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Señor Director
DIRECCIÓN DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 378
Actuación : 523

Referencia : Expediente No. **11.065.644**
Asunto : Solicitud de patente para: **COMBINACIONES ANTITUMORALES QUE CONTIENEN ANTICUERPOS QUE RECONOCEN ESPECÍFICAMENTE CD38 Y MELFALAN**
Solicitante : SANOFI
Fecha de solicitud : 27 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. **13422** notificado por fijación en lista el 30 de julio de 2013.

2. Mediante oficio No. **13422** 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 la claridad del pliego reivindicatorio, a las reivindicaciones 6 a 10 relativas a usos, a la falta de unidad de invención, y al nivel inventivo de las reivindicaciones 1 y 2 en vista de los documentos **D1**: WO2006099875 y **D2**: WO9962526, y al nivel inventivo de las reivindicaciones 3 a 5 en vista del documento **D3**: WO2008047242.

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:

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 7 reivindicaciones.

Se han introducido las siguientes modificaciones al pliego reivindicatorio:

- Reivindicación 1 se ha modificado para especificar los CDRs de los anticuerpos anti-CD38 humanizados descritos en la presente solicitud.
- La definición de los CDR de huSB3819 (reivindicación 1 (iii)) se ha completado aún más mediante la referencia a tres CDR secuenciales que tienen secuencias de aminoácidos representadas por las SEQ ID NOS: 13, 15 y posiciones 50 a 66 de la SEQ ID NO: 66.
- La reivindicación 2 se ha modificado para añadir una referencia a los anticuerpos quiméricos.
- La reivindicación 3 se ha eliminado.
- Las reivindicaciones 4 y 5 (nuevas reivindicaciones 3 y 4) se han modificado para eliminar las características ya presentes en la reivindicación 1. Las reivindicaciones se han modificado además para aclarar que las cadenas pesadas y ligeras comprenden las secuencias SEQ ID NO 66, 62, 64, 72, 68 o 70. De esta manera es claro a partir de la presente solicitud que estas secuencias representan sólo la región variable de las cadenas ligera y pesada, y no las secuencias de cadena pesada y ligera de longitud completa.
- Las reivindicaciones 6 a 10 han sido eliminadas.
- La nueva reivindicación 5 independiente ha sido añadida, y corresponde a la reivindicación 1 iii).
- La nueva reivindicación 6 ha sido añadida, y se encuentra dirigida a una combinación farmacéutica según la reivindicación 5, en donde dicho anticuerpo consiste en una cadena ligera que comprende una secuencia de aminoácidos de SEQ ID NO: 62 y una cadena pesada que comprende una secuencia de aminoácidos de la SEQ ID NO: 66.
- La nueva reivindicación 7 ha sido añadida, y se encuentra dirigida a una combinación farmacéutica según la reivindicación 6, en donde el anticuerpo

que reconoce específicamente CD38 y melfalan son administrados simultáneamente o por separado.

- En cuanto a las reivindicaciones 1 a 5 atentamente señalamos que la reivindicación independiente 1 se ha modificado y se ha limitado a una combinación farmacéutica que comprende un anticuerpo anti-CD38 que tiene CDR de secuencias definidas. Por lo tanto, dichas reivindicaciones ahora definen los anticuerpos en términos de características estructurales.

Así, las reivindicaciones son ahora muy claras y precisas en el momento de señalar la naturaleza de la invención reivindicada y es evidente que las características técnicas esenciales de la invención están establecidas.

Por lo anterior, las objeciones formuladas por el Examinador en cuanto a la claridad y concisión del pliego reivindicatorio se ven superadas. En consecuencia, se solicita atentamente tener en cuenta este nuevo pliego reivindicatorio para el nuevo análisis de patentabilidad.

Con respecto a las objeciones realizadas por el señor Examinador, en la cual manifiesta que no se encuentra soporte del desarrollo de un producto que comprenda la combinación reclamada en la solicitud tal como una composición y se observa que el eje central de la solicitud es un método de tratamiento y no al desarrollo de un producto, respetuosamente manifestamos nuestro desacuerdo por las siguientes razones:

- En primer lugar, señalamos que la especificación de la página 1 a 7 se describen las características específicas de los anticuerpos que se componen de la combinación farmacéutica de la invención. En este sentido en la descripción página, 9, líneas 5-20, se especifica la función de la combinación farmacéutica de acuerdo con la invención, pero no describe un método de tratamiento. Adicionalmente, la página 10, línea 35 de la presente solicitud se refiere a la actividad de la combinación farmacéutica descrita en la reivindicación 1. Por lo tanto, estas especificaciones son necesarias para informar sobre las características específicas del producto que son novedosas e inventivas, pero no se refieren a un método de tratamiento.

