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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 06-049473- -00009-0000

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

Fecha: 2011-02-07 17:01:22 Dep. 2020 DIR.NUEVASCR
Tra. 11 PATENTE/YII Eve: 378 FASENACIONALI
Act. 444 RESPUESTAREQUE Folios: 30

Trámite : 011
Evento : 378
Actuación : 444

Referencia : Expediente No. 06049473
Asunto : Solicitud de patente para: **PROCEDIMIENTO PARA LA PRODUCCIÓN DE UNA COMPOSICIÓN FARMACÉUTICA SÓLIDA DE ADMINISTRACIÓN ORAL**
Solicitante : BAYER SCHERING PHARMA AG
Clase : A61K 009/020, A61K 031/5377, A61K 9/20, A61P 007/002
Fecha solicitud : 23 de mayo de 2006

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. **14767** notificado por fijación en lista del 01 de octubre de 2010.

2. Mediante oficio No. **14767** 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 son las siguientes:

2.1 Nivel inventivo

Para la evaluación de este requerimiento, el Examinador ha citado los documentos D1: US 6514529 y D2: WO 2002/038126 considerando que la combinación de sus enseñanzas afecta el nivel inventivo de la presente solicitud.

Específicamente, el Examinador afirma que el experto en la materia habría recurrido a D1 para formular composiciones con una oxazolidinona como la de la presente solicitud y para optimizar su solubilidad, habría recurrido a las enseñanzas del documento D2.

3. Respuesta a las objeciones

Con el fin de superar la objeción que por falta de nivel inventivo formula el Examinador, se desea poner de presente la siguiente información:

3.1 Argumentos a favor del nivel inventivo de la solicitud

Siguiendo los lineamientos de la Decisión 486 y específicamente del artículo 18, se considera que una invención resulta inventiva cuando no es obvia a la luz de las enseñanzas del arte previo, para una persona medianamente versada en la materia.

De acuerdo con el Tribunal de Justicia de la Comunidad Andina: “Lo obvio es aquello que salta a la vista de manera clara y directa; lo que se encuentra o pone delante de los ojos, muy claro o que no tiene dificultad. Lo evidente consiste en la certeza clara y manifiesta de la que no se puede dudar; cierto, claro, patente y sin la menor duda (Ver proceso 13-IP-2010).

Consecuentemente, para que una anterioridad pueda afectar el nivel inventivo de una solicitud de patente, debe comprender enseñanzas claras y directas (obvias) para que la persona medianamente versada en la materia pueda considerarlas y aplicarlas para un fin determinado.

En este sentido, nos apartamos nuevamente de la opinión del Examinador respecto a la obviedad de la presente invención y consideramos que se está pasando por alto que la presente invención no sólo resulta no obvia sino que además aporta un efecto técnico inesperado y de relevancia en el campo tecnológico de la invención. Por lo tanto, solicitamos atentamente la reconsideración de la objeción por falta de nivel inventivo, en vista de lo siguiente:

3.1.1 La presente invención

La presente invención busca resolver el problema de proveer una composición farmacéutica sólida, oralmente administrable para el compuesto 5-cloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morfolinil)fenil]-1,3-oxazolidin-5-il)-metil}-2-tiofencarboxamida (rivaroxaban), la cual conlleva a la biodisponibilidad mejorada de la formulación obtenida (ver página 3, líneas 1 a 7 de la descripción). El objetivo también se relaciona con proveer un proceso para la producción de esta composición farmacéutica.

Este problema fue resuelto por medio de una composición oralmente administrable que contiene rivaroxaban en forma hidrofílica. Esta composición farmacéutica es producida por granulación húmeda.

La granulación húmeda consiste en un tratamiento especial de la superficie del compuesto activo (rivaroxaban) y el cual permite un comportamiento de absorción mejorado.

