii). También se agregó la nueva reivindicación 6 que está dirigida a una combinación farmacéutica de acuerdo con la reivindicación 5, en donde dicho anticuerpo consiste de una cadena ligera que comprende una secuencia de aminoácidos de SEQ ID Nos: 62 y una cadena pesada que comprende una secuencia de aminoácidos de SEQ ID NO: 66. El soporte para dicha reivindicación se encuentra en la página 6, líneas 8 a 23 de la descripción. Nuevas reivindicaciones 7 y 8 que han sido agregadas están basadas en la página 8, líneas 14 a 18 de la descripción. Las reivindicaciones originales 6 a 10 fueron eliminadas, por lo que se ve superada la objeción a reivindicaciones relativas a un uso.

Con respecto a las objeciones de claridad del Examinador, se establece que la nueva reivindicación 1 ha sido modificada para definir que el anticuerpo anti-CD38 comprende regiones determinantes CDRs y sus secuencias específicas, de tal manera que ahora las reivindicaciones definen los anticuerpos en términos de sus características esenciales estructurales y de acuerdo con lo que se encuentra debidamente soportado en la solicitud.

Teniendo en cuenta las modificaciones realizadas al capítulo reivindicatorio y los argumentos presentados, todas las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, debido a que se han superado las objeciones formuladas por su Despacho y que se cumple con los requisitos del artículo 30 de la Decisión 486, se solicita amablemente aceptar este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

3.2 Argumentos a favor de la unidad de invención de la presente solicitud

El Examinador considera que los anticuerpos de las reivindicaciones originales 4 y 5 se refieren a dos conceptos inventivos y que por ende las reivindicaciones no cumplen con el requisito de unidad de invención. Respetuosamente manifestamos nuestro desacuerdo con el Examinador, ya que dichas reivindicaciones si comparten un concepto inventivo común.

El concepto inventivo común que comparten las reivindicaciones es una combinación que comprende un anticuerpo anti-CD38 y vincristina, en donde el anticuerpo es capaz de matar una célula CD38⁺ por apoptosis, ADCC y CDC. Como se demostrará a continuación, este concepto sí es inventivo en vista del estado de la técnica y por ende las reivindicaciones sí comparten un mismo concepto inventivo y cumplen con el requisito de unidad de invención.

3.3 Argumentos a favor del nivel inventivo de la presente solicitud

El artículo 18 de la Decisión 486 señala lo siguiente:

“Artículo 18.- Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.”

Consecuentemente, una invención se considerará inventiva si la misma no hubiese resultado obvia a partir del arte previo, para una persona del oficio normalmente versada en la materia. Esto a su vez implica que el Examinador a cargo de esta evaluación debe colocarse en el momento exacto en el que el inventor buscaba resolver el problema técnico contemplado en la solicitud y para el cual poseía la literatura y el conocimiento disponibles en dicho momento.

Siguiendo entonces los lineamientos de la Jurisprudencia aplicable al análisis del nivel inventivo de una solicitud de patente, se considera que una anterioridad o una combinación de dos anterioridades puede afectar dicho requerimiento de patentabilidad, si una persona medianamente versada en la materia encuentra enseñanzas o sugerencias claras que, a partir de un conocimiento medio en dicho campo, le permitan llegar de manera obvia a la invención reivindicada. Adicionalmente se considera que una mejora sustancial, un efecto inesperado o una ventaja con respecto al arte previo es un indicio de nivel inventivo, por cuanto aporta un salto tecnológico en la regla técnica.

A este respecto, respetuosamente manifestamos nuestro desacuerdo con el análisis llevado a cabo por el Examinador y con las conclusiones del mismo y solicitamos

atentamente la reconsideración de las razones por las cuales se objeta el nivel inventivo, con base en la siguiente información:

El Examinador considera que la presente solicitud no tiene nivel inventivo en vista de los documentos D1 y D2, los cuales divulgan una composición farmacéutica que comprende un agente de unión anti-CD38 con vincristina.

El Examinador considera que la única diferencia entre la invención y D1 y/o D2 es que la invención se refiere a la combinación específica con vincristina, y que el efecto técnico asociado con esta diferencia es una mayor inhibición del crecimiento tumoral.

De esta manera, el Examinador establece que el problema técnico es “como modificar la composición terapéutica conocida en D1 o D2 para lograr mayor inhibición tumoral”. Luego considera que sería obvio para la persona versada en la materia modificar dichas composiciones para llegar a la combinación reivindicada. Respetuosamente manifestamos nuestro desacuerdo.

El documento D1 da a conocer inmuno-conjugados que comprenden anticuerpos anti-CD38 de acuerdo con la presente invención y vincristina. Por consiguiente, consideramos que el documento D1 representa el estado de la técnica más cercano a la invención como se encuentra actualmente reclamada.

Las presentes reivindicaciones se refieren a una combinación farmacéutica que comprende un anticuerpo que reconoce específicamente CD38 y vincristina. Una combinación farmacéutica es una combinación de dos o más principios activos, administrados en conjunto o por separado.

El documento D1 no divulga una combinación farmacéutica que comprende un anticuerpo que específicamente reconoce CD38 y vincristina. D1 solo da a conocer conjugados de anticuerpos que comprenden un anticuerpo que reconoce específicamente CD38 y vincristina. Un conjugado de anticuerpo es una sola molécula que actúa como un único agente. Los conjugados actúan mediante el uso de la porción del anticuerpo para

CAVELIER

A B O G A D O S

apuntar como blanco la porción citotóxica hacia el sitio del tumor. En otras palabras, la porción del anticuerpo y la porción citotóxica actúan juntas para formar una sola molécula activa. El mecanismo de acción es específico para el conjugado, ni el anticuerpo ni el agente citotóxico actúan como el conjugado.

Por el contrario, el principio inventivo detrás de la presente invención se basa en el efecto combinado de los dos componentes individuales de la combinación reivindicada, cada uno ejerciendo un efecto anti-tumor que se ve aumentado por un efecto sinérgico en combinación.

Cabe señalar que las agencias reguladoras como la FDA y la EMEA distingue entre combinaciones (tanto combinaciones de "dosis fija" como "producto de combinaciones", utilizando la nomenclatura de FDA) y conjugados. Los dos no son considerados equivalentes y requieren autorizaciones separadas, incluso si comprenden los mismos agentes.

Un ejemplo real de tal producto de combinación se da en el sitio web de la FDA como el régimen BEXXAR, el cual combina la administración de Tositumomab y Iodine I 131 Tositumomab (véase el documento adjunto, disponible en línea en http://www.accessdata.fda.gov/drugsatfda_docs/label/2003/tosicor062703LB.pdf).

Tositumomab es un anticuerpo monoclonal que se une al antígeno CD20 del tumor. Iodine I 131 Tositumomab es un derivado de Tositumomab que ha sido covalentemente unido a Iodine-131, un isótopo radiactivo de yodo. Los mecanismos de acción del régimen BEXXAR son descritos como incluyendo la inducción de apoptosis, CDC y ADCC por el anticuerpo y la muerte celular asociada con la radiación ionizante del isótopo (ver página 5 del PDF adjunto).

Los anticuerpos monoclonales marcados y no marcados se consideran partes constituyentes por separado del producto de combinación. Notablemente, sin embargo, Iodine I 131 Tositumomab como tal, aunque comprende un anticuerpo conjugado a un isótopo radioactivo, cada uno de estos el cual contribuye al efecto

terapéutico a través de diferentes mecanismos, es considerado un constituyente singular en lugar de una 'combinación' de dos constituyentes activos.

Por lo tanto, es evidente que la FDA no considera un anticuerpo conjugado a un agente citotóxico para representar una "combinación". Del mismo modo, una persona versada en la materia correspondiente no consideraría un conjugado o una proteína de fusión como una "combinación farmacéutica" de ingredientes activos, sino como un solo ingrediente activo.

De esta manera, el documento D1 no sugiere la combinación específica de anticuerpos anti-CD38 y vincristina en donde los compuestos individuales están físicamente separados.

El documento D1 ni siquiera revela la realización de un conjugado que comprende un anticuerpo anti-CD38 y vincristina. D1 describe desde la página 31 a 63 una lista de clases de agentes quimioterapéuticos que podrían, en teoría, estar vinculados a un anticuerpo anti-CD38. La vincristina es sólo uno de los numerosos ejemplos de los agentes quimioterapéuticos citados.

Además, el uso de conjugados anticuerpo-fármaco se divulga exclusivamente en el contexto de conjugados que comprenden un agente citotóxico (ej. vincristina) y un agente de unión a CD38 (ej. anticuerpo) que dirige el fármaco al tumor. Ver D1, párrafos 0127-0130:

"La presente invención también incluye conjugados citotóxicos. Estos conjugados citotóxicos comprenden dos componentes principales, un agente de unión celular y un agente citotóxico... el agente de unión celular reconoce específicamente la proteína CD38 para que los conjugados estén en contacto con la célula blanco por un período de tiempo suficiente para permitir que la porción del fármaco citotóxica del conjugado para actuar en la célula, y/o...sea internalizada por la célula..."

CAVELIER

A B O G A D O S

“... El anticuerpo 38SB19 es capaz de específicamente reconocer CD38, y dirige el agente citotóxico a una célula anormal o un tejido, tales como las células cancerosas, en una manera dirigida”

En vista de lo anterior, la persona versada en la materia no hubiera estado motivada a hacer una combinación farmacéutica que comprende un anticuerpo anti-CD38 y vincristina. La completa divulgación de D1 describe que el anticuerpo anti-CD38 funciona para dirigir la porción del fármaco al sitio del tumor (ver más arriba). Claramente, el anticuerpo anti-CD38 no podría servir a este propósito en un combinación farmacéutica de un anticuerpo anti-CD38 y vincristina, en la que vincristina no está vinculada al anticuerpo.

Por otro lado, observamos en primer lugar que los pasajes del documento D2 a los que se refiere el Examinador no parecen corresponder con la divulgación descrita por él. En particular, la referencia a la página 176 parece ser errónea, ya que la publicación PCT de D2 tiene sólo 56 páginas, incluyendo las figuras.

El documento D2 se refiere a proteínas de fusión que comprenden al menos una porción de un agente de unión a CD38, tales como un anticuerpo anti-CD38, y una molécula de unión a ADN.

Las únicas combinaciones descritas en el documento D2 son composiciones terapéuticas que comprenden dichas proteínas de fusión y una molécula de ADN que codifica un agente citotóxico (ver página 3, líneas 22-24).

El documento D2 no divulga una composición terapéutica que comprende vincristina, aunque vincristina está enumerado en la descripción como un agente citotóxico (ver página 10, línea 2). Las composiciones terapéuticas divulgadas en D2 no contienen vincristina, porque (i) las composiciones contienen sólo una molécula de ADN que codifica un agente citotóxico, y no el agente citotóxico como tal, y (ii) una molécula de ADN no puede codificar vincristina, que no es una proteína o aminoácido. La vincristina es un alcaloide de la vinca. Por lo tanto, no puede ser codificado por un ácido nucleico. De

esta forma, el documento D2 no es relevante como antecedente para el nivel inventivo de las presentes reivindicaciones.

Efecto sinérgico

La diferencia técnica entre la presente invención y el estado de la técnica más cercano (D1) es que el documento D1 se refiere a un inmuno-conjugado, en donde un anticuerpo anti-CD38 está vinculado junto con un compuesto citotóxico, mientras que la presente invención se refiere a una combinación farmacéutica, en donde los compuestos individuales están físicamente separados.

El efecto técnico asociado con la combinación específica de la presente invención es un sorprendente efecto sinérgico. No hay ninguna divulgación de algún efecto sinérgico en el documento D1. Ni siquiera hay alguna sugerencia en D1 de que vincristina sería un agente particularmente adecuado o efectivo para ser utilizado en conjugación con anti-CD38 debido a algún efecto sinérgico entre dichos agentes.

Sostenemos que las reivindicaciones son inventivas en vista del documento D1, porque la combinación de un anticuerpo anti-CD38 y vincristina tiene efectos sorprendentes y beneficiosos que no son predecibles a partir del estado de la técnica, específicamente, el efecto sinérgico observado entre anti-CD38 y vincristina.

El Examinador afirma que "no se encuentra evidencia que demuestre que la combinación [de anti-CD38 y vincristina] produzca un efecto sinérgico y que demuestre que no es un efecto meramente aditivo" y por lo tanto considera que la combinación es obvia.

No es el caso de que no haya evidencia que demuestre que la combinación produce un efecto sinérgico. Los Ejemplos divulgados en la descripción demuestran un claro efecto sinérgico para la combinación.

La Tabla I y la descripción en la página 11, líneas 5 a 14 describen que el anti-CD38 (hu38SB19) sólo retrasó el crecimiento del tumor por sólo 6.1 días en ratones implantados con células-T humanas avanzadas de leucemia linfoblástica aguda DND-41 (columna 6). El número de sobrevivientes libres de tumores al final del experimento (columna 8) fue 0.

Del mismo modo, el número de sobrevivientes libres de tumores tratados con sólo vincristina fue 0 al final del experimento, incluso a la dosis más alta tolerada.