En este sentido, teniendo en cuenta las anteriores aclaraciones y las modificaciones realizadas al pliego reivindicatorio, atentamente señalamos que las

objeciones anteriormente argumentadas, con respecto a la claridad y concisión del pliego reivindicatorio carecen de validez y por lo tanto, se consideran superadas.

3.2 Argumentos a favor de la falta de Unidad de Invención

El artículo 25 de la Decisión 486, hace referencia a:

*"**Artículo 25**.-La solicitud de patente sólo podrá comprender una invención o un grupo de invenciones relacionadas entre sí, de manera que conformen un único concepto inventivo."*

A este respecto respetuosamente manifestamos nuestro desacuerdo con el señor Examinador. De esta manera, atentamente indicamos que el concepto común inventivo de la presente invención se refiere a una combinación que comprende un anticuerpo anti-CD38 y melfalan, en el que el anticuerpo es capaz de matar a una célula CD38' por apoptosis, ADCC y CDC. En consecuencia, y como se discutirá más adelante afirmamos que este concepto inventivo es novedoso e inventivo en vista del arte previo.

3.3 Argumentos a favor de la falta de Nivel Inventivo

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."*

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:

En primer lugar, amablemente señalamos que las reivindicaciones de la presente solicitud se refieren a una combinación farmacéutica, y por lo tanto, una combinación farmacéutica no es lo mismo que una composición farmacéutica.

De esta manera, subrayamos que las agencias reguladoras como la FDA y la EMA distinguen entre combinaciones (combinaciones de 'dosis fijas' y 'combinaciones de productos', utilizando la nomenclatura FDA) y conjugados. Los dos no se consideran equivalentes y requieren autorizaciones diferentes, incluso si contienen los mismos agentes.

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

El Tositumomab es un anticuerpo monoclonal que se une al antígeno CD20 tumoral. El Yodo I 131 Tositumomab es un derivado de Tositumomab que ha sido unido covalentemente a Yodo-131, un isótopo radiactivo de yodo. Los mecanismos de acción del régimen de Bexxar se describen incluyendo la inducción de la apoptosis, CDC y ADCC mediante el anticuerpo y la muerte celular asociada con la radiación ionizante del isótopo (página 5 del documento adjunto o en línea).

Los anticuerpos monoclonales marcados y no marcados se consideran partes constituyentes separadas del producto de combinación. Sin embargo, notablemente el mismo Yodo I 131 Tositumomab, a pesar de que comprende un anticuerpo conjugado a

un isótopo radioactivo, cada uno de los cuales contribuye al efecto terapéutico a través de diferentes mecanismos, se considera un único constituyente en lugar de una "combinación" de dos componentes 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 no consideraría con respecto a un conjugado o una proteína de fusión como una "combinación farmacéutica" de ingredientes activos, sino como un solo ingrediente activo.

En segundo lugar, con respecto a los argumentos de nivel inventivo atentamente señalamos que el documento D2 se refiere a proteínas de fusión que comprenden al menos una porción de un agente de unión a CD38, tal como un anticuerpo anti-CD38, y una molécula de unión a ADN (página 2, líneas 10-13). Se describen además composiciones farmacéuticas que comprenden tanto un polipéptido de fusión como una molécula de ADN que codifica un agente citotóxico (página 3, líneas 22-24).

Aunque el melfalan está en la lista en la memoria descriptiva como un agente citotóxico (página 9, línea 28) su mención parece errónea para una persona versada en la materia ya que el melfalan es un derivado de fenilalanina de mecloretamina. Por lo tanto, no puede estar codificado por un ácido nucleico.

Por consiguiente, el documento D2 no se considera como un documento del estado de la técnica más cercano.

Por otro lado, el documento D1 describe proteínas de unión monoclonales anti-CD38, que incluyen anticuerpos, y su uso para el tratamiento del mieloma múltiple.