3.1.2 Anterioridad D1

Este documento se relaciona con derivados de oxazolidinona tales como linezolid. Una persona medianamente versada en la materia podría determinar que el compuesto linezolid tiene una solubilidad de 3 mg/ml (es decir, 3000 mg/l), de forma que no resulta escasamente soluble. El compuesto linezolid ha sido comercializado como una solución para administración intravenosa bajo la marca Zyvoxid® (solución de infusión 2 mg/ml, ver documento anexo 1: "Gebrauchsinformation: information für den anwender"). Esta formulación contiene como ingredientes adicionales glucosa monohidrato (Ph. Eur.) (un tipo de azúcar), citrato de sodio (Ph. Eur.) (E331), ácido cítrico anhidro (Ph. Eur.) (E330), 10% de ácido hidrocórico (E507) o hidróxido de sodio (E524) y agua, para fines de inyección. Esta formulación con su alta concentración de compuesto activo 2 mg linezolid/ml no hubiese sido posible si el linezolid fuera escasamente soluble.

De acuerdo con el anexo 2: "The Biopharmaceutics Classification System (BCS) Guidance" el linezolid está clasificado como un compuesto activo con alta solubilidad. Por el contrario, la solubilidad de rivaroxaban de sólo 7 mg/l es más de 400 veces menor que la de linezolid, cuya baja solubilidad está comprobada científicamente de acuerdo con el anexo 2.

Por su parte el anexo 3: "British Pharmacopoeia 2009" provee una descripción más detallada sobre la solubilidad: de acuerdo con este documento, el linezolid es "ligeramente soluble" mientras que el rivaroxaban es "prácticamente insoluble". Esto nuevamente confirma la opinión generalmente aceptada de que diferentes estructuras tienen propiedades totalmente diferentes, aún si tienen características estructurales individuales similares. Las propiedades de un compuesto son determinadas teniendo en cuenta las características estructurales en su totalidad y no se miden por componentes individuales. Esto es bien conocido por una persona medianamente versada en la materia.

El hecho de que dos compuestos activos tengan diferencias estructurales hace que la persona medianamente versada en la materia encuentre suficientes razones para no emplear el documento D1 con el fin de encontrar una formulación para el rivaroxaban.

Adicionalmente, debido a la solubilidad 400 veces mayor del linezolid respecto al rivaroxaban la persona medianamente versada en la materia no hubiese empleado la formulación revelada en D1, en vista de la escasa solubilidad del rivaexaban.

Por lo tanto, se considera que el objeto de la presente invención no resulta obvio para la persona medianamente versada en la materia, en vista de las enseñanzas específicas de dicho documento y los conocimientos en el momento del desarrollo de la invención.

3.1.3 Anterioridad D2

El documento D2 está dirigido al mejoramiento de la biodisponibilidad de un compuesto farmacéuticamente activo, suministrando el compuesto activo como una dispersión sólida en un derivado de un polisacárido. Específicamente, D2 revela la dispersión de un compuesto farmacéuticamente activo en acetato de hidroxipropil-metilcelulosa succinato (HPMCAS) (ver página 2, líneas 4 a 11 de D2).

La invención de D2 provee un proceso en donde el compuesto farmacéuticamente activo es eficientemente dispersado en una matriz de HPMCAS. Preferiblemente, el compuesto farmacéuticamente activo es molecularmente dispersado en la matriz de HPMCAS (ver página 6, líneas 8 a 12 de D2). Adicionalmente, en D2 el compuesto farmacéuticamente es resuelto durante el proceso para preparar la dispersión sólida en un líquido no acuoso. D2 menciona: "preferiblemente, el líquido es no acuoso y puede proveer una solución verdadera de HPMCAS con el compuesto farmacéuticamente activo" (página 7, líneas 13 a 15 de D2).

De otro lado el documento D2 menciona que el proceso incluye el recubrimiento de un núcleo con uno o más depósitos, que comprende hidroxipropil-metilcelulosa succinato (HPMCAS) y un compuesto farmacéuticamente activo escasamente soluble en agua por medio de la pulverización de la solución o dispersión en una partícula de núcleo suspendida en un gas dentro de una cámara (ver página 3, líneas 16 a 26 de D2). Partículas de núcleo quiere decir perlas de cristal de celulosa microcristalina. El proceso por lo tanto se centra realmente en el recubrimiento del medicamento y no se refiere a la granulación en absoluto.