Por el contrario, cuando el anti-CD38 (hu38SB19) y vincristina se combinaron, la tasa de supervivencia libre de tumores fue más del 80%. Casi todos los animales tratados (5 de 6) sobrevivieron libres de tumor al final del experimento. Este fue el caso utilizando una dosis de vincristina menos de la dosis máxima tolerada: 5 de 6 animales sobrevivieron cuando vincristina se dosificó a 0.5 mg/kg/inyección, la misma tasa observada con la dosis más alta no tóxica (0.8 mg/kg/inyección) en la combinación.

Esto es una mejora dramática y mucho mayor que la que se observaría por solo efectos aditivos.

Por lo tanto, se puede observar a partir de estos resultados que anti-CD38 y vincristina pueden actuar sinérgicamente para disminuir el crecimiento del tumor, dando mucho mejores resultados en combinación, que lo que se esperaría de los resultados obtenidos con cualquiera de los agentes por separado. Por ende, la combinación representa una mejora sustancial sobre los efectos exhibidos por los compuestos solos, y por lo tanto es inventiva. Adicionalmente, como se demostró anteriormente la presente invención no es obvia a partir de los documentos D1 y D2, es decir, la persona versada en la materia no hubiera encontrado en los documento D1 y/o D2 alguna motivación para lograr la combinación farmacéutica que se reclama en la presente solicitud.

3.4 Conclusiones

De acuerdo a todos los argumentos presentados, la presente solicitud cumple a cabalidad con los requerimientos exigidos en la Decisión 486 y las objeciones formuladas por el Examinador se ven superadas. Con respecto al nivel inventivo, consideramos que el Examinador está excluyendo el hecho de que el inventor en el momento de solucionar el problema técnico de la solicitud tuvo que emplear habilidad inventiva, pues la presente invención no resulta de la mera extrapolación de las enseñanzas del arte previo, como se afirma. Se está desconociendo el mérito investigativo empleado y que está aportando una ventaja al arte previo.

4. Puesto que se ha dado respuesta a todas las objeciones formuladas por el Examinador, se solicita atentamente proceder al otorgamiento de la solicitud de patente. En este sentido, respetuosamente recordamos al Examinador que la patente no podrá ser negada con base en objeciones diferentes a las expuestas en la acción oficial No. 22873, toda vez que al no haber sido trasladadas a mi representada, dicha decisión violaría tanto el tenor literal del artículo 45 de la Decisión 486 como el derecho constitucional al debido proceso. En este evento, y con base en el inciso 2 del artículo 45, respetuosamente solicitamos al Examinador expedir una nueva acción oficial que permita a mi representada contra argumentar las mismas o modificar la solicitud con el fin de cumplir los requisitos de patentabilidad.

Respetuosamente manifiesto que a pesar de eliminar materia del pliego reivindicatorio originalmente presentado, mi representada no renuncia a la protección que pueda obtener sobre dicha materia y se reserva el derecho de presentar una solicitud divisional que la contenga durante el trámite de la presente solicitud, beneficiándose de la fecha de prioridad inicialmente reivindicada.

5. Anexos

- Nuevo pliego reivindicatorio conformado por 8 reivindicaciones.
- Copia del régimen BEXXAR.

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

COLO-00751-0841-003-5
FBJ\FBJ\ID-261777\WPCL0751
No. M-2014-261777\FBJ

REIVINDICACIONES

1. Una combinación farmacéutica que comprende un anticuerpo que reconoce específicamente CD38 y al menos vincristina, en donde dicho anticuerpo puede destruir una célula CD38⁺ por apoptosis, citotoxicidad mediada por células dependientes de anticuerpos (ADCC) y citotoxicidad dependiente del complemento (CDC), y en donde dicho anticuerpo comprende al menos una cadena pesada y al menos una cadena ligera, en donde

(i) dicha cadena pesada comprende tres regiones determinantes de complementariedad secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 1, 2, y 3, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 4, 5 y 6;

(ii) dicha cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 7, 8, y 9, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 10, 11 y 12;

(iii) dicha cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 13, 15 y posiciones 50 a 66 de SEQ ID NO: 66, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 16, 17 y 18;

(iv) dicha cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 19, 20, y 21, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 22, 23 y 24;

(v) dicha cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 25, 26, y 27, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 28, 29 y 30; o

(vi) dicha cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 31, 32, y 33, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 34, 35 y 36.

2. La combinación de la reivindicación 1, en donde dicho anticuerpo es un anticuerpo humanizado o quimérico.

3. La combinación de la reivindicación 1 o 2, en donde dicha cadena pesada comprende una secuencia de aminoácidos, representada por la SEQ ID NO: 66, y en donde dicha cadena ligera comprende una secuencia de aminoácidos seleccionada del grupo de SEQ ID NOS: 62 y 64.

4. La combinación de la reivindicación 1 o 2, en donde dicha cadena pesada comprende una secuencia de aminoácidos, representada por la SEQ ID NO: 72, y en donde dicha cadena ligera comprende una secuencia de aminoácidos seleccionada del grupo de SEQ ID NOS: 68 y 70.

5. Una combinación farmacéutica que comprende un anticuerpo que reconoce específicamente CD38 y al menos vincristina, en donde dicho anticuerpo puede destruir una célula CD38⁺ por apoptosis, citotoxicidad mediada por células dependientes de anticuerpos (ADCC) y citotoxicidad dependiente del complemento (CDC), y en donde dicho anticuerpo es un anticuerpo humanizado que comprende al menos una cadena pesada y al menos una cadena ligera, en donde la cadena pesada comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representadas por SEQ ID Nos: 13, 15, y posiciones 50 a 66 de SEQ ID NO: 66, y en donde dicha cadena ligera comprende tres CDRs secuenciales que tienen secuencias de aminoácidos representados por SEQ ID Nos: 16, 17 y 18.

6. Una combinación farmacéutica de la reivindicación 5, que comprende un anticuerpo que reconoce específicamente CD38 y al menos vincristina, en donde dicho anticuerpo consiste de:

- una cadena ligera que comprende una secuencia de aminoácido de SEQ ID NO: 62; y

- una cadena pesada que comprende una secuencia de aminoácido de SEQ ID NO: 66.

7. Una combinación farmacéutica de acuerdo con la reivindicación 5, en donde anticuerpo que reconoce específicamente CD38 y vincristina son administrados simultáneamente.

8. Una combinación farmacéutica de acuerdo con la reivindicación 5, en donde anticuerpo que reconoce específicamente CD38 y vincristina son administrados por separado.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28

Rx Only

BEXXAR®

Tositumomab and Iodine I 131 Tositumomab

WARNINGS

Hypersensitivity Reactions, including Anaphylaxis: Medications for the treatment of severe hypersensitivity reactions should be available for immediate use. Patients who develop severe hypersensitivity reactions should have infusions of the BEXXAR therapeutic regimen discontinued and receive medical attention (See **WARNINGS**).

Prolonged and Severe Cytopenias: The majority of patients who received the BEXXAR therapeutic regimen experienced severe thrombocytopenia and neutropenia. The BEXXAR therapeutic regimen should not be administered to patients with >25% lymphoma marrow involvement and/or impaired bone marrow reserve (See **WARNINGS** and **ADVERSE REACTIONS**).

Pregnancy Category X: The BEXXAR therapeutic regimen can cause fetal harm when administered to a pregnant woman.

Special requirements: The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) contains a radioactive component and should be administered only by physicians and other health care professionals qualified by training in the safe use and handling of therapeutic radionuclides. The BEXXAR therapeutic regimen should be administered only by physicians who are in the process of being or have been certified by Corixa Corporation in dose calculation and administration of the BEXXAR therapeutic regimen.

DESCRIPTION

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is an anti-neoplastic radioimmunotherapeutic monoclonal

29 antibody-based regimen composed of the monoclonal antibody,
30 Tositumomab, and the radiolabeled monoclonal antibody, Iodine I 131
31 Tositumomab.

32 **Tositumomab**

33 Tositumomab is a murine IgG_{2a} lambda monoclonal antibody directed
34 against the CD20 antigen, which is found on the surface of normal and
35 malignant B lymphocytes. Tositumomab is produced in an antibiotic-free
36 culture of mammalian cells and is composed of two murine gamma 2a
37 heavy chains of 451 amino acids each and two lambda light chains of 220
38 amino acids each. The approximate molecular weight of Tositumomab is
39 150 kD.

40 Tositumomab is supplied as a sterile, pyrogen-free, clear to opalescent,
41 colorless to slightly yellow, preservative-free liquid concentrate. It is
42 supplied at a nominal concentration of 14 mg/mL Tositumomab in 35 mg
43 and 225 mg single-use vials. The formulation contains 10% (w/v) maltose,
44 145 mM sodium chloride, 10 mM phosphate, and Water for Injection, USP.
45 The pH is approximately 7.2.

46 **Iodine I 131 Tositumomab**

47 Iodine I 131 Tositumomab is a radio-iodinated derivative of Tositumomab
48 that has been covalently linked to Iodine-131. Unbound radio-iodine and
49 other reactants have been removed by chromatographic purification steps.
50 Iodine I 131 Tositumomab is supplied as a sterile, clear, preservative-free
51 liquid for IV administration. The dosimetric dosage form is supplied at
52 nominal protein and activity concentrations of 0.1 mg/mL and 0.61 mCi/mL
53 (at date of calibration), respectively. The therapeutic dosage form is
54 supplied at nominal protein and activity concentrations of 1.1 mg/mL and
55 5.6 mCi/mL (at date of calibration), respectively. The formulation for the
56 dosimetric and the therapeutic dosage forms contains 5.0%–6.0% (w/v)
57 povidone, 1–2 mg/mL maltose (dosimetric dose) or 9–15 mg/mL maltose
58 (therapeutic dose), 0.85–0.95 mg/mL sodium chloride, and 0.9–1.3 mg/mL
59 ascorbic acid. The pH is approximately 7.0.

60

BEXXAR Therapeutic Regimen

The BEXXAR therapeutic regimen is administered in two discrete steps: the dosimetric and therapeutic steps. Each step consists of a sequential infusion of Tositumomab followed by Iodine I 131 Tositumomab. The therapeutic step is administered 7-14 days after the dosimetric step. The Bexxar therapeutic regimen is supplied in two distinct package configurations as follows:

BEXXAR Dosimetric Packaging

- A carton containing two single-use 225 mg vials and one single-use 35 mg vial of Tositumomab supplied by McKesson Biosciences and
- A package containing a single-use vial of Iodine I 131 Tositumomab (0.61mCi/mL at calibration), supplied by MDS Nordion.

BEXXAR Therapeutic Packaging

- A carton containing two single-use 225 mg vials and one single-use 35 mg vial of Tositumomab, supplied by McKesson Biosciences and
- A package containing one or two single-use vials of Iodine I 131 Tositumomab (5.6 mCi/mL at calibration), supplied by MDS Nordion.

Physical/Radiochemical Characteristics of Iodine-131

Iodine-131 decays with beta and gamma emissions with a physical half-life of 8.04 days. The principal beta emission has a mean energy of 191.6 keV and the principal gamma emission has an energy of 364.5 keV (Ref 1).

External Radiation: The specific gamma ray constant for Iodine-131 is 2.2 R/millicurie hour at 1 cm. The first half-value layer is 0.24 cm lead (Pb) shielding. A range of values is shown in Table 1 for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of Pb. To facilitate control of the

91 radiation exposure from this radionuclide, the use of a 2.55 cm thickness of
 92 Pb will attenuate the radiation emitted by a factor of about 1,000.

93

94

95

Table 1
Radiation Attenuation by Lead Shielding

Shield Thickness (Pb) cm	Attenuation Factor
0.24	0.5
0.89	10 ⁻¹
1.60	10 ⁻²
2.55	10 ⁻³
3.7	10 ⁻⁴

96

97 The fraction of Iodine-131 radioactivity that remains in the vial after the
 98 date of calibration is calculated as follows:

99 Fraction of remaining radioactivity of Iodine-131 after x days =2^{-(x/8.04)}.

100 Physical decay is presented in Table 2.

101

102
103

Table 2
Physical Decay Chart: Iodine-131: Half-Life 8.04 Days

Days	Fraction Remaining
0*	1.000
1	0.917
2	0.842
3	0.772
4	0.708
5	0.650
6	0.596
7	0.547
8	0.502
9	0.460
10	0.422
11	0.387
12	0.355
13	0.326
14	0.299

104

*(Calibration day)

105

CLINICAL PHARMACOLOGY

106

General Pharmacology

107

Tositumomab binds specifically to the CD20 (human B-lymphocyte–restricted differentiation antigen, Bp 35 or B1) antigen. This antigen is a transmembrane phosphoprotein expressed on pre-B lymphocytes and at higher density on mature B lymphocytes (Ref. 2). The antigen is also expressed on >90% of B-cell non-Hodgkin’s lymphomas (NHL) (Ref. 3). The recognition epitope for Tositumomab is found within the extracellular domain of the CD20 antigen. CD20 does not shed from the cell surface and does not internalize following antibody binding (Ref. 4).