Así, el documento D1 sugiere la administración de una proteína de unión monoclonal anti-CD38 en combinación con un agente quimioterapéutico, que puede ser, entre otros, melfalan (página 176, línea 19).

Sin embargo, en el documento D1 los anticuerpos anti-CD38 no son anticuerpos que pueden matar las células $CD38^+$ por apoptosis, ADCC y CDC.

Los ejemplos describen anticuerpos anti-CD38 que son capaces de inducir ADCC de las células $CD38^+$ (es decir, los anticuerpos -003, -005 y -024; Ejemplo 5, página 205).

Sin embargo, sólo uno de estos anticuerpos fue capaz de inducir CDC en células Daudi (anticuerpo -005, Ejemplo 6, página 206), y ninguno de estos anticuerpos fueron capaces de inducir la apoptosis (Ejemplo 14, página 211).

Dado que el documento D1 no consigue revelar anticuerpos anti-CD38 de acuerdo con la presente invención, D1 no se considera como un documento del arte previo cercano a la presente invención.

Por otra parte, el documento D3 da a conocer inmuno-conjugados que comprenden anticuerpos anti-CD38 de acuerdo con la presente invención y melfalan. Por consiguiente, se considera que el documento D3 es el documento del arte previo más cercano.

La **diferencia técnica** entre la presente invención y el documento D3 es que D3 se refiere a un inmunoconjugado, en el que un anticuerpo anti-CD38 está ligado junto con un compuesto citotóxico, mientras que la presente invención se refiere a una combinación farmacéutica, en la que los compuestos individuales se separan físicamente.

El **efecto técnico** asociado con la combinación específica de la invención es el sorprendente efecto sinérgico.

El **problema técnico objetivo** resuelto por la presente invención es, por tanto, proporcionar un farmacéutico mejorado que comprende un anticuerpo anti-CD38 y melfalan.

Por su parte, el documento D3 describe inmunoconjugados, en el que los anticuerpos anti-CD38 y los compuestos citotóxicos están unidos entre sí. Aun así, el documento D3 no sugiere la combinación específica de anticuerpos anti-CD38 y melfalan en el que los compuestos individuales se separan físicamente.

Así, el documento D3 ni siquiera divulga la fabricación real de un conjugado que comprende un anticuerpo anti-CD38 y melfalan. D3 describe de la página 31 a 63, una lista de clases de agentes quimioterapéuticos que podrían, en teoría, estar vinculados a un anticuerpo anti-CD38. El melfalan es sólo uno de los numerosos ejemplos de los agentes quimioterapéuticos citados.

Por otra parte, el uso de conjugados anticuerpo-fármaco se da a conocer exclusivamente en el contexto de los conjugados, que comprenden un agente citotóxico (por ejemplo Melfalan) y un agente de unión a CD38 (por ejemplo, anticuerpos) que dirige el fármaco al tumor (D3: página 30, líneas 3 a 20):

> *'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 de manera que los conjugados estarán en contacto con la célula diana por un período de tiempo suficiente para permitir que la porción de fármaco citotóxico del conjugado actúe en la célula, y/o... sea internalizado por la célula... '*
> *'...El anticuerpo 38SB19 es capaz de reconocer específicamente CD38, y dirige el agente citotóxico a una célula anormal o a un tejido, tales como las células cancerosas, de una manera específica'*

A la luz de esto, la persona del oficio normalmente versada en la materia no habría estado motivada a hacer una combinación farmacéutica que comprende un anticuerpo anti-CD38 y melfalan, La descripción completa de D3 describe que los anticuerpos anti-CD38 funcionan para orientar la fracción de fármaco al sitio del tumor (ver anteriormente). Claramente, el anticuerpo anti-CD38 no podría servir para este propósito en una combinación farmacéutica de un anticuerpo anti-CD38 y melfalan, en el que melfalan no está ligado al anticuerpo.

Además, y más importante aún, no hay divulgación de ningún efecto sinérgico en D3. No hay ni siquiera ninguna sugerencia en el documento D3 que indique que el melfalan sería un agente particularmente adecuado o eficaz para ser usado en conjugación con anticuerpos anti-CD38 debido a cualquier efecto sinérgico entre dichos agentes.

Sin embargo, según el análisis realizado por el señor Examinador, considera que no se encontró ninguna evidencia que demuestra que la presente invención no describe un efecto sinérgico.