La materia reivindicada en la presente solicitud resulta entonces completamente diferente respecto a la materia enseñada en el documento D2. En la presente invención el rivaroxaban es preparado en forma hidrofílica. La granulación húmeda mencionada en la presente invención se refiere a un tratamiento especial de la superficie del rivaroxaban. El rivaroxaban todavía está presente en forma cristalina y por lo tanto, no es una dispersión sólida. No resulta un objetivo de la presente invención recibir un tamaño de partícula menor y dispersar

molecularmente el compuesto activo en una matriz. Por el contrario, se busca tratar la superficie del rivaroxaban, así como prepararlo en forma hidrofílica. Durante la preparación de rivaroxaban en forma hidrofílica dicho compuesto activo es suspendido en agua y no disuelto en un líquido (ver ejemplos 1 a 5, tableta B). Adicionalmente, el recubrimiento de medicamentos no hace parte de la presente invención (pulverizar una solución o dispersión que contiene rivaroxaban en una partícula de núcleo (cristal) suspendida en un gas dentro de una cámara). La invención se centra en la granulación húmeda.

El documento D2 no revela el rivaroxaban ni tampoco el proceso de granulación húmeda para dicho compuesto, el cual está producido en su forma hidrofílica.

Por lo tanto, las enseñanzas del documento D2 difieren notablemente de la presente invención y no permitirían obtener de manera obvia el objeto reivindicado.

Adicionalmente, la combinación de las enseñanzas de los documentos D1 y D2 no solucionan los defectos ya mencionados, por lo que tampoco podría afectar el nivel inventivo de la presente invención.

3.1.4 Comentarios adicionales

El problema técnico objetivo de la presente invención se relaciona con proveer una composición farmacéutica de rivaroxaban con biodisponibilidad mejorada y no solamente una composición con liberación *in vitro* aceptable.

El problema de proveer una composición con una liberación *in vitro* aceptable sería resuelto con la fabricación de tabletas de rivaroxaban sin granulación previa. Tal como demuestran las tabletas A y B de la descripción, se provee una liberación *in vitro* similar. La tableta es obtenida de manera directa, pero el rivaroxaban no está presente en forma hidrofílica y es precisamente esta forma una característica técnica de la invención, la cual contribuye a resolver el problema que muestran los resultados de las tabletas A y B. La biodisponibilidad de la tableta B es incrementada en un 35%.

Por todo lo anterior, consideramos que ninguno de los documentos D3, D4 ó D5 (solos o en combinación) resultan anterioridades capaces de afectar el nivel inventivo de la presente invención y que la objeción en este sentido se ve superada.

4. Puesto que se han atendido a cabalidad las observaciones hechas por su Despacho sobre la presente solicitud de patente, atentamente solicito que se continúe su tramitación.

5. ANEXOS

- Anexo 1: "Gebrauchsinformation: information für den anwender"
- Anexo 2: "The Biopharmaceutics Classification System (BCS) Guidance"
- Anexo 3: "British Pharmacopoeia 2009"

Señor Director,


LUZ CLEMENCIA DE PÁEZ

C.C. 35.456.344 de Usaquén

T.P.A. No. 23.555

COLO-15846-845-014-9
COLO-14033-841-024-8
JMS\JMS\ID-186685\WPC15846
No. M-2011-186685\JMS

D4



Gebrauchsinformation Zyvoxid® 2 mg / ml Infusionslösung

GEBRAUCHSINFORMATION: INFORMATION FÜR DEN ANWENDER**Zyvoxid® 2 mg / ml Infusionslösung**

Wirkstoff: Linezolid

Lesen Sie die gesamte Packungsbeilage sorgfältig durch, bevor Sie dieses Arzneimittel verabreicht bekommen.

- Heben Sie die Packungsbeilage auf. Vielleicht möchten Sie diese später nochmals lesen.
- Wenn Sie weitere Fragen haben, wenden Sie sich an Ihren Arzt oder Apotheker.
- Dieses Arzneimittel wurde Ihnen persönlich verschrieben. Geben Sie es nicht an Dritte weiter. Es kann anderen Menschen schaden, auch wenn diese die gleichen Beschwerden haben wie Sie.
- Wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind, informieren Sie bitte Ihren Arzt oder Apotheker.