108

109

110

111

112

113

114

115

Mechanism of Action: Possible mechanisms of action of the BEXXAR therapeutic regimen include induction of apoptosis (Ref. 5), complement-dependent cytotoxicity (CDC) (Ref. 6), and antibody-dependent cellular cytotoxicity (ADCC) (Ref. 5) mediated by the antibody. Additionally, cell death is associated with ionizing radiation from the radioisotope.

116

117

118

119

120

121 **Pharmacokinetics/Pharmacodynamics**

122 The phase 1 study of Iodine I 131 Tositumomab determined that a 475 mg
 123 predose of unlabeled antibody decreased splenic targeting and increased
 124 the terminal half-life of the radiolabeled antibody. The median blood
 125 clearance following administration of 485 mg of Tositumomab in
 126 110 patients with NHL was 68.2 mg/hr (range: 30.2–260.8 mg/hr).
 127 Patients with high tumor burden, splenomegaly, or bone marrow
 128 involvement were noted to have a faster clearance, shorter terminal half-
 129 life, and larger volume of distribution. The total body clearance, as
 130 measured by total body gamma camera counts, was dependent on the
 131 same factors noted for blood clearance. Patient-specific dosing, based on
 132 total body clearance, provided a consistent radiation dose, despite
 133 variable pharmacokinetics, by allowing each patient's administered activity
 134 to be adjusted for individual patient variables.

135 Elimination of Iodine-131 occurs by decay (see Table 2) and excretion in
 136 the urine. Urine was collected for 49 dosimetric doses. After 5 days, the
 137 whole body clearance was 67% of the injected dose. Ninety-eight percent
 138 of the clearance was accounted for in the urine.

139 Administration of the BEXXAR therapeutic regimen results in sustained
 140 depletion of circulating CD20 positive cells. The impact of administration
 141 of the BEXXAR therapeutic regimen on circulating CD20 positive cells was
 142 assessed in two clinical studies, one conducted in chemotherapy naïve
 143 patients and one in heavily pretreated patients. The assessment of
 144 circulating lymphocytes did not distinguish normal from malignant cells.
 145 Consequently, assessment of recovery of normal B cell function was not
 146 directly assessed. At seven weeks, the median number of circulating
 147 CD20 positive cells was zero (range: 0 - 490 cells/ mm³). Lymphocyte
 148 recovery began at approximately 12 weeks following treatment. Among
 149 patients who had CD20 positive cell counts recorded at baseline and at 6
 150 months, 8 of 58 (14%) chemotherapy naïve patients had CD20 positive
 151 cell counts below normal limits at six months and 6 of 19 (32%) heavily
 152 pretreated patients had CD20 positive cell counts below normal limits at
 153 six months. There was no consistent effect of the BEXXAR therapeutic
 154 regimen on post-treatment serum IgG, IgA, or IgM levels.

155
156
157

158
159
160
161
162
163

164

Radiation Dosimetry

Estimations of radiation-absorbed doses for Iodine I 131 Tositumomab were performed using sequential whole body images and the MIRDose 3 software program. Patients with apparent thyroid, stomach, or intestinal imaging were selected for organ dosimetry analyses. The estimated radiation-absorbed doses to organs and marrow from a course of the BEXXAR therapeutic regimen are presented in Table 3.

164
165
166

Table 3
Estimated Radiation-Absorbed Organ Doses

		BEXXAR mGy/MBq	BEXXAR mGy/MBq
From Organ ROIs		Median	Range
	Thyroid	2.71	1.4 - 6.2
	Kidneys	1.96	1.5 - 2.5
	ULI Wall	1.34	0.8 - 1.7
	LLI Wall	1.30	0.8 - 1.6
	Heart Wall	1.25	0.5 - 1.8
	Spleen	1.14	0.7 - 5.4
	Testes	0.83	0.3 - 1.3
	Liver	0.82	0.6 - 1.3
	Lungs	0.79	0.5 - 1.1
	Red Marrow	0.65	0.5 - 1.1
	Stomach Wall	0.40	0.2 - 0.8
From Whole Body ROIs			
	Urine Bladder Wall	0.64	0.6 - 0.9
	Bone Surfaces	0.41	0.4 - 0.6
	Pancreas	0.31	0.2 - 0.4
	Gall Bladder Wall	0.29	0.2 - 0.3
	Adrenals	0.28	0.2 - 0.3
	Ovaries	0.25	0.2 - 0.3
	Small Intestine	0.23	0.2 - 0.3
	Thymus	0.22	0.1 - 0.3
	Uterus	0.20	0.2 - 0.2
	Muscle	0.18	0.1 - 0.2
	Breasts	0.16	0.1 - 0.2
	Skin	0.13	0.1 - 0.2
	Brain	0.13	0.1 - 0.2
	Total Body	0.24	0.2 - 0.3

167

168

CLINICAL STUDIES

169

170

171

172

173

174

175

176

177

178

179

180

181

The efficacy of the BEXXAR therapeutic regimen was evaluated in a multi-center, single-arm study in patients with low grade or transformed low-grade or follicular large-cell lymphoma whose disease had not responded to or had progressed after Rituximab therapy. Determination of clinical benefit of the BEXXAR therapeutic regimen was based on evidence of durable responses without evidence of an effect on survival. All patients in the study were required to have received prior treatment with at least four doses of Rituximab without an objective response, or to have progressed following treatment. Patients were also required to have a platelet count $\geq 100,000/\text{mm}^3$; an average of $\leq 25\%$ of the intratrabecular marrow space involved by lymphoma, and no evidence of progressive disease arising in a field irradiated with >3500 cGy within 1 year of completion of irradiation.

182

183

184

185

186

187

188

189

190

191

192

193

194

195

196

Forty patients initiated treatment with the BEXXAR therapeutic regimen. The median age was 57 (range: 35–78); the median time from diagnosis to protocol entry was 50 months (range: 11–70); and the median number of prior chemotherapy regimens was 4 (range: 1–11). Twenty-four patients had disease that did not respond to their last treatment with Rituximab, 11 patients had disease that responded to Rituximab for less than 6 months, and five patients had disease that responded to Rituximab, with a duration of response of 6 months or greater. Overall, 35 of the 40 patients met the definition of “Rituximab refractory”, defined as no response or a response of less than 6 months duration. Table 4 summarizes efficacy outcome data from this study, as determined by an independent panel that reviewed patient records and radiologic studies. The median duration of follow-up was 26 months for all patients and 26 months for the Rituximab-refractory subset.

196
197

Table 4
Efficacy Outcomes Patients

	Objective Responses to the BEXXAR Therapeutic Regimen in Patients Refractory to Rituximab		Objective Responses to the BEXXAR Therapeutic Regimen in All Patients	
	Response Rate (%) (95% CI ^a) (n=35)	Median duration of response (Mos) (Range)	Response Rate (%) (95% CI ^a) (n=40)	Median Duration of Response (Mos) (Range)
Overall Response	63% (45%, 79%)	25 (4+, 35+)	68% (51%, 81%)	16 (1+, 35+)
Complete Response ^c	29% (15%, 46%)	NR ^b (4, 35+)	33% (19%, 49%)	NR (4, 35+)
^a C.I. = Confidence Interval ^b NR = Not reached ^c Complete response rate = Pathologic and clinical complete responses				

198
199

The results of this study were supported by demonstration of durable objective responses in four single arm studies enrolling 190 patients evaluable for efficacy with Rituximab-naïve, follicular non-Hodgkin's lymphoma with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47% to 64% and the median durations of response ranged from 12 to 18 months.

207

INDICATIONS AND USAGE

The BEXXAR therapeutic regimen (Tositumomab and Iodine I 131 Tositumomab) is indicated for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy. The BEXXAR therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive non-Hodgkin's lymphoma.

The BEXXAR therapeutic regimen is intended as a single course of treatment. The safety of multiple courses of the BEXXAR therapeutic

218 regimen, or combination of this regimen with other forms of irradiation or
219 chemotherapy, has not been evaluated.

220

221 **CONTRAINDICATIONS**

222 The BEXXAR therapeutic regimen is contraindicated in patients with
223 known hypersensitivity to murine proteins or any other component of the
224 BEXXAR therapeutic regimen.

225 **PREGNANCY CATEGORY X**

226 Iodine I 131 Tositumomab (a component of the BEXXAR therapeutic
227 regimen) is contraindicated for use in women who are pregnant. Iodine-
228 131 may cause harm to the fetal thyroid gland when administered to
229 pregnant women. Review of the literature has shown that transplacental
230 passage of radioiodide may cause severe, and possibly irreversible,
231 hypothyroidism in neonates. While there are no adequate and well-
232 controlled studies of the BEXXAR therapeutic regimen in pregnant
233 animals or humans, use of the BEXXAR therapeutic regimen in women of
234 childbearing age should be deferred until the possibility of pregnancy has
235 been ruled out. If the patient becomes pregnant while being treated with
236 the BEXXAR therapeutic regimen, the patient should be apprised of the
237 potential hazard to the fetus. (See **BOXED WARNING, Pregnancy**
238 **Category X**).

239 **WARNINGS**

240 **Prolonged and Severe Cytopenias (See BOXED WARNINGS;**
241 **ADVERSE REACTIONS, Hematologic Events):**

242 The most common adverse reactions associated with the BEXXAR
243 therapeutic regimen were severe or life-threatening cytopenias (NCI CTC
244 grade 3 or 4) with 71% of the 230 patients enrolled in clinical studies
245 experiencing grade 3 or 4 cytopenias. These consisted primarily of grade
246 3 or 4 thrombocytopenia (53%) and grade 3 or 4 neutropenia (63%). The
247 time to nadir was 4 to 7 weeks and the duration of cytopenias was
248 approximately 30 days. Thrombocytopenia, neutropenia, and anemia
249 persisted for more than 90 days following administration of the BEXXAR

250 therapeutic regimen in 16 (7%), 15 (7%), and 12 (5%) patients
251 respectively (this includes patients with transient recovery followed by
252 recurrent cytopenia). Due to the variable nature in the onset of cytopenias,
253 complete blood counts should be obtained weekly for 10-12 weeks. The
254 sequelae of severe cytopenias were commonly observed in the clinical
255 studies and included infections (45% of patients), hemorrhage (12%), a
256 requirement for growth factors (12% G- or GM-CSF; 7% Epoetin alfa) and
257 blood product support (15% platelet transfusions; 16% red blood cell
258 transfusions). Prolonged cytopenias may also influence subsequent
259 treatment decisions.

260 The safety of the BEXXAR therapeutic regimen has not been established
261 in patients with >25% lymphoma marrow involvement, platelet count
262 <100,000 cells/mm³ or neutrophil count <1,500 cells/mm³.

263 **Hypersensitivity Reactions Including Anaphylaxis (See BOXED**
264 **WARNINGS; ADVERSE REACTIONS, Immunogenicity):**
265 Hypersensitivity reactions, including anaphylaxis, were reported during
266 and following administration of the BEXXAR therapeutic regimen.
267 Emergency supplies including medications for the treatment of
268 hypersensitivity reactions, e.g., epinephrine, antihistamines and
269 corticosteroids, should be available for immediate use in the event of an
270 allergic reaction during administration of the BEXXAR therapeutic
271 regimen. Patients who have received murine proteins should be screened
272 for human anti-mouse antibodies (HAMA). Patients who are positive for
273 HAMA may be at increased risk of anaphylaxis and serious
274 hypersensitivity reactions during administration of the BEXXAR
275 therapeutic regimen.

276 **Secondary Malignancies:** Myelodysplastic syndrome (MDS) and/or
277 acute leukemia were reported in 8% (19/230) of patients enrolled in the
278 clinical studies and 2% (13/765) of patients included in expanded access
279 programs, with median follow-up of 35 and 20 months, respectively.
280 Among the 32 reported new cases, the median time to development of
281 MDS/leukemia was 27 months following treatment; however, the
282 cumulative rate continues to increase. The pretreatment characteristics
283 (e.g., median age, number of prior chemotherapy regimens) were similar

284 in patients developing MDS/secondary leukemias as compared with those
285 who did not. Additional malignancies were also reported in 52 of the 995
286 patients enrolled in clinical studies or included in the expanded access
287 program. Approximately half of these were non-melanomatous skin
288 cancers. The remainder which occurred in 2 or more patients included
289 breast cancer, lung cancer, bladder cancer, head and neck cancer, colon
290 cancer and melanoma, in order of decreasing incidence. The relative risk
291 of developing secondary malignancies in patients receiving the BEXXAR
292 therapeutic regimen over the background rate in this population cannot be
293 determined, due to the absence of controlled studies (See **ADVERSE**
294 **REACTIONS**).

295 **Pregnancy Category X:** (See **BOXED WARNINGS**;
296 **CONTRAINDICATIONS**).