A este respecto, atentamente manifestamos nuestro desacuerdo. En este sentido, señalamos que la combinación de un anticuerpo anti-CD38 y melfalan tiene efectos

sorprendentes y beneficiosos, como se demuestra en los Ejemplos descritos en la descripción de la presente solicitud.

Así, la Tabla II muestra que el anti-CD38 (hu38SB19) sólo, retrasó el crecimiento del tumor por sólo 1,1 días en ratones implantados con mieloma LP1 múltiple humano avanzado. Esta diferencia no es estadísticamente significativa, por lo que el anticuerpo se considera inactivo contra el tumor en este modelo. Incluso la dosis más alta probada era inactiva en las condiciones ensayadas.

El melfalan en una dosis de 10 mg/kg/inyección (la dosis máxima tolerada) retrasó el crecimiento del tumor por 46,5 días y por 17,4 días en una dosis de 6,2 mg/kg/inyección.

En contraste, cuando el anti-CD38 (hu38SB19) y melfalan se combinaron, se observó un mayor retraso en el crecimiento del tumor. El melfalan en una dosis de 10 mg/kg/inyección en combinación con anti-CD38 retardó el crecimiento del tumor por 94,1 días y por 48,3 días a una dosis de 6,2 mg/kg/inyección en combinación con anti-CD38. Este es un aumento dramático en la eficacia, y uno el cual sería totalmente inesperado dada la falta de efecto de la sola CD38 en este modelo.

Para expresar los resultados en otra forma, el registro de muerte celular de melfalan en una dosis de 10 mg/kg/inyección fue 9,3, mientras que el anticuerpo anti-CD38 solo fue inactivo en las condiciones ensayadas. En contraste, el registro de muerte celular de melfalan a la misma dosis en combinación con anti-CD38 fue 18,9. Por lo tanto, se observó una duplicación en el registro de muerte celular con la combinación de agentes.

Por lo tanto, se puede observar a partir de estos resultados que el anti-CD38 y melfalan pueden actuar de forma sinérgica para disminuir el crecimiento del tumor, dando resultados mucho mejores en combinación en comparación con los que se esperaría a partir de los resultados obtenidos con cualquiera de los agentes por separado. Así, la combinación representa una mejora sustancial sobre los efectos exhibidos por los compuestos por sí solos, y es por lo tanto inventiva en vista de los documentos citados.

Por lo tanto, un técnico con conocimientos medios en la materia no estaba en condiciones de plantearse el problema, tampoco de resolverlo en la forma en que se

reivindica y tampoco de prever el resultado, por lo que la presente solicitud posee la altura inventiva para que se le conceda el privilegio solicitado.

En consecuencia de lo anterior, la invención de la presente invención tiene nivel inventivo en vista de los documentos D1 y D2 del estado de la técnica citados por el Examinador.

3.4 Concesión de Solicitudes equivalentes

Si bien entendemos y aceptamos que cada país es autónomo en la concesión o negación de los privilegios de patente, queremos resaltar el hecho que el análisis de los requisitos para el otorgamiento de esos derechos es prácticamente universal. La presente invención fue concedida por la Oficina de Patentes de Marruecos, patente No. MA32896 (B1).

3.5 Conclusión

Por todo lo anterior, el documento D1, el documento D2, el documento D3, o su combinación, no resultan anterioridades válidas capaces de afectar el nivel inventivo de la invención de la presente solicitud. Por lo tanto, 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. 13422, 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.

De otro lado, 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. <u>Anexos</u>

- Nuevo pliego reivindicatorio conformado por 7 reivindicaciones
- Anexo 1: Producto de Combinación Bexxar - FDA

Señor Director,

LUZ CLEMENCIA DE PAEZ
C.C. 35.456.344 de Usaquén
T.P.A. No. 23.555

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REIVINDICACIONES

1. Una combinación farmacéutica que comprende un anticuerpo que reconoce específicamente CD38 y al menos melfalan, en la que dicho anticuerpo es capaz de destruir una célula $CD38^+$ por apoptosis, por citotoxicidad mediada por células dependientes de anticuerpos (ADCC) y por citotoxicidad dependiente del complemento (CDC), y en donde dicho anticuerpo comprende por lo menos una cadena pesada y por lo menos una cadena liviana, en donde