Diese Packungsbeilage beinhaltet:

1. Was ist Zyvoxid und wofür wird es angewendet?
2. Was müssen Sie vor der Behandlung mit Zyvoxid beachten?
3. Wie wird Zyvoxid verabreicht?
4. Welche Nebenwirkungen sind möglich?
5. Wie ist Zyvoxid aufzubewahren?
6. Weitere Informationen

1. WAS IST ZYVOXID UND WOFÜR WIRD ES ANGEWENDET?

Zyvoxid ist ein Antibiotikum aus der Gruppe der Oxazolidinone. Es wirkt, indem es das Wachstum bestimmter Bakterien (Krankheitskeime) hemmt, die Infektionen verursachen. Es wird zur Behandlung von Lungenentzündung oder von bestimmten Infektionen in oder unter der Haut eingesetzt. Ihr Arzt hat entschieden, dass Zyvoxid zur Behandlung Ihrer Infektion geeignet ist.

2. WAS MÜSSEN SIE VOR DER BEHANDLUNG MIT ZYVOXID BEACHTEN?

Sie dürfen nicht mit Zyvoxid behandelt werden,

- wenn Sie überempfindlich (allergisch) gegen Linezolid oder einen der sonstigen Bestandteile dieses Arzneimittels sind;
- wenn Sie Arzneimittel einnehmen oder innerhalb der letzten zwei Wochen eingenommen haben, die man als Monoaminoxidase-Hemmer (MAO-Hemmer z. B. Phenelzin, Isocarboxazid, Selegilin, Moclobemid) bezeichnet. Diese können zur Behandlung von Depressionen oder der Parkinson-Krankheit eingesetzt werden;
- wenn Sie stillen. Das kommt daher, weil es in die Muttermilch übergeht und den Säugling beeinträchtigen kann.

Zyvoxid kann für Sie nicht geeignet sein, wenn Sie eine der nachfolgenden Fragen mit „Ja“ beantworten. Besprechen Sie dies bitte mit Ihrem Arzt, da dieser dann vor und während Ihrer Behandlung Ihren Gesundheitszustand und den Blutdruck überprüfen muss, oder möglicher-



weise auch entscheidet, dass eine andere Behandlung für Sie besser geeignet ist.

Fragen Sie Ihren Arzt, wenn Sie sich nicht ganz sicher sind, ob diese Fragen auf Sie zutreffen.

- Leiden Sie an hohem Blutdruck (unabhängig davon, ob Sie dagegen Arzneimittel einnehmen oder nicht)?
- Wurde bei Ihnen eine Überfunktion der Schilddrüse festgestellt?
- Leiden Sie an einem Tumor des Nebennierenmarks (Phäochromozytom) oder an einem Karzinoid-Syndrom (ausgelöst durch Tumore des Hormonsystems mit Beschwerden wie Durchfall, Hautrötung oder pfeifende Atmung)?
- Leiden Sie an manischer Depression, schizoaffektiver Psychose, Gemütskrankungen oder an anderen seelischen Problemen?
- Nehmen Sie eines der folgenden Arzneimittel ein?
 - Abschwellende Erkältungs- oder Grippemittel, die Pseudoephedrin oder Phenylpropanolamin enthalten.
 - Arzneimittel zur Behandlung von Asthma, wie z. B. Salbutamol, Terbutalin oder Fenoterol.
 - Antidepressiva, die als trizyklische Antidepressiva bezeichnet werden, oder selektive Serotonin-Wiederaufnahmehemmer (SSRIs) z. B. Amitriptylin, Cipramil, Clomipramin, Doxulepin, Doxepin, Fluoxetin, Fluvoxamin, Imipramin, Lofepramin, Paroxetin oder Sertralin
 - Arzneimittel zur Behandlung von Migräne, wie Sumatriptan und Zolmitriptan.
 - Arzneimittel zur Behandlung von plötzlichen, schweren allergischen Reaktionen, wie z. B. Adrenalin (Epinephrin).
 - Arzneimittel, die Ihren Blutdruck erhöhen, wie z. B. Noradrenalin (Norepinephrin), Dopamin und Dobutamin.
 - Arzneimittel zur Behandlung von mäßigen bis starken Schmerzen, wie z. B. Pethidin.
 - Arzneimittel zur Behandlung von Angstzuständen, wie z. B. Buspiron

Besondere Vorsicht bei der Anwendung von Zyvoxid ist erforderlich

Bevor sie mit diesem Arzneimittel behandelt werden, sprechen Sie mit Ihrem Arzt, wenn Sie

- leicht einen Bluterguss bekommen oder bluten,
- an Blutarmut leiden,
- zu Infektionen neigen,
- in der Vergangenheit einmal Krampfanfälle hatten,
- an Leber- oder Nierenproblemen leiden, besonders, wenn Sie mit der Dialyse behandelt werden,
- an Durchfall leiden.