297 **Hypothyroidism:** Administration of the BEXXAR therapeutic regimen
298 may result in hypothyroidism (See **ADVERSE REACTIONS**,
299 **Hypothyroidism**). Thyroid-blocking medications should be initiated at
300 least 24 hours before receiving the dosimetric dose and continued until
301 14 days after the therapeutic dose (see **DOSAGE and**
302 **ADMINISTRATION**). All patients must receive thyroid blocking agents;
303 any patient who is unable to tolerate thyroid blocking agents should not
304 receive the BEXXAR therapeutic regimen. Patients should be evaluated
305 for signs and symptoms of hypothyroidism and screened for biochemical
306 evidence of hypothyroidism annually.

307

308 **PRECAUTIONS**

309 **Radionuclide Precautions:** Iodine I 131 Tositumomab is radioactive.
310 Care should be taken, consistent with the institutional radiation safety
311 practices and applicable federal guidelines, to minimize exposure of
312 medical personnel and other patients.

313 **Renal Function:** Iodine I 131 Tositumomab and Iodine-131 are excreted
314 primarily by the kidneys. Impaired renal function may decrease the rate of
315 excretion of the radiolabeled iodine and increase patient exposure to the
316 radioactive component of the BEXXAR therapeutic regimen. There are no

317 data regarding the safety of administration of the BEXXAR therapeutic
318 regimen in patients with impaired renal function.

319 **Immunization:** The safety of immunization with live viral vaccines
320 following administration of the BEXXAR therapeutic regimen has not been
321 studied. The ability of patients who have received the BEXXAR
322 therapeutic regimen to generate a primary or anamnestic humoral
323 response to any vaccine has not been studied.

324 **Information for Patients:** Prior to administration of the BEXXAR
325 therapeutic regimen, patients should be advised that they will have a
326 radioactive material in their body for several days upon their release from
327 the hospital or clinic. After discharge, patients should be provided with
328 both oral and written instructions for minimizing exposure of family
329 members, friends and the general public. Patients should be given a copy
330 of the written instructions for use as a reference for the recommended
331 precautionary actions.

332 The pregnancy status of women of childbearing potential should be
333 assessed and these women should be advised of the potential risks to the
334 fetus (See **CONTRAINDICATIONS**). Women who are breastfeeding
335 should be instructed to discontinue breastfeeding and should be apprised
336 of the resultant potential harmful effects to the infant if these instructions
337 are not followed.

338 Patients should be advised of the potential risk of toxic effects on the male
339 and female gonads following the BEXXAR therapeutic regimen, and be
340 instructed to use effective contraceptive methods during treatment and for
341 12 months following the administration of the BEXXAR therapeutic
342 regimen.

343
344 Patients should be informed of the risks of hypothyroidism and be advised
345 of the importance of compliance with thyroid blocking agents and need for
346 life-long monitoring.

347
348 Patients should be informed of the possibility of developing a HAMA
349 immune response and that HAMA may affect the results of *in vitro* and

350 *in vivo* diagnostic tests as well as results of therapies that rely on murine
351 antibody technology.

352
353 Patients should be informed of the risks of cytopenias and symptoms
354 associated with cytopenia, the need for frequent monitoring for up to
355 12 weeks after treatment, and the potential for persistent cytopenias
356 beyond 12 weeks.

357
358 Patients should be informed that certain anti-neoplastic agents used in the
359 treatment of malignancy, e.g., alkylating agents, topoisomerase II
360 inhibitors, and ionizing radiation, have been associated with the
361 development of MDS, secondary leukemia and solid tumors. Patients
362 should be informed that MDS, secondary leukemia, and solid tumors have
363 also been observed in patients receiving the BEXXAR therapeutic
364 regimen.

365
366 **Laboratory Monitoring:** A complete blood count (CBC) with differential
367 and platelet count should be obtained prior to, and at least weekly
368 following administration of the BEXXAR therapeutic regimen. Weekly
369 monitoring of blood counts should continue for a minimum of 10 weeks or,
370 if persistent, until severe cytopenias have completely resolved. More
371 frequent monitoring is indicated in patients with evidence of moderate or
372 more severe cytopenias (see **BOXED WARNINGS** and **WARNINGS**).
373 Thyroid stimulating hormone (TSH) level should be monitored before
374 treatment and annually thereafter. Serum creatinine levels should be
375 measured immediately prior to administration of the BEXXAR therapeutic
376 regimen.

377 **Drug Interactions:** No formal drug interaction studies have been
378 performed. Due to the frequent occurrence of severe and prolonged
379 thrombocytopenia, the potential benefits of medications that interfere with
380 platelet function and/or anticoagulation should be weighed against the
381 potential increased risk of bleeding and hemorrhage.

382 **Drug/Laboratory Test Interactions:** Administration of the BEXXAR
383 therapeutic regimen may result in the development of human anti-murine

384 antibodies (HAMA). The presence of HAMA may affect the accuracy of the
385 results of *in vitro* and *in vivo* diagnostic tests and may affect the toxicity
386 profile and efficacy of therapeutic agents that rely on murine antibody
387 technology. Patients who are HAMA positive may be at increased risk for
388 serious allergic reactions and other side effects if they undergo *in vivo*
389 diagnostic testing or treatment with murine monoclonal antibodies.

390 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** No long-term
391 animal studies have been performed to establish the carcinogenic or
392 mutagenic potential of the BEXXAR therapeutic regimen or to determine
393 its effects on fertility in males or females. However, radiation is a potential
394 carcinogen and mutagen. Administration of the BEXXAR therapeutic
395 regimen results in delivery of a significant radiation dose to the testes.
396 The radiation dose to the ovaries has not been established. There have
397 been no studies to evaluate whether administration of the BEXXAR
398 therapeutic regimen causes hypogonadism, premature menopause,
399 azoospermia and/or mutagenic alterations to germ cells. There is a
400 potential risk that the BEXXAR therapeutic regimen may cause toxic
401 effects on the male and female gonads. Effective contraceptive methods
402 should be used during treatment and for 12 months following
403 administration of the BEXXAR therapeutic regimen.

404 **Pregnancy Category X: See CONTRAINDICATIONS; WARNINGS.**

405 **Nursing Mothers:** Radioiodine is excreted in breast milk and may reach
406 concentrations equal to or greater than maternal plasma concentrations.
407 Immunoglobulins are also known to be excreted in breast milk. The
408 absorption potential and potential for adverse effects of the monoclonal
409 antibody component (Tositumomab) in the infant are not known.
410 Therefore, formula feedings should be substituted for breast feedings
411 before starting treatment. Women should be advised to discontinue
412 nursing.

413 **Pediatric Use:** The safety and effectiveness of the BEXXAR therapeutic
414 regimen in children have not been established.

Geriatric Use: Clinical studies of the BEXXAR therapeutic regimen did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. In clinical studies, 230 patients received the BEXXAR therapeutic regimen at the recommended dose. Of these, 27% (61 patients) were age 65 or older and 4% (10 patients) were age 75 or older. Across all studies, the overall response rate was lower in patients age 65 and over (41% vs. 61%) and the duration of responses were shorter (10 months vs. 16 months), however these findings are primarily derived from 2 of the 5 studies. While the incidence of severe hematologic toxicity was lower, the duration of severe hematologic toxicity was longer in those age 65 or older as compared to patients less than 65 years of age. Due to the limited experience greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

The most serious adverse reactions observed in the clinical trials were severe and prolonged cytopenias and the sequelae of cytopenias which included infections (sepsis), and hemorrhage in thrombocytopenic patients, allergic reactions (bronchospasm and angioedema), secondary leukemia and myelodysplasia. (See BOXED WARNINGS and WARNINGS).

The most common adverse reactions occurring in the clinical trials included neutropenia, thromobocytopenia, and anemia that are both prolonged and severe. Less common but severe adverse reactions included pneumonia, pleural effusion and dehydration.

Data regarding adverse events were primarily obtained in 230 patients with non-Hodgkin's lymphoma enrolled in five clinical trials using the recommended dose and schedule. Patients had a median follow-up of 35 months and 79% of the patients were followed at least 12 months for survival and selected adverse events. Patients had a median of 3 prior chemotherapy regimens, a median age of 55 years, 60% male, 27% had transformation to a higher grade histology, 29% were intermediate grade and 2% high grade histology (IWF) and 68% had Ann Arbor stage IV

448 disease. Patients enrolled in these studies were not permitted to have
449 prior hematopoietic stem cell transplantation or irradiation to more than
450 25% of the red marrow. In the expanded access program, which included
451 765 patients, data regarding clinical serious adverse events and HAMA
452 and TSH levels were used to supplement the characterization of delayed
453 adverse events. (See **ADVERSE REACTIONS, Hypothyroidism,**
454 **Secondary Leukemia and Myelodysplastic Syndrome,**
455 **Immunogenicity.**)

456 Because clinical trials are conducted under widely varying conditions,
457 adverse reaction rates observed in the clinical trials of a drug cannot be
458 directly compared to rates in the clinical trials of another drug and may not
459 reflect the rates observed in practice. The adverse reaction information
460 from clinical trials does, however, provide a basis for identifying the
461 adverse events that appear to be related to drug use and for
462 approximating rates.

463 **Hematologic Events:** Hematologic toxicity was the most frequently
464 observed adverse event in clinical trials with the BEXXAR therapeutic
465 regimen (Table 6). Sixty-three (27%) of 230 patients received one or
466 more hematologic supportive care measures following the therapeutic
467 dose: 12% received G-CSF; 7% received Epoetin alfa; 15% received
468 platelet transfusions; and 16% received packed red blood cell
469 transfusions. Twenty-eight (12%) patients experienced hemorrhagic
470 events; the majority were mild to moderate.

471 **Infectious Events:** One hundred and four of the 230 (45%) patients
472 experienced one or more adverse events possibly related to infection.
473 The majority were viral (e.g. rhinitis, pharyngitis, flu symptoms, or herpes)
474 or other minor infections. Nineteen of 230 (8%) patients experienced
475 infections that were considered serious because the patient was
476 hospitalized to manage the infection. Documented infections included
477 pneumonia, bacteremia, septicemia, bronchitis, and skin infections.

478 **Hypersensitivity Reactions:** Fourteen patients (6%) experienced one or
479 more of the following adverse events: allergic reaction, face edema,

480 injection site hypersensitivity, anaphylactoid reaction, laryngismus, and
481 serum sickness.

482

483 **Gastrointestinal toxicity:** Eighty-seven patients (38%) experienced one
484 or more gastrointestinal adverse events, including nausea, emesis,
485 abdominal pain, and diarrhea. These events were temporally related to
486 the infusion of the antibody. Nausea, vomiting, and abdominal pain were
487 often reported within days of infusion, whereas diarrhea was generally
488 reported days to weeks after infusion.

489

490 **Infusional Toxicity:** A constellation of symptoms, including fever, rigors
491 or chills, sweating, hypotension, dyspnea, bronchospasm, and nausea,
492 have been reported during or within 48 hours of infusion. Sixty-seven
493 patients (29%) reported fever, rigors/chills, or sweating within 14 days
494 following the dosimetric dose. Although all patients in the clinical studies
495 received pretreatment with acetaminophen and an antihistamine, the
496 value of premedication in preventing infusion-related toxicity was not
497 evaluated in any of the clinical studies. Infusional toxicities were managed
498 by slowing and/or temporarily interrupting the infusion. Symptomatic
499 management was required in more severe cases. Adjustment of the rate
500 of infusion to control adverse reactions occurred in 16 patients (7%);
501 seven patients required adjustments for only the dosimetric infusion, two
502 required adjustments for only the therapeutic infusion, and seven required
503 adjustments for both the dosimetric and the therapeutic infusions.
504 Adjustments included reduction in the rate of infusion by 50%, temporary
505 interruption of the infusion, and in 2 patients, infusion was permanently
506 discontinued.

507 Table 5 lists clinical adverse events that occurred in $\geq 5\%$ of patients.
508 Table 6 provides a detailed description of the hematologic toxicity.

509
510
511
512
513

Table 5
Incidence of Clinical Adverse Experiences Regardless of Relationship to
Study Drug Occurring in ≥5% of the Patients Treated with BEXXAR
Therapeutic Regimen^a
(N = 230)

Body System Preferred Term	All Grades	Grade 3/4
Total	(96%)	(48%)
Non-Hematologic AEs		
Body as a Whole	81%	12%
Asthenia	46%	2%
Fever	37%	2%
Infection ^b	21%	<1%
Pain	19%	1%
Chills	18%	1%
Headache	16%	0%
Abdominal pain	15%	3%
Back pain	8%	1%
Chest pain	7%	0%
Neck pain	6%	1%
Cardiovascular System	26%	3%
Hypotension	7%	1%
Vasodilatation	5%	0%
Digestive System	56%	9%
Nausea	36%	3%
Vomiting	15%	1%
Anorexia	14%	0%
Diarrhea	12%	0%
Constipation	6%	1%
Dyspepsia	6%	<1%
Endocrine System	7%	0%
Hypothyroidism	7%	0%
Metabolic and Nutritional Disorders	21%	3%
Peripheral edema	9%	0%
Weight loss	6%	<1%
Musculoskeletal System	23%	3%
Myalgia	13%	<1%
Arthralgia	10%	1%
Nervous System	26%	3%
Dizziness	5%	0%
Somnolence	5%	0%

514

515

516

517

518

519

520

Table 5 (cont'd)
Incidence of Clinical Adverse Experiences Regardless of Relationship to
Study Drug Occurring in ≥5% of the Patients Treated with BEXXAR
Therapeutic Regimen^a
(N =230)

Respiratory System	44%	8%
Cough increased	21%	1%
Pharyngitis	12%	0%
Dyspnea	11%	3%
Rhinitis	10%	0%
Pneumonia	6%	0%
Skin and Appendages	44%	5%
Rash	17%	<1%
Pruritus	10%	0%
Sweating	8%	<1%
^a Excludes laboratory derived hematologic adverse events (See Table 6).		
^b The COSTART term for infection includes a subset of infections (e.g., upper respiratory infection). Other terms are mapped to preferred terms (e.g., pneumonia and sepsis). For a more inclusive summary see ADVERSE REACTIONS, Infectious Events.		