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

(ii) dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 7, 8 y 9, y en donde dicha cadena liviana comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 10, 11 y 12;

(iii) dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 13, 15 y posiciones 50 a 66 de la SEQ ID NO: 66, y en donde dicha cadena liviana comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 16, 17 y 18;

(iv) dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 19, 20 y 21, y en donde dicha cadena liviana comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 22, 23 y 24;

(v) dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 25, 26 y 27, y en donde dicha cadena liviana

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comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 28, 29 y 30; o

(vi) dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: .31, 32 y 33, y en donde dicha cadena liviana comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 34, 35 y 36.

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

3. La combinación según 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 elegida entre el grupo de las SEQ ID NOS: 62 y 64.

4. La combinación según 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 elegida entre el grupo de las SEQ ID NOS: 68 y 70.

5. Una combinación farmacéutica que comprende un anticuerpo que reconoce específicamente CD38 y por lo menos melfalan, en la que dicho anticuerpo es capaz de destruir una célula CD38+ por apoptosis, por citotoxicidad mediada por células dependientes de anticuerpos (ADCC) y por citotoxicidad dependiente del complemento (CDC), y en donde dicho anticuerpo es un anticuerpo humanizado que comprende por lo menos una cadena pesada y por lo menos una cadena liviana, en donde dicha cadena pesada comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 13, 15 y posiciones 50 a 66 de la SEQ ID NO: 66, y en donde dicha cadena liviana comprende tres regiones determinantes de la complementariedad secuenciales que tienen las secuencias de aminoácidos representadas por las SEQ ID NOS: 16, 17 y 18.

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

- una cadena liviana que comprende una secuencia de aminoácidos de SEQ ID NO: 62; y
- una cadena pesada que comprende una secuencia de aminoácidos de SEQ ID NO: 66.

7. Una combinación farmacéutica según la reivindicación 5, en donde el anticuerpo que reconoce específicamente CD38 y melfalan son administrados simultáneamente o por separado.

NS

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

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

Tositumomab

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

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

Iodine I 131 Tositumomab

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

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

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

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}

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

Fraction of remaining radioactivity of Iodine-131 after x days $=2^{-(x/8.04)}$. Physical decay is presented in Table 2.

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

*(Calibration day)

CLINICAL PHARMACOLOGY

General Pharmacology

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).

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.

Pharmacokinetics/Pharmacodynamics

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

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

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

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 **Table 3**

166 **Estimated Radiation-Absorbed Organ Doses**

From Organ ROIs		BEXXAR mGy/MBq Median	BEXXAR mGy/MBq 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

CLINICAL STUDIES

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/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.

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.

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

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.

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

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

CONTRAINDICATIONS

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

PREGNANCY CATEGORY X

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

WARNINGS

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

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

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

The safety of the BEXXAR therapeutic regimen has not been established in patients with >25% lymphoma marrow involvement, platelet count <100,000 cells/mm^3 or neutrophil count <1,500 cells/mm^3.

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Pregnancy Category X: See CONTRAINDICATIONS; WARNINGS.

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

Pediatric Use: The safety and effectiveness of the BEXXAR therapeutic 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

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

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

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

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

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

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

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

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

Table 5 lists clinical adverse events that occurred in ≥5% of patients. Table 6 provides a detailed description of the hematologic toxicity.

509 **Table 5**
510 **Incidence of Clinical Adverse Experiences Regardless of Relationship to**
511 **Study Drug Occurring in ≥5% of the Patients Treated with BEXXAR**
512 **Therapeutic Regimen[a]**
513 **(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

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.

Table 6
Hematologic Toxicity[a] (N=230)

Endpoint	Values
Platelets	
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)
ANC	
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)
Hemoglobin	
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.

Delayed Adverse Reactions

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

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

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

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

Hypothyroidism: Twelve percent (27/230) of the patients included from the clinical studies had an elevated TSH level (8%) or no TSH level obtained (4%) prior to treatment. Of the 203 patients documented to be euthyroid at entry, 137 (67%) patients had at least one follow-up TSH value. The overall incidence of hypothyroidism, in the clinical study patients was 14% with cumulative incidences of 4.2% at 6 months and 8.1%, 12.6%, and 15.0% at 1, 2, and 4 years, respectively. New events have been observed up to 72 months post treatment. Twelve percent (117/990) of the patients included in clinical studies or the expanded 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 IgG_1 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

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

OVERDOSAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dose

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

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

Dosimetric step

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

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

Therapeutic step

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

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

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

    - Patients with ≥ 150,000 platelets/mm^3: The recommended dose is the activity of Iodine-131 calculated to deliver 75cGy total body irradiation and 35 mg Tositumomab, administered intravenously over 20 minutes.