Sprechen Sie umgehend mit Ihrem Arzt, wenn es bei Ihnen während der Behandlung zu folgenden Erscheinungen kommt:

- Probleme mit Ihren Augen, wie z. B. verschwommenes Sehen, gestörtes Farbsehen, Schwierigkeiten, Details zu erkennen, oder wenn Ihr Sehfeld eingeschränkt ist
- Durchfall, besonders blutiger Durchfall, der möglicherweise zu einer Unterbrechung der Behandlung führen kann. Dies kann ein Anzeichen für eine Darmentzündung sein, die nach einer Antibiotika-Behandlung auftreten kann.
- Wiederholte Übelkeit oder Erbrechen, Bauchschmerzen oder schnelles Atmen.

Bei Anwendung von Zyvoxid mit anderen Arzneimitteln

Es besteht die Möglichkeit, dass sich Zyvoxid und bestimmte andere Arzneimittel manchmal gegenseitig beeinflussen, was zu Nebenwirkungen wie Veränderungen des Blutdrucks, der Körpertemperatur oder der Herzfrequenz führen kann

Informieren Sie Ihren Arzt, wenn Sie derzeit oder während der letzten 2 Wochen die folgenden Arzneimittel eingenommen haben, da Zyvoxid nicht angewendet werden darf,



wenn Sie diese Arzneimittel einnehmen oder vor Kurzem eingenommen haben (siehe auch in Abschnitt 2 „Sie dürfen nicht mit Zyvoxid behandelt werden“):

- Monoaminoxidase-Hemmer (MAO-Hemmer z. B. Phenelzin, Isocarboxazid, Selegilin, Moclobemid) Diese können zur Behandlung von Depressionen oder der Parkinson-Krankheit eingesetzt werden.

Informieren Sie Ihren Arzt ebenfalls, wenn Sie die folgenden Arzneimittel anwenden. Ihr Arzt kann sich trotzdem noch entscheiden, Zyvoxid bei Ihnen einzusetzen, wird aber vor und während der Behandlung Ihren allgemeinen Gesundheitszustand und Ihren Blutdruck überprüfen müssen. Andererseits kann Ihr Arzt auch zu der Entscheidung kommen, dass eine andere Behandlung besser für Sie geeignet ist.

- Abschwellende Erkältungs- oder Grippemittel, die Pseudoephedrin oder Phenylpropanolamin enthalten.
- Einige Arzneimittel zur Behandlung von Asthma, wie z. B. Salbutamol, Terbutalin oder Fenoterol.
- Bestimmte Antidepressiva, die als trizyklische Antidepressiva bekannt sind, oder selektive Serotonin-Wiederaufnahmehemmer (SSRIs), von denen es eine Vielzahl gibt, wie z. B. Amitriptylin, Cipramil, Clomipramin, Dosulepin, Doxepin, Fluoxetin, Fluvoxamin, Imipramin, Lofepramin, Paroxetin oder Sertralin.
- Arzneimittel zur Behandlung von Migräne, wie Sumatriptan und Zolmitriptan.
- Arzneimittel zur Behandlung von plötzlichen, schweren allergischen Reaktionen, wie Adrenalin (Epinephrin).
- Arzneimittel, die Ihren Blutdruck erhöhen, wie z. B. Noradrenalin (Norepinephrin) und Dopamin.
- Arzneimittel zur Behandlung von mäßigen bis starken Schmerzen, wie z. B. Pethidin.
- Arzneimittel zur Behandlung von Angstzuständen, wie z. B. Buspiron.
- Arzneimittel, die die Blutgerinnung hemmen, wie etwa Warfarin.

Bitte informieren Sie Ihren Arzt oder Apotheker, wenn Sie andere Arzneimittel einnehmen / anwenden bzw. vor kurzem eingenommen / angewendet haben, auch wenn es sich um nicht verschreibungspflichtige Arzneimittel handelt.