521

522

522
523
524

Table 6
Hematologic Toxicity^a (N=230)

Endpoint	Values
<u>Platelets</u>	
Median nadir (cells/mm ³)	43,000
Per patient incidence ^a platelets <50,000/mm ³	53% (n=123)
Median ^b duration of platelets <50,000/mm ³ (days)	32
Grade 3/4 without recovery to Grade 2, N (%)	16 (7%)
Per patient incidence ^c platelets <25,000/mm ³	21% (n=47)
<u>ANC</u>	
Median nadir (cells/mm ³)	690
Per patient incidence ^a ANC<1,000 cells/mm ³ (%)	63% (n=145)
Median ^b duration of ANC<1,000 cells/mm ³ (days)	31
Grade 3/4 without recovery to Grade 2, N (%)	15 (7%)
Per patient incidence ^c ANC< 500 cells/mm ³ , N (%)	25% (n=57)
<u>Hemoglobin</u>	
Median nadir (gm/dL)	10
Per patient incidence ^a < 8 gm/dL	29% (n=66)
Median ^b duration of hemoglobin < 8.0 gm/dL (days)	23
Grade 3/4 without recovery to Grade 2, N (%)	12 (5%)
Per patient incidence ^c hemoglobin <6.5 gm/dL, N (%)	5% (n=11)
^a Grade 3/4 toxicity was assumed if patient was missing 2 or more weeks of hematology data between Week 5 and Week 9.	
^b Duration of grade 3/4 of 1000+ days (censored) was assumed for those patients with undocumented grade 3/4 and no hematologic data on or after Week 9.	
^c Grade 4 toxicity was assumed if patient had documented Grade 3 toxicity and was missing 2 or more weeks of hematology data between Week 5 and Week 9.	

525
526
527

Delayed Adverse Reactions

528 Delayed adverse reactions, including hypothyroidism, HAMA, and
529 myelodysplasia/leukemia, were assessed in 230 patients included in
530 clinical studies and 765 patients included in expanded access programs.
531 The entry characteristics of patients included from the expanded access

532 programs were similar to the characteristics of patients enrolled in the
533 clinical studies, except that the median number of prior chemotherapy
534 regimens was fewer (2 vs. 3) and the proportion with low-grade histology
535 was higher (77% vs. 70%) in patients from the expanded access
536 programs.

537 **Secondary Leukemia and Myelodysplastic Syndrome (MDS):** There
538 were 32 new cases of MDS/secondary leukemia reported among 994
539 (3.2%) patients included in clinical studies and expanded access
540 programs, with a median follow-up of 21 months. The overall incidence of
541 MDS/secondary leukemia among the 229 patients included in the clinical
542 studies, was 8.3% (19/229), with a median follow-up of 35 months and a
543 median time to development of MDS of 30 months. The cumulative
544 incidence of MDS/secondary leukemia was 4.2% at 2 years and 10.7% at
545 4 years. Among the 765 patients included in the expanded access
546 program, where the median duration of follow-up was shorter (20 months),
547 the overall incidence of MDS/secondary leukemia was 1.7% (13/765) and
548 the median time to development of MDS was 23 months. In the expanded
549 access population, the cumulative incidence of MDS/secondary leukemia
550 was 1.4% at 2 years and 4.8% at 4 years.

551 **Secondary Malignancies:** There were 52 reports of second
552 malignancies, excluding secondary leukemias. The most common
553 included non-melanomatous skin cancers, breast, lung, bladder, and head
554 and neck cancers. Some of these events included recurrence of an earlier
555 diagnosis of cancer.

556 **Hypothyroidism:** Twelve percent (27/230) of the patients included from
557 the clinical studies had an elevated TSH level (8%) or no TSH level
558 obtained (4%) prior to treatment. Of the 203 patients documented to be
559 euthyroid at entry, 137 (67%) patients had at least one follow-up TSH
560 value. The overall incidence of hypothyroidism, in the clinical study
561 patients was 14% with cumulative incidences of 4.2% at 6 months and
562 8.1%, 12.6%, and 15.0% at 1, 2, and 4 years, respectively. New events
563 have been observed up to 72 months post treatment. Twelve percent
564 (117/990) of the patients included in clinical studies or the expanded
565 access programs had an elevated TSH level (8%) or a history of

hypothyroidism (4%) prior to treatment and 5 patients had no baseline information. Of the 873 who were euthyroid at entry, 583 (67%) had at least one post-treatment TSH value obtained. With a median observation period of 18 months, 54 patients (9%) became hypothyroid as determined by elevated TSH. The cumulative incidence of hypothyroidism in the combined populations was 9.1% and 17.4% at 2 and 4 years, respectively.

Immunogenicity: Two percent (4/230) of the chemotherapy-relapsed or refractory patients included in the clinical studies had a positive serology for HAMA prior to treatment and six patients had no baseline assessment for HAMA. Of the 220 patients who were seronegative prior to treatment, 219 (99.5%) had at least one post-treatment HAMA value obtained. With a median observation period for HAMA seroconversion of 6 months, 23 patients (11%) seroconverted to HAMA positivity. The median time to development of HAMA was 6 months. In a study of 77 patients who were chemotherapy-naïve, the incidence of conversion to HAMA seropositivity was 70%, with a median time to development of HAMA of 27 days.

One percent (11/989) of the chemotherapy-relapsed or refractory patients included in the clinical studies or the expanded access program had a positive serology for HAMA prior to treatment and six patient had no baseline assessment for HAMA. Of the 978 patients who were seronegative for HAMA prior to treatment, 785 (80%) had at least one post-treatment HAMA value obtained. With a median observation period of 6 months, a total of 76 patients (10%) became seropositive for HAMA post-treatment. The median time of HAMA development was 148 days, with 45 (59%) patients seropositive for HAMA by 6 months. No patient became seropositive for HAMA more than 30 months after administration of the BEXXAR therapeutic regimen.

The data reflect the percentage of patients whose test results were considered positive for HAMA in an ELISA assay that detects antibodies to the Fc portion of IgG₁ murine immunoglobulin and are highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of

600 HAMA in patients treated with the BEXXAR therapeutic regimen with the
601 incidence of HAMA in patients treated with other products may be
602 misleading.

603 **OVERDOSAGE**

604 The maximum dose of the BEXXAR therapeutic regimen that was
605 administered in clinical trials was 88 cGy. Three patients were treated with
606 a total body dose of 85 cGy of Iodine I 131 Tositumomab in a dose
607 escalation study. Two of the 3 patients developed Grade 4 toxicity of 5
608 weeks duration with subsequent recovery. In addition, accidental
609 overdose of the BEXXAR therapeutic regimen occurred in one patient at
610 total body doses of 88 cGy. The patient developed Grade 3 hematologic
611 toxicity of 18 days duration. Patients who receive an accidental overdose
612 of Iodine I 131 Tositumomab should be monitored closely for cytopenias
613 and radiation-related toxicity. The effectiveness of hematopoietic stem
614 cell transplantation as a supportive care measure for marrow injury has
615 not been studied; however, the timing of such support should take into
616 account the pharmacokinetics of the BEXXAR therapeutic regimen and
617 decay rate of the Iodine-131 in order to minimize the possibility of
618 irradiation of infused hematopoietic stem cells.

619

620 **DOSAGE AND ADMINISTRATION**

621 **Recommended Dose**

622 The BEXXAR therapeutic regimen consists of four components
623 administered in two discrete steps: the dosimetric step, followed 7-14 days
624 later by a therapeutic step.

625 Note: the safety of the BEXXAR therapeutic regimen was established only
626 in the setting of patients receiving thyroid blocking agents and
627 premedication to ameliorate/prevent infusion reactions (See **Concomitant**
628 **Medications**).

629 **Dosimetric step**

630 • Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride
 631 over 60 minutes. Reduce the rate of infusion by 50% for mild to
 632 moderate infusional toxicity; interrupt infusion for severe infusional
 633 toxicity. After complete resolution of severe infusional toxicity, infusion
 634 may be resumed with a 50% reduction in the rate of infusion.

635 • Iodine I 131 Tositumomab (containing 5.0 mCi I-131 and 35 mg
 636 tositumomab) intravenously in 30 ml 0.9% Sodium Chloride over 20
 637 minutes. Reduce the rate of infusion by 50% for mild to moderate
 638 infusional toxicity; interrupt infusion for severe infusional toxicity. After
 639 complete resolution of severe infusional toxicity, infusion may be
 640 resumed with a 50% reduction in the rate of infusion.

641 **Therapeutic step**

642 Note: Do not administer the therapeutic step if biodistribution is altered.
 643 (See **Assessment of Biodistribution of Iodine I 131 Tositumomab**)

644 • Tositumomab 450 mg intravenously in 50 ml 0.9% Sodium Chloride
 645 over 60 minutes. Reduce the rate of infusion by 50% for mild to
 646 moderate infusional toxicity; interrupt infusion for severe infusional
 647 toxicity. After complete resolution of severe infusional toxicity, infusion
 648 may be resumed with a 50% reduction in the rate of infusion.

649 • Iodine I 131 Tositumomab (See **CALCULATION OF IODINE-131**
 650 **ACTIVITY FOR THE THERAPEUTIC DOSE**). Reduce the rate of
 651 infusion by 50% for mild to moderate infusional toxicity; interrupt
 652 infusion for severe infusional toxicity. After complete resolution of
 653 severe infusional toxicity, infusion may be resumed with a 50%
 654 reduction in the rate of infusion.

655 • Patients with $\geq 150,000$ platelets/mm³: The recommended dose is
 656 the activity of Iodine-131 calculated to deliver 75cGy total body
 657 irradiation and 35 mg Tositumomab, administered intravenously
 658 over 20 minutes.

659 • Patients with NCI Grade 1 thrombocytopenia (platelet counts =100,
 660 000 but <150,000 platelets/mm³): the recommended dose is the

661 activity of Iodine-131 calculated to deliver 65 cGy total body
 662 irradiation and 35 mg Tositumomab, administered intravenously
 663 over 20 minutes.

664 **Concomitant Medications:** The safety of the BEXXAR therapeutic
 665 regimen was established in studies in which all patients received the
 666 following concurrent medications:

- 667 • Thyroid protective agents: Saturated solution of potassium iodide
 668 (SSKI) 4 drops orally t.i.d; Lugol's solution 20 drops orally t.i.d.; or
 669 Potassium iodide tablets 130 mg orally q.d. Thyroid protective agents
 670 should be initiated at least 24 hours prior to administration of the
 671 Iodine-131 Tositumomab dosimetric dose and continued until 2 weeks
 672 after administration of the Iodine I 131 Tositumomab therapeutic dose.

673 **Patients should not receive the dosimetric dose of Iodine I 131**
 674 **Tositumomab if they have not yet received at least 3 doses of**
 675 **SSKI, three doses of Lugol's solution, or one dose of 130 mg**
 676 **potassium iodide tablet (at least 24 hours prior to the dosimetric**
 677 **dose).**

- 678 • Acetaminophen 650 mg orally and diphenhydramine 50 mg orally 30
 679 minutes prior to administration of Tositumomab in the dosimetric and
 680 therapeutic steps.