    - Patients with NCI Grade 1 thrombocytopenia (platelet counts =100, 000 but <150,000 platelets/mm^3): the recommended dose is the

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

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

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

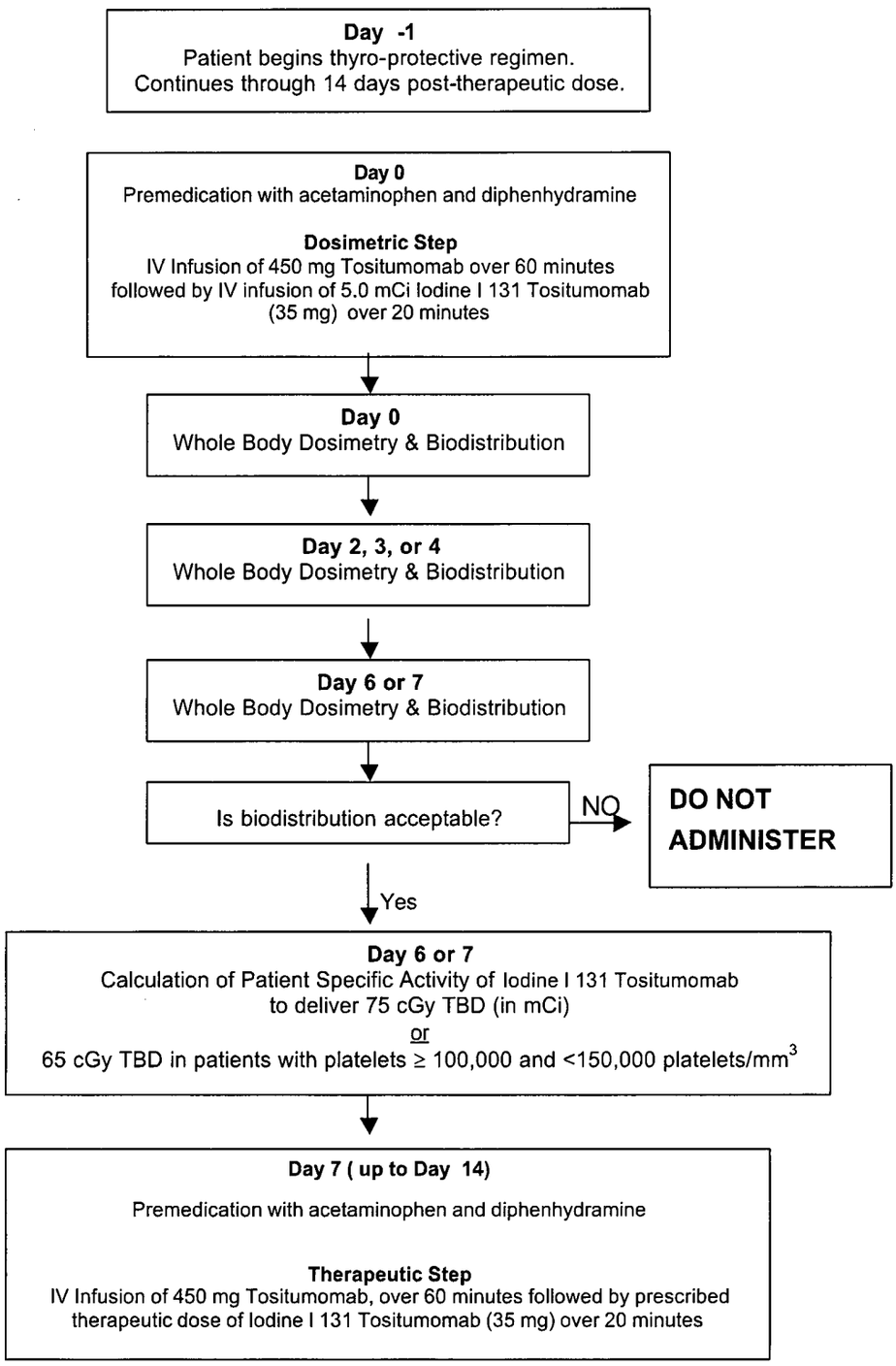
  Patients should not receive the dosimetric dose of Iodine I 131 Tositumomab if they have not yet received at least 3 doses of SSKI, three doses of Lugol's solution, or one dose of 130 mg potassium iodide tablet (at least 24 hours prior to the dosimetric dose).