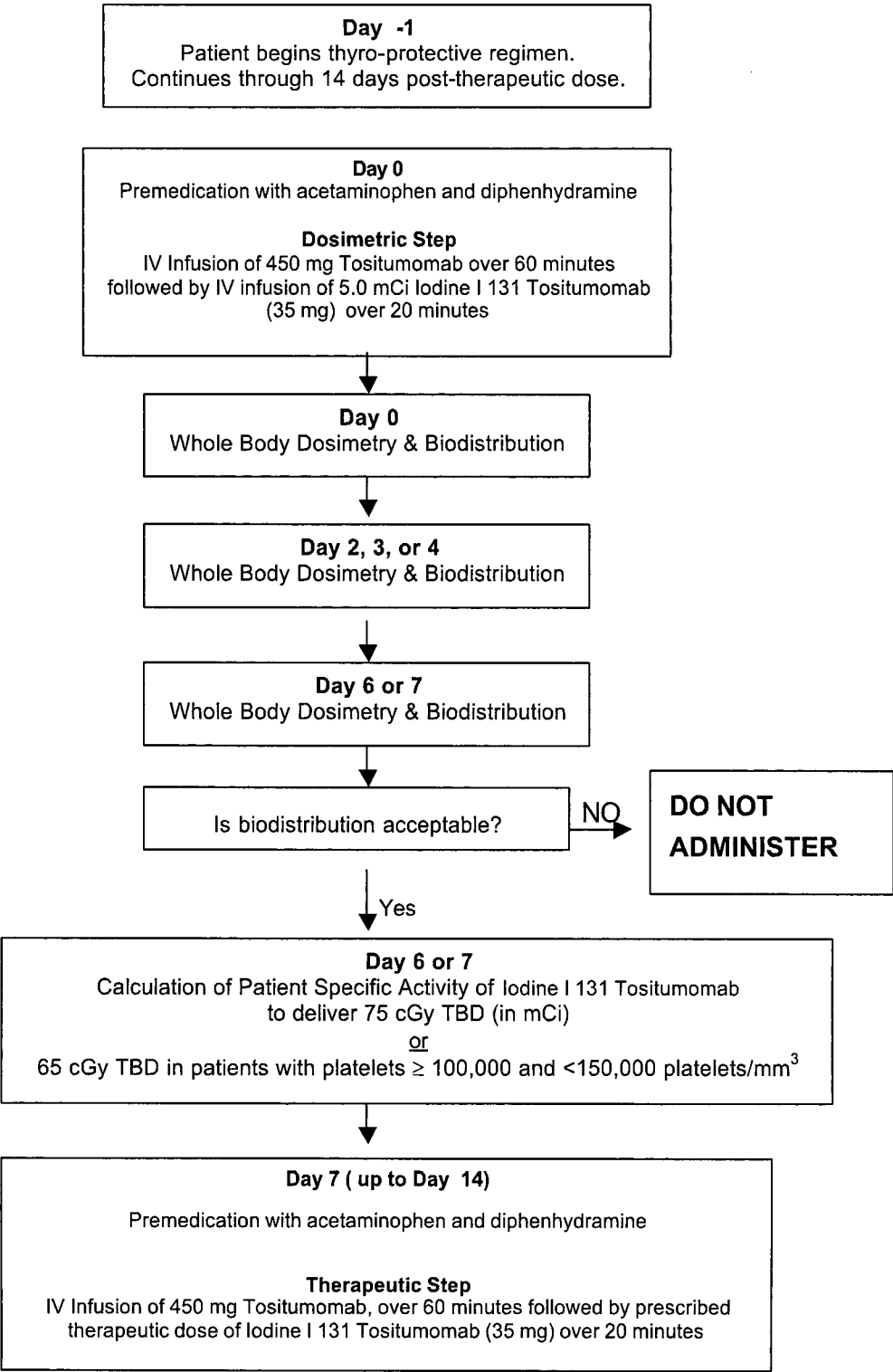
681 The BEXXAR therapeutic regimen is administered via an IV tubing set
 682 with an in-line 0.22 µ filter. **THE SAME IV TUBING SET AND FILTER**
 683 **MUST BE USED THROUGHOUT THE ENTIRE DOSIMETRIC OR**
 684 **THERAPEUTIC STEP. A CHANGE IN FILTER CAN RESULT IN LOSS**
 685 **OF DRUG.**

686 Figure 1 shows an overview of the dosing schedule.

687

687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734

Figure 1
Dosing Schedule



734

735

PREPARATION OF THE BEXXAR THERAPEUTIC REGIMEN

736

GENERAL

737

738

Read all directions thoroughly and assemble all materials before preparing the dose for administration.

739

740

741

742

743

The Iodine I 131 Tositumomab dosimetric and therapeutic doses should be measured by a suitable radioactivity calibration system immediately prior to administration. The dose calibrator must be operated in accordance with the manufacturer's specifications and quality control for the measurement of Iodine-131.

744

745

746

747

All supplies for preparation and administration of the BEXXAR therapeutic regimen should be sterile. Use appropriate aseptic technique and radiation precautions for the preparation of the components of the BEXXAR therapeutic regimen.

748

749

750

751

752

Waterproof gloves should be utilized in the preparation and administration of the product. Iodine I 131 Tositumomab doses should be prepared, assayed, and administered by personnel who are licensed to handle and/or administer radionuclides. Appropriate shielding should be used during preparation and administration of the product.

753

754

755

Restrictions on patient contact with others and release from the hospital must follow all applicable federal, state, and institutional regulations.

756

Preparation for the Dosimetric Step

757

Tositumomab Dose

758

Required materials not supplied

759

760

761

A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450 mg of Tositumomab from two vials each containing 225 mg Tositumomab)

762

B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP.

- 763 C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the
764 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

765 Method

- 766 1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile
767 0.9% Sodium Chloride for Injection, USP.
- 768 2. Withdraw the entire contents from each of the two 225-mg vials (a total
769 of 450 mg Tositumomab in 32 mL) and transfer to the infusion bag
770 containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a
771 final volume of 50 mL.
- 772 3. Gently mix the solution by inverting/rotating the bag. DO NOT SHAKE.
- 773 4. The diluted Tositumomab may be stored for up to 24 hours when
774 stored refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at
775 room temperature.

776 Note: Tositumomab solution may contain particulates that are generally
777 white in nature. The product should appear clear to opalescent, colorless
778 to slightly yellow.

779 **Preparation of Iodine I 131 Tositumomab Dosimetric Dose**

780 **Required materials not supplied:**

- 781
- 782 A. Lead shielding for preparation vial and syringe pump
- 783 B. Two 30 mL syringes with 18 gauge needles: one to withdraw the
784 calculated volume of Iodine I 131 Tositumomab from the Iodine I 131
785 Tositumomab vial and one to withdraw the volume from the
786 preparation vial into a syringe for administration.
- 787 C. One 20 mL syringe with attached needle, filled with 0.9% Sodium
788 Chloride for Injection, USP
- 789 D. One 3 mL syringe with attached needle to withdraw Tositumomab from
790 35-mg vial
- 791 E. One sterile, 30 or 50 mL preparation vial
- 792 F. Two lead pots, both kept at room temperature. One pot is used to
793 thaw the labeled antibody and the second pot is used to hold the
794 preparation vial.

795
796
797
798

799
800
801
802

803
804

805

806
807

808

809
810
811
812
813
814
815
816
817

818
819
820
821

822
823
824
825
826
827
828
829

830
831
832

- Method:**
1. Allow approximately 60 minutes for thawing (at ambient temperature) of the Iodine I 131 Tositumomab dosimetric vial with appropriate lead shielding.
 2. Based on the activity concentration of the vial (see actual product specification sheet for the vial supplied in the dosimetric package), calculate the volume required for an Iodine I 131 Tositumomab activity of 5.0 mCi.
 3. Withdraw the calculated volume from the Iodine I 131 Tositumomab vial.
 4. Transfer this volume to the shielded preparation vial.
 5. Assay the dose to ensure that the appropriate activity (mCi) has been prepared.
 - a. If the assayed dose is 5.0 mCi (+/- 10%) proceed with step 6.
 - b. If the assayed dose does not contain 5.0 mCi (+/- 10%) recalculate the activity concentration of the Iodine I 131 Tositumomab at this time, based on the volume and the activity in the preparation vial. Recalculate the volume required for an Iodine I 131 Tositumomab activity of 5.0 mCi. Using the same 30 mL syringe, add or subtract the appropriate volume from the Iodine I 131 Tositumomab vial so that the preparation vial contains the volume required for an Iodine I 131 Tositumomab activity of 5.0 mCi (+/- 10%). Re-assay the preparation vial and proceed with step 6.
 6. Calculate the amount of Tositumomab contained in the solution of Iodine I 131 Tositumomab in the shielded preparation vial, based on the volume and protein concentration (see actual product specification sheet supplied in the dosimetric package).
 7. If the shielded preparation vial contains less than 35 mg, calculate the amount of additional Tositumomab needed to yield a total of 35 mg protein. Calculate the volume needed from the 35 mg vial of Tositumomab, based on the protein concentration. Withdraw the calculated volume of Tositumomab from the 35 mg vial of Tositumomab, and transfer this volume to the shielded preparation vial. The preparation vial should now contain a total of 35 mg of Tositumomab.
 8. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection, USP, add a sufficient quantity to the shielded preparation vial to yield a final volume of 30 mL. Gently mix the solutions.

- 833 9. Withdraw the entire contents from the preparation vial into a 30 mL
834 syringe using a large bore needle (18 gauge).
835 10. Assay and record the activity.

836
837
838

Administration of the Dosimetric Step

839

840 Required materials not supplied:

- 841 A. One I.V. Filter set (0.22 µm filter), 15 inch with injection site (port) and
842 luer lock
843 B. One Primary IV infusion set
844 C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
845 D. Two Secondary I.V infusion sets
846 E. One I.V. Extension set, 30 inch luer lock
847 F. One 3-way stopcock
848 G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
849 H. One Infusion pump for Tositumomab infusion
850 I. One Syringe Pump for Iodine I 131 Tositumomab infusion
851 J. Lead shielding for use in the administration of the dosimetric dose

852 Tositumomab Infusion:

853 (See Figure 1 in the “**Workbook for Dosimetry Methodology and**
854 **Administration Set-Up**” for diagrammatic illustration of the configuration of
855 the infusion set components).
856

- 857 1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set
858 (Item A) and the 100 mL bag of sterile 0.9% Sodium Chloride for Injection,
859 USP (Item C).
860 2. After priming the primary IV infusion set (Item B) and IV filter set (Item A),
861 connect the infusion bag containing 450 mg Tositumomab (50 mL) via a
862 secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at
863 a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60
864 minutes.

865

866 3. After completion of the Tositumomab infusion, disconnect the secondary
 867 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and
 868 the in-line IV filter set (Item A) with 0.9% Sodium Chloride. Discard the
 869 Tositumomab bag and secondary IV infusion set.

870

871 **Iodine I 131 Tositumomab Dosimetric Infusion**

872 (See Figure 2 in the “**Workbook for Dosimetry Methodology and**
 873 **Administration Set-Up**” for diagrammatic illustration of the configuration of
 874 the infusion set components).

875 1. Appropriate shielding should be used in the administration of the
 876 dosimetric dose.

877 2. The dosimetric dose is delivered in a 30 mL syringe.

878 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).

879 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
 880 (Item G) to a secondary IV infusion set (Item D) and connect the infusion
 881 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set
 882 (Item D) and the extension set (Item E). Connect the extension set (Item
 883 E) to a port in the primary IV infusion set (Item B), distal to the filter.

884 (**Note:** You **must** use the same primary infusion set (Item B) and IV filter set
 885 (Item A) with pre-wetted filter that was used for the Tositumomab infusion. A
 886 change in filter can result in loss of up to 7% of the Iodine I 131 Tositumomab
 887 dose.)

888

889 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way
 890 stopcock (Item F).

891 6. Set syringe pump to deliver the entire 5.0 mCi (35 mg) dose of Iodine I
 892 131 Tositumomab over 20 minutes.

893 7. After completion of the infusion of Iodine I 131 Tositumomab, close the
 894 stopcock (Item F) to the syringe. Flush the extension set (Item E) and the
 895 secondary IV infusion set (Item D) with 0.9% Sodium Chloride for
 896 Injection, USP from the 50 mL bag (Item G).

- 897 8. After the flush, disconnect the extension set (Item E), 3-way stopcock
898 (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and
899 in-line filter set (Item A). Determine the combined residual activity of the
900 syringe and infusion set components (stopcock, extension set, primary
901 infusion set and in-line filter set) by assaying these items in a suitable
902 radioactivity calibration system immediately following completion of
903 administration of all components of the dosimetric step. Calculate and
904 record the dose delivered to the patient by subtracting the residual activity
905 in the syringe and the infusion set components from the activity of Iodine I
906 131 Tositumomab in the syringe prior to infusion.
- 907 9. Discard all materials used to deliver the Iodine I 131 Tositumomab (e.g.,
908 syringes, vials, in-line filter set, extension set and infusion sets) in
909 accordance with local, state, and federal regulations governing radioactive
910 and biohazardous waste.

911

912 **Determination of Dose for the Therapeutic Step (See CALCULATION OF**
913 **IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE)**

914 The methodology for determining and calculating the patient-specific dose of
915 Iodine I 131 activity (mCi) to be administered in the therapeutic step involves
916 the following steps:

- 917 1. Following infusion of the Iodine I 131 Tositumomab dosimetric dose,
918 obtain total body gamma camera counts and whole body images at the
919 following timepoints:
- 920 a. Within one hour of infusion and prior to urination
- 921 b. 2-4 days after infusion of the dosimetric dose, following urination
- 922 c. 6-7 days after infusion of the dosimetric dose, following urination
- 923 2. Assess biodistribution. If biodistribution is altered, the therapeutic step
924 should not be administered.
- 925 3. Determine total body residence time (See Graph 1, "**Determination of**
926 **Residence Time**", in the "**Workbook for Dosimetry Methodology and**
927 **Administration Set-Up**").
- 928 4. Determine activity hours, (See Table 2, "**Determination of Activity**
929 **Hours**", in the "**Workbook for Dosimetry Methodology and**
930 **Administration Set-Up**") according to gender. Use actual patient mass
931 (in kg) or maximum effective mass (in kg) whichever is lower (See
932 Table 1, "**Determination of Maximum Effective Mass**", in the
933 "**Workbook for Dosimetry Methodology and Administration Set-Up**").

- 934
- 935
- 936
- 937
- 938
5. Determine whether the desired total body dose should be reduced (to 65 cGy) due to a platelet count of 100,000 to <150,000 cells/mm³.
6. Based on the total body residence time and activity hours, calculate the Iodine-131 activity (mCi) to be administered to deliver the therapeutic dose of 65 or 75 cGy.

939

940

The following equation is used to calculate the activity of Iodine-131 required for delivery of the desired total body dose of radiation.

941

942

943

$$\text{Iodine-131 Activity (mCi)} = \frac{\text{Activity Hours (mCi hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$$

944

Preparation for the Therapeutic Step

945

Tositumomab Dose

946

Required materials not supplied

- 947
- 948
- 949
- 950
- 951
- 952
- A. One 50 mL syringe with attached 18 gauge needle (to withdraw 450 mg of Tositumomab from two vials each containing 225 mg Tositumomab)
- B. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
- C. One 50 mL syringe for drawing up 32 mL of saline for disposal from the 50 mL bag of sterile 0.9% Sodium Chloride for Injection USP

953

Method

- 954
- 955
- 956
- 957
- 958
- 959
- 960
1. Withdraw and dispose of 32 mL of saline from a 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP.
2. Withdraw the entire contents from each of the two 225-mg vials (a total of 450 mg Tositumomab in 32 mL) and transfer to the infusion bag containing 18 mL of 0.9% Sodium Chloride for Injection, USP to yield a final volume of 50 mL.
3. Gently mix the solutions by inverting/rotating the bag. DO NOT SHAKE.

961 4. The diluted Tositumomab may be stored for up to 24 hours when stored
 962 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room
 963 temperature.

964 Note: Tositumomab solution may contain particulates that are generally
 965 white in nature. The product should appear clear to opalescent, colorless
 966 to slightly yellow.
 967
 968

969 **Preparation of Iodine I 131 Tositumomab Therapeutic Dose**

970 **Required materials not supplied:**

- 971 A. Lead shielding for preparation vial and syringe pump
- 972 B. Two or four 30 mL syringes with 18 gauge needles: one or two to
 973 withdraw the calculated volume of Iodine I 131 Tositumomab from
 974 the Iodine I 131 Tositumomab vial(s) and one or two to withdraw
 975 the volume from the preparation vial into a syringe for
 976 administration.
- 977 C. One 20 mL syringe with attached needle filled with 0.9% Sodium
 978 Chloride for Injection, USP
- 979 D. One 3 mL sterile syringe with attached needle to draw up
 980 Tositumomab from the 35 mg vial
- 981 E. One sterile, 30 or 50 mL preparation vial
- 982 F. Two lead pots both kept at room temperature. One pot is used to
 983 thaw the labeled antibody, and the second pot is used to hold the
 984 preparation vial.

985 **Method:**

- 986
- 987 1. Allow approximately 60 minutes for thawing (at a mbient temperature)
 988 of the Iodine I 131 Tositumomab therapeutic vial with appropriate lead
 989 shielding.
- 990 2. Calculate the dose of Iodine I 131 Tositumomab required (See
 991 **CALCULATION OF IODINE-131 ACTIVITY FOR THERAPEUTIC**
 992 **DOSE)**
- 993 3. Based on the activity concentration of the vial (see actual product
 994 specification sheet for each vial supplied in the therapeutic package),
 995 calculate the volume required for the Iodine I 131 Tositumomab activity
 996 required for the therapeutic dose.

- 997 4. Using one or more 30 mL syringes with an 18-gauge needle, withdraw
998 the calculated volume from the Iodine I 131 Tositumomab vial.
- 999 5. Transfer this volume to the shielded preparation vial.
- 1000 6. Assay the dose to ensure that the appropriate activity (mCi) has been
1001 prepared.
- 1002 a. If the assayed dose is the calculated dose (+/- 10%) needed for the
1003 therapeutic step, proceed with step 7.
- 1004 b. If the assayed dose does not contain the desired dose (+/- 10%),
1005 re-calculate the activity concentration of the Iodine I 131
1006 Tositumomab at this time, based on the volume and the activity in
1007 the preparation vial. Re-calculate the volume required for an Iodine
1008 I 131 Tositumomab activity for the therapeutic dose. Using the
1009 same 30 mL syringe, add or subtract the appropriate volume from
1010 the Iodine I 131 Tositumomab vial so that the preparation vial
1011 contains the volume required for the Iodine I 131 Tositumomab
1012 activity required for the therapeutic dose. Re-assay the preparation
1013 vial. Proceed to step 7.
- 1014 7. Calculate the amount of Tositumomab protein contained in the solution
1015 of Iodine I 131 Tositumomab in the shielded preparation vial, based on
1016 the volume and protein concentration. (See product specification
1017 sheet.)
- 1018 8. If the shielded preparation vial contains less than 35 mg, calculate the
1019 amount of additional Tositumomab needed to yield a total of 35 mg
1020 protein. Calculate the volume needed from the 35 mg vial of
1021 Tositumomab, based on the protein concentration. Withdraw the
1022 calculated volume of Tositumomab from the 35 mg vial of
1023 Tositumomab, and transfer this volume to the shielded preparation vial.
1024 The preparation vial should now contain a total of 35 mg of
1025 Tositumomab.
- 1026 **Note:** If the dose of Iodine I 131 Tositumomab requires the use of 2
1027 vials of Iodine I 131 Tositumomab or the entire contents of a single vial
1028 of Iodine I 131 Tositumomab, there may be no need to add protein
1029 from the 35 mg vial of Tositumomab.
- 1030 9. Using the 20 mL syringe containing 0.9% Sodium Chloride for
1031 Injection, USP, add a sufficient volume (if needed) to the shielded
1032 preparation vial to yield a final volume of 30 mL. Gently mix the
1033 solution.
- 1034 10. Withdraw the entire volume from the preparation vial into a one or
1035 more sterile 30 mL syringes using a large bore needle (18 gauge).

1036 11. Assay and record the activity.

1037

1038

1039

1040

1041

1042

Administration of the Therapeutic Step

Note: Restrictions on patient contact with others and release from the hospital must follow all applicable federal, state, and institutional regulations.

1043

Required materials not supplied:

1044

1045

A. One I.V. Filter set (0.22 μ m filter), 15 inch with injection site (port) and luer lock

1046

B. One Primary I.V. infusion set

1047

C. One 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

1048

D. Two Secondary I.V. infusion sets

1049

E. One I.V. extension set, 30 inch luer lock

1050

F. One 3-way stopcock

1051

G. One 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP

1052

H. One Infusion pump for Tositumomab infusion

1053

I. One Syringe Pump for Iodine I 131 Tositumomab infusion

1054

J. Lead shielding for use in the administration of the therapeutic dose

1055

1056

Tositumomab Infusion:

1057

(See Figure 1 in the "**Workbook for Dosimetry Methodology and**

1058

Administration Set-Up" for diagrammatic illustration of the configuration of the infusion set components).

1059

1060

1061

1062

1. Attach a primary IV infusion set (Item B) to the 0.22 micron in-line filter set (Item A) and a 100 mL bag of sterile 0.9% Sodium Chloride for Injection, USP (Item C).

1063

1064

1065

1066

1067

2. After priming the primary IV infusion set (Item B) and filter set (Item A), connect the infusion bag containing 450 mg Tositumomab (50 mL) via a secondary IV infusion set (Item D) to the primary IV infusion set (Item B) at a port distal to the 0.22 micron in-line filter. Infuse Tositumomab over 60 minutes.

- 1068 3. After completion of the Tositumomab infusion, disconnect the secondary
 1069 IV infusion set (Item D) and flush the primary IV infusion set (Item B) and
 1070 the IV filter set (Item A) with 0.9% Sodium Chloride. Discard the
 1071 Tositumomab bag and secondary IV infusion set.

1072

1073 **Iodine I 131 Tositumomab Therapeutic Infusion:**

1074 (See Figure 2 in the “**Workbook for Dosimetry Methodology and**
 1075 **Administration Set-Up**” for diagrammatic illustration of the configuration of
 1076 the infusion set components).

1077

- 1078 1. Appropriate shielding should be used in the administration of the
 1079 therapeutic dose.

- 1080 2. The therapeutic dose is delivered in one or more 30 mL syringes.

- 1081 3. Connect the extension set (Item E) to the 3-way stopcock (Item F).

- 1082 4. Connect the 50 mL bag of sterile 0.9% Sodium Chloride for Injection, USP
 1083 (Item G) to a secondary IV infusion set (Item D) and connect the infusion
 1084 set to the 3-way stopcock (Item F). Prime the secondary IV infusion set
 1085 (Item D) and the extension set (Item E). Connect the extension set (Item
 1086 E) to a port in the primary IV infusion set (Item B), distal to the filter.

1087 (**Note:** You **must** use the same primary infusion set (Item B) and IV filter set
 1088 (Item A) with pre-wetted filter that was used for the Tositumomab infusion. A
 1089 change in filter can result in loss of up to 7% of the Iodine I 131 Tositumomab
 1090 dose.)

1091

- 1092 5. Attach the syringe filled with the Iodine I 131 Tositumomab to the 3-way
 1093 stopcock (Item F).

- 1094 6. Set syringe pump to deliver the entire therapeutic dose of Iodine I 131
 1095 Tositumomab over 20 minutes. (Note: if more than one syringe is
 1096 required, remove the syringe and repeat steps 5 and 6.)

- 1097 7. After completion of the infusion of Iodine I 131 Tositumomab, close the
 1098 stopcock (Item F) to the syringe. Flush the secondary IV infusion set (Item
 1099 D) and the extension set (Item E) with 0.9% Sodium Chloride from the 50
 1100 mL bag of sterile, 0.9% Sodium Chloride for Injection, USP (Item G).

- 1101
- 1102
- 1103
- 1104
- 1105
- 1106
- 1107
- 1108
- 1109
- 1110
- 1111
- 1112
- 1113
- 1114
- 1115
- 1116
- 1117
- 1118
- 1119
- 1120
- 1121
- 1122
- 1123
- 1124
- 1125
- 1126
- 1127
- 1128
- 1129
- 1130
- 1131
- 1132
- 1133
- 1134
- 1135
- 1136
- 1137
8. After the flush, disconnect the extension set (Item E), 3-way stopcock (Item F) and syringe. Disconnect the primary IV infusion set (Item B) and in-line filter set (Item A). Determine the combined residual activity of the syringe(s) and infusion set components (stopcock, extension set, primary infusion set and in-line filter set) by assaying these items in a suitable radioactivity calibration system immediately following completion of administration of all components of the therapeutic step. Calculate and record the dose delivered to the patient by subtracting the residual activity in the syringe and infusion set components from the activity of Iodine I 131 Tositumomab in the syringe prior to infusion.
9. Discard all materials used to deliver the Iodine I 131 Tositumomab (e.g., syringes, vials, in-line filter set, extension set and infusion sets) in accordance with local, state, and federal regulations governing radioactive and biohazardous waste.

DOSIMETRY

The following sections describe the procedures for image acquisition for collection of dosimetry data, interpretation of biodistribution images, calculation of residence time, and calculation of activity hours. Please read all sections carefully.

IMAGE ACQUISITION AND INTERPRETATION

Gamma Camera and Dose Calibrator Procedures

Manufacturer-specific quality control procedures should be followed for the gamma camera/computer system, the collimator, and the dose calibrator. Less than 20% variance between maximum and minimum pixel count values in the useful field of view is acceptable on Iodine-131 intrinsic flood fields and variability <10% is preferable. Iodine-131-specific camera uniformity corrections are strongly recommended, rather than applying lower energy correction to the Iodine-131 window. Camera extrinsic uniformity should be assessed at least monthly using 99mTc or 57 Co as a source with imaging at the appropriate window.

Additional (non-routine) quality control procedures are required. To assure the accuracy and precision of the patient total body counts, the gamma camera must undergo validation and daily quality control on each day it is used to collect patient images.

1138 Use the same setup and region of interest (ROI) for calibration, determination
1139 of background, and whole body patient studies.

1140 **Gamma Camera Set-Up**

1141 The **same** camera, collimator, region of interest (ROI), scanning speed,
1142 energy window, and setup must be used for all studies. The gamma camera
1143 must be capable of whole body imaging and have a large or extra large field
1144 of view with a digital interface. It must be equipped with a parallel-hole
1145 collimator rated to at least 364 keV by the manufacturer with a septal
1146 penetration for Iodine-131 of <7%.