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

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

Figure 1 shows an overview of the dosing schedule.

Figure 1
Dosing Schedule



PREPARATION OF THE BEXXAR THERAPEUTIC REGIMEN

GENERAL

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

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.

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.

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.

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

Preparation for the Dosimetric Step

Tositumomab Dose

Required materials not supplied

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

Method

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 solution by inverting/rotating the bag. DO NOT SHAKE.

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

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

Preparation of Iodine I 131 Tositumomab Dosimetric Dose

Required materials not supplied:

A. Lead shielding for preparation vial and syringe pump

B. Two 30 mL syringes with 18 gauge needles: one to withdraw the calculated volume of Iodine I 131 Tositumomab from the Iodine I 131 Tositumomab vial and one to withdraw the volume from the preparation vial into a syringe for administration.

C. One 20 mL syringe with attached needle, filled with 0.9% Sodium Chloride for Injection, USP

D. One 3 mL syringe with attached needle to withdraw Tositumomab from 35-mg vial

E. One sterile, 30 or 50 mL preparation vial

F. Two lead pots, both kept at room temperature. One pot is used to thaw the labeled antibody and the second pot is used to hold the preparation vial.

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.

9. Withdraw the entire contents from the preparation vial into a 30 mL syringe using a large bore needle (18 gauge).

10. Assay and record the activity.

Administration of the Dosimetric Step

Required materials not supplied:

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

B. One Primary IV infusion set

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

D. Two Secondary I.V infusion sets

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

F. One 3-way stopcock

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

H. One Infusion pump for Tositumomab infusion

I. One Syringe Pump for Iodine I 131 Tositumomab infusion

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

Tositumomab Infusion:

(See Figure 1 in the "**Workbook for Dosimetry Methodology and Administration Set-Up**" for diagrammatic illustration of the configuration of the infusion set components).

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

2. After priming the primary IV infusion set (Item B) and IV 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.

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

Iodine I 131 Tositumomab Dosimetric Infusion

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

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

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

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

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

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

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

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

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

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 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 dosimetric step. Calculate and record the dose delivered to the patient by subtracting the residual activity in the syringe and the 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.

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

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

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

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/mm^3.

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.

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

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

Preparation for the Therapeutic Step

Tositumomab Dose

Required materials not supplied

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

Method

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.

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

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

Preparation of Iodine I 131 Tositumomab Therapeutic Dose

Required materials not supplied:

A. Lead shielding for preparation vial and syringe pump

B. Two or four 30 mL syringes with 18 gauge needles: one or two to withdraw the calculated volume of Iodine I 131 Tositumomab from the Iodine I 131 Tositumomab vial(s) and one or two to withdraw the volume from the preparation vial into a syringe for administration.

C. One 20 mL syringe with attached needle filled with 0.9% Sodium Chloride for Injection, USP

D. One 3 mL sterile syringe with attached needle to draw up Tositumomab from the 35 mg vial

E. One sterile, 30 or 50 mL preparation vial

F. Two lead pots both kept at room temperature. One pot is used to thaw the labeled antibody, and the second pot is used to hold the preparation vial.

Method:

1. Allow approximately 60 minutes for thawing (at ambient temperature) of the Iodine I 131 Tositumomab therapeutic vial with appropriate lead shielding.
2. Calculate the dose of Iodine I 131 Tositumomab required (See **CALCULATION OF IODINE-131 ACTIVITY FOR THERAPEUTIC DOSE**)
3. Based on the activity concentration of the vial (see actual product specification sheet for each vial supplied in the therapeutic package), calculate the volume required for the Iodine I 131 Tositumomab activity required for the therapeutic dose.

4. Using one or more 30 mL syringes with an 18-gauge needle, withdraw the calculated volume from the Iodine I 131 Tositumomab vial.