1147 The camera and computer must be set up for scanning as follows:

1148
1149 • Parallel hole collimator rated to at least 364 keV with a septal penetration
1150 for Iodine-131 of <7%

1151 • Symmetric window (20-25%) centered on the 364 keV photo peak of
1152 Iodine-131 (314 - 414 keV)

1153 • Matrix: minimum 128 x 128

1154 • Scanning speed: 10-30 cm/minute

1155

1156 **Counts from Calibrated Source for Quality Control**

1157 Camera sensitivity for Iodine-131 must be determined each day.

1158 Determination of the gamma camera's sensitivity is obtained by scanning a
1159 calibrated activity of Iodine-131 (e.g., 200–250 μ Ci in at least 20 mL of saline
1160 within a sealed pharmaceutical vial). The radioactivity of the Iodine-131
1161 source is first determined using a NIST-traceable-calibrated clinical dose
1162 calibrator at the Iodine-131 setting.

1163

1164 **Background Counts**

1165 The background count is obtained from a scan with no radioactive source.

1166 This should be obtained following the count of the calibrated source and just
1167 prior to obtaining the patient count.

1168 If abnormally high background counts are measured, the source should be
1169 identified and, if possible, removed. If abnormally low background counts are

1170 measured, the camera energy window setting and collimator should be
 1171 verified before repeating the background counts.

1172 The counts per μCi are obtained by dividing the background-corrected source
 1173 count by the calibrated activity for that day. For a specific camera and
 1174 collimator, the counts per μCi should be relatively constant. When values
 1175 vary more than 10% from the established ratio, the reason for the discrepancy
 1176 should be ascertained and corrected and the source count repeated.

1177 **Patient Total Body Counts**

1178 The source and background counts are obtained first and the camera
 1179 sensitivity (i.e., constant counting efficiency) is established prior to obtaining
 1180 the patient count. The same rectangular region of interest (ROI) must be
 1181 used for the whole body counts, the quality control counts of the radioactive
 1182 source, and the background counts.

1183 Acquire anterior and posterior whole body images for gamma camera counts.
 1184 For any particular patient, the same gamma camera must be used for all
 1185 scans. To obtain proper counts, extremities must be included in the images,
 1186 and arms should not cross over the body. The scans should be centered on
 1187 the midline of the patient. Record the time of the start of the radiolabeled
 1188 dosimetric infusion and the time of the start of each count acquisition.

1189 Gamma camera counts will be obtained at the three imaging time points:

- 1190 • **Count 1:** *Within an hour of end of the infusion* of the Iodine I 131
 1191 Tositumomab dosimetric dose prior to patient voiding.
- 1192 • **Count 2:** Two to 4 days after administration of the Iodine I 131
 1193 Tositumomab dosimetric dose and immediately following patient voiding.
- 1194 • **Count 3:** Six to 7 days after the administration of the Iodine I 131
 1195 Tositumomab dosimetric dose and immediately following patient voiding

1196 **Assessment of Biodistribution of Iodine I 131 Tositumomab**

1197 The biodistribution of Iodine I 131 Tositumomab should be assessed by
 1198 determination of total body residence time and by visual examination of whole

body camera images from the first image taken at the time of Count 1 (within an hour of the end of the infusion) and from the second image taken at the time of Count 2 (at 2 to 4 days after administration). To resolve ambiguities, an evaluation of the third image at the time of Count 3 (6 to 7 days after administration) may be necessary. If either of these methods indicates that the biodistribution is altered, the Iodine I 131 Tositumomab therapeutic dose should not be administered.

Expected Biodistribution

- On the first imaging timepoint: Most of the activity is in the blood pool (heart and major blood vessels) and the uptake in normal liver and spleen is less than in the heart.
- On the second and third imaging timepoints: The activity in the blood pool decreases significantly and there is decreased accumulation of activity in normal liver and spleen. Images may show uptake by thyroid, kidney, and urinary bladder and minimal uptake in the lungs. Tumor uptake in soft tissues and in normal organs is seen as areas of increased intensity.

Results Indicating Altered Biodistribution

- On the first imaging timepoint: If the blood pool is not visualized or if there is diffuse, intense tracer uptake in the liver and/or spleen or uptake suggestive of urinary obstruction the biodistribution is altered. Diffuse lung uptake greater than that of blood pool on the first day represents altered biodistribution.
- On the second and third imaging timepoints: uptake suggestive of urinary obstruction and diffuse lung uptake greater than that of the blood pool represent altered biodistribution.
- Total body residence times of less than 50 hours and more than 150 hours.

CALCULATION OF IODINE-131 ACTIVITY FOR THE THERAPEUTIC DOSE

The methods for determining the residence time (hr) and activity hours (mCi hr) are described below.

1233 **Residence Time (hr)**

1234 For each time point, calculate the background corrected total body count at
1235 each timepoint (defined as the geometric mean). The following equation is
1236 used:

1237 Geometric mean of counts = $\sqrt{(C_A - C_{BA})(C_P - C_{BP})}$

1238

1239 In this equation, C_A = the anterior counts, C_{BA} = the anterior background
1240 counts, C_P = the posterior counts, and C_{BP} = the posterior background counts.

1241

1242 Once the geometric mean of the counts has been calculated for each of the 3
1243 timepoints, the % injected activity remaining for each timepoint is calculated
1244 by dividing the geometric mean of the counts from that timepoint by the
1245 geometric mean of the counts from Day 0 and multiplying by 100.

1246

1247 The residence time (h) is then determined by plotting the time from the start of
1248 infusion and the % injected activity values for the 3 imaging timepoints on
1249 Graph 1 (See Worksheet “**Determination of Residence Time**” in the
1250 “**Workbook for Dosimetry Methodology and Administration Set-Up**”
1251 supplied with Dosimetric Dose Packaging). A best-fit line is then drawn from
1252 100% (the pre-plotted Day 0 value) through the other 2 plotted points (if the
1253 line does not intersect the two points, one point must lie above the best-fit line
1254 and one point must lie below the best-fit line). The residence time (h) is read
1255 from the x-axis of the graph at the point where the fitted line intersects with
1256 the horizontal 37% injected activity line.

1257

1258 **Activity Hours (mCi hr)**

1259 In order to determine the activity hours (mCi hr), look up the patient’s
1260 maximum effective mass derived from the patient’s sex and height (See
1261 Worksheet “**Determination of Maximum Effective Mass**” in the “**Workbook**
1262 **for Dosimetry Methodology and Administration Set-Up**” supplied with
1263 Dosimetric Dose Packaging). If the patient’s actual weight is less than the
1264 maximum effective mass, the actual weight should be used in the activity
1265 hours table (See Worksheet “**Determination of Activity Hours**” in the

1266 **"Workbook for Dosimetry Methodology and Administration Set-Up"**
1267 supplied with Dosimetric Dose Packaging). If the patient's actual weight is
1268 greater than the maximum effective mass, the mass from the worksheet for
1269 **"Determination of Maximum Effective Mass"** should be used.

1270 **Calculation of Iodine-131 Activity for the Therapeutic Dose**

1271 The following equation is used to calculate the activity of Iodine-131 required
1272 for delivery of the desired total body dose of radiation.

1273

1274 **Iodine-131 Activity (mCi)** = $\frac{\text{Activity Hours (mCi \cdot hr)}}{\text{Residence Time (hr)}} \times \frac{\text{Desired Total Body Dose (cGy)}}{75 \text{ cGy}}$

1275

1276 **HOW SUPPLIED**

1277 **TOSITUMOMAB DOSIMETRIC PACKAGING**

1278 The components of the dosimetric step will be shipped **ONLY** to individuals
1279 who are participating in the certification program or have been certified in the
1280 preparation and administration of the BEXXAR therapeutic regimen. The
1281 components are shipped from separate sites; when ordering, ensure that the
1282 components are scheduled to arrive on the same day. The components of
1283 the Tositumomab Dosimetric Step include:

1284 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use
1285 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL
1286 supplied by McKesson Biosciences.

1287 NDC 67800-101-31

1288 2. Iodine I 131 Tositumomab: A single-use vial of Iodine I 131 Tositumomab
1289 within a lead pot, supplied by MDS Nordion. Each single-use vial contains
1290 not less than 20 mL of Iodine I 131 Tositumomab at nominal protein and
1291 activity concentrations of 0.1 mg/mL and 0.61 mCi/mL (at calibration),
1292 respectively. (Refer to the product specification sheet for the lot-specific
1293 protein concentration, activity concentration, total activity and expiration date.)

1294 NDC 67800-111-10

1295

1296 **TOSITUMOMAB THERAPEUTIC PACKAGING**

1297 The components of the therapeutic step will be shipped **ONLY** to individuals
1298 who are participating in the certification program or have been certified in the
1299 preparation and administration of the BEXXAR therapeutic regimen for an
1300 individual patient who has completed the Dosimetric Step. The components of
1301 the therapeutic step are shipped from separate sites; when ordering, ensure
1302 that the components are scheduled to arrive on the same day. The
1303 components of the Tositumomab Therapeutic Step include:

1304 1. Tositumomab: Two single-use 225 mg vials (16.1 mL) and one single-use
1305 35 mg vial (2.5 mL) of Tositumomab at a protein concentration of 14 mg/mL
1306 supplied by McKesson Biosciences.

1307 NDC 67800-101-32

1308 2. One or two single-use vials of Iodine I 131 Tositumomab within a lead pot,
1309 supplied by MDS Nordion. Each single-use vial contains not less than 20 mL
1310 of Iodine I 131 Tositumomab at nominal protein and activity concentrations of
1311 1.1 mg/mL and 5.6 mCi/mL (at calibration), respectively. Refer to the product
1312 specification sheet for the lot-specific protein concentration, activity
1313 concentration, total activity and expiration date.

1314 NDC 67800-121-10.

1315

1316 **STABILITY AND STORAGE**

1317 **TOSITUMOMAB**

1318 Vials of Tositumomab (35 mg and 225 mg) should be stored refrigerated at
1319 2°C-8°C (36°F-46°F) prior to dilution. Do not use beyond expiration date.
1320 Protect from strong light. **DO NOT SHAKE.** Do not freeze. Discard any
1321 unused portions left in the vial.

1322 Solutions of diluted Tositumomab are stable for up to 24 hours when stored
1323 refrigerated at 2°C–8°C (36°F–46°F) and for up to 8 hours at room
1324 temperature. However, it is recommended that the diluted solution be stored

1325 refrigerated at 2°C–8°C (36°F–46°F) prior to administration because it does
1326 not contain preservatives. Any unused portion must be discarded. Do not
1327 freeze solutions of diluted Tositumomab.

1328

1329 **IODINE I 131 TOSITUMOMAB**

1330 **Store frozen in the original lead pots.** The lead pot containing the product
1331 must be stored in a freezer at a temperature of -20°C or below until it is
1332 removed for thawing prior to administration to the patient. Do not use beyond
1333 the expiration date on the label of the lead pot.

1334 Thawed dosimetric and therapeutic doses of Iodine I 131 Tositumomab are
1335 stable for up to 8 hours at 2°C–8°C (36°F–46°F) or at room temperature.
1336 Solutions of Iodine I 131 Tositumomab diluted for infusion contain no
1337 preservatives and should be stored refrigerated at 2°C–8°C (36°F–46°F) prior
1338 to administration (do not freeze). Any unused portion must be discarded
1339 according to federal and state laws.

1340

1341 **REFERENCES**

1342

1343 1. Weber DA, Eckman KF, Dillman LT, Ryman JC. In: MIRD: radionuclide data
1344 and decay schemes. New York: Society of Nuclear Medicine Inc. 1989:229.

1345 2. Tedder T, Boyd A, Freedman A, Nadler L, Schlossman S. The B cell
1346 surface molecule is functionally linked with B cell activation and
1347 differentiation. J Immunol 1985; 135(2): 973-979.

1348 3. Anderson, KC, Bates MP, Slaughenhaupt BL, Pinkus GS, Schlossman SF,
1349 Nadler LM. Expression of human B cell-associated antigens on leukemias
1350 and lymphomas: a model of human B cell differentiation. Blood 1984; 63(6):
1351 1424-1433.

1352 4. Press OW, Howell-Clark J, Anderson S, Bernstein I. Retention of
1353 B-cell-specific monoclonal antibodies by human lymphoma cells.
1354 Blood 1994;83:1390–7

1355 5. Cardarelli PM, Quinn M, Buckman D, Fang Y, Colcher D, King DJ,
1356 Bebbington C, et al. Binding to CD20 by anti-B1 antibody or F(ab')(2) is
1357 sufficient for induction of apoptosis in B-cell lines. Cancer Immunol
1358 Immunother 2002 Mar;51(1):15-24

- 1359 6. Stashenko P, Nadler LM, Hardy R, Schlossman SF. Characterization of a
1360 human B lymphocyte-specific antigen. J Immunol 1980;
1361 125:1678–85.
1362

1362

1363 Manufactured by

1364

1365

1366 Corixa Corporation

1367 1124 Columbia Street, Suite 200

1368 Seattle, WA 98104

1369

1370 U.S. Lic. 1614

1371

1372

1373

1374

1375

Jointly Marketed by:

1376

1377 Corixa Corp.

GlaxoSmithKline

1378 Seattle, WA 98104

Philadelphia, PA 19101

1379

1380 Issued: DATE

1381 © 2003 Corixa Corp. and GlaxoSmithKline

P/N: 400009-A

1382

<June 2003>

1383

1384