5. Transfer this volume to the shielded preparation vial.

6. Assay the dose to ensure that the appropriate activity (mCi) has been prepared.

   a. If the assayed dose is the calculated dose (+/- 10%) needed for the therapeutic step, proceed with step 7.

   b. If the assayed dose does not contain the desired dose (+/- 10%), re-calculate the activity concentration of the Iodine I 131 Tositumomab at this time, based on the volume and the activity in the preparation vial. Re-calculate the volume required for an Iodine I 131 Tositumomab activity for the therapeutic dose. 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 the Iodine I 131 Tositumomab activity required for the therapeutic dose. Re-assay the preparation vial. Proceed to step 7.

7. Calculate the amount of Tositumomab protein contained in the solution of Iodine I 131 Tositumomab in the shielded preparation vial, based on the volume and protein concentration. (See product specification sheet.)

8. 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.

   Note: If the dose of Iodine I 131 Tositumomab requires the use of 2 vials of Iodine I 131 Tositumomab or the entire contents of a single vial of Iodine I 131 Tositumomab, there may be no need to add protein from the 35 mg vial of Tositumomab.

9. Using the 20 mL syringe containing 0.9% Sodium Chloride for Injection, USP, add a sufficient volume (if needed) to the shielded preparation vial to yield a final volume of 30 mL. Gently mix the solution.

10. Withdraw the entire volume from the preparation vial into a one or more sterile 30 mL syringes using a large bore needle (18 gauge).

11. Assay and record the activity.

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.

Required materials not supplied:

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

B. One Primary I.V. infusion set

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

D. Two Secondary I.V. infusion sets

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

F. One 3-way stopcock

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

H. One Infusion pump for Tositumomab infusion

I. One Syringe Pump for Iodine I 131 Tositumomab infusion

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

Tositumomab Infusion:

(See Figure 1 in the "**Workbook for Dosimetry Methodology and Administration Set-Up**" for diagrammatic illustration of the configuration of the infusion set components).

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).

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.

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

Iodine I 131 Tositumomab Therapeutic Infusion:

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

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

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

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

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

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

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

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

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

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.

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

Gamma Camera Set-Up

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

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

- Parallel hole collimator rated to at least 364 keV with a septal penetration for Iodine-131 of <7%
- Symmetric window (20-25%) centered on the 364 keV photo peak of Iodine-131 (314 - 414 keV)
- Matrix: minimum 128 x 128
- Scanning speed: 10-30 cm/minute

Counts from Calibrated Source for Quality Control

Camera sensitivity for Iodine-131 must be determined each day. Determination of the gamma camera's sensitivity is obtained by scanning a calibrated activity of Iodine-131 (e.g., 200–250 μCi in at least 20 mL of saline within a sealed pharmaceutical vial). The radioactivity of the Iodine-131 source is first determined using a NIST-traceable-calibrated clinical dose calibrator at the Iodine-131 setting.

Background Counts

The background count is obtained from a scan with no radioactive source. This should be obtained following the count of the calibrated source and just prior to obtaining the patient count.

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

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

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

Patient Total Body Counts

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

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

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

- **Count 1:** ***Within an hour of end of the infusion*** of the Iodine I 131 Tositumomab dosimetric dose prior to patient voiding.

- **Count 2:** Two to 4 days after administration of the Iodine I 131 Tositumomab dosimetric dose and immediately following patient voiding.

- **Count 3:** Six to 7 days after the administration of the Iodine I 131 Tositumomab dosimetric dose and immediately following patient voiding

Assessment of Biodistribution of Iodine I 131 Tositumomab

The biodistribution of Iodine I 131 Tositumomab should be assessed by 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.

Residence Time (hr)

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

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

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

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

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

Activity Hours (mCi hr)

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

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

Calculation of Iodine-131 Activity for the Therapeutic Dose

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

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

HOW SUPPLIED

TOSITUMOMAB DOSIMETRIC PACKAGING

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

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

NDC 67800-101-31

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

NDC 67800-111-10

TOSITUMOMAB THERAPEUTIC PACKAGING

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

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

NDC 67800-101-32

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

NDC 67800-121-10.

STABILITY AND STORAGE

TOSITUMOMAB

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

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

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

IODINE I 131 TOSITUMOMAB

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

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

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