Bei Anwendung von Zyvoxid zusammen mit Nahrungsmitteln und Getränken

- Sie können Zyvoxid vor, während oder nach einer Mahlzeit anwenden.
- Vermeiden Sie den Genuß großer Mengen reifen Käses, Hefe- oder Sojabohnen-Extrakts (z. B. Sojasauce) und Alkohol (besonders Bier und Wein), weil dieses Arzneimittel mit einer als Tyramin bezeichneten Substanz, die natürlicherweise in einigen Nahrungsmitteln vorhanden ist, reagieren, und zu einer Erhöhung Ihres Blutdrucks führen kann.
- Wenn Sie nach dem Essen oder Trinken klopfende Kopfschmerzen verspüren, wenden Sie sich unverzüglich an Ihren Arzt oder Apotheker.

Schwangerschaft und Stillzeit

Die Wirkungen von Zyvoxid bei schwangeren Frauen sind nicht bekannt. Daher darf es in der Schwangerschaft nicht angewendet werden, es sei denn, dass es Ihr Arzt empfohlen hat. Informieren Sie Ihren Arzt, wenn Sie schwanger sind, glauben schwanger zu sein oder vorhaben, schwanger zu werden.

Wenn Sie mit Zyvoxid behandelt werden, dürfen Sie nicht stillen, da es in die Muttermilch übergeht und den Säugling schädigen könnte.



Verkehrstüchtigkeit und das Bedienen von Maschinen

Unter Zyvoxid können Sie sich schwindelig fühlen. Fahren Sie in diesem Fall kein Auto und bedienen Sie keine Maschine. Denken Sie daran, dass Ihre Fähigkeit ein Kraftfahrzeug zu lenken oder eine Maschine zu bedienen beeinträchtigt sein kann, wenn Sie sich nicht wohlfühlen.

Wichtige Informationen über bestimmte sonstige Bestandteile von Zyvoxid

Glukose

Ein Milliliter der Zyvoxid-Lösung enthält 45,7 mg Glukose (13,7 g pro Beutel). Bitte informieren Sie Ihren Arzt oder die Krankenschwester, wenn Sie Diabetiker sind.

Natrium

Ein Milliliter der Zyvoxid-Lösung enthält 0,38 mg Natrium (114 mg pro Beutel). Bitte informieren Sie Ihren Arzt oder die Krankenschwester, wenn Sie eine kontrollierte natriumarme Diät einhalten müssen.

3. WIE WIRD ZYVOXID VERABREICHT?

Erwachsene

Sie werden dieses Arzneimittel von einem Arzt oder dem medizinischen Fachpersonal infundiert (über eine Infusion in die Vene) bekommen.

Die Standarddosis für Erwachsene (ab 18 Jahre) beträgt 300 ml (600 mg Linezolid) zweimal täglich direkt in das Blut (intravenös) über einen Zeitraum von 30 bis 120 Minuten infundiert.

Wenn Sie wegen Ihrer Nieren dialysepflichtig sind, müssen Sie Zyvoxid nach der Dialyse erhalten.

Eine Behandlung dauert üblicherweise 10 bis 14 Tage. Sie kann sich jedoch auch über bis zu 28 Tage erstrecken. Die Sicherheit und Wirksamkeit dieses Arzneimittels wurde für Behandlungszeiten über 28 Tage hinaus nicht nachgewiesen. Ihr Arzt wird entscheiden, wie lange Sie behandelt werden müssen.

Während Sie mit Zyvoxid behandelt werden, sollte Ihr Arzt zur Kontrolle des Blutbilds Ihr Blut regelmäßig untersuchen.

Wenn Sie Zyvoxid über einen längeren Zeitraum als 28 Tage anwenden, sollte Ihr Arzt Ihre Sehkraft kontrollieren.

Kinder

Zur Behandlung von Kindern und Jugendlichen unter 18 Jahren wird Zyvoxid normalerweise nicht angewendet.

Wenn Sie eine größere Menge von Zyvoxid erhalten haben, als Sie sollten

Wenn Sie befürchten, dass Sie zu viel Zyvoxid erhalten haben, dann informieren Sie bitte umgehend Ihren Arzt oder die Krankenschwester.

Wenn eine Anwendung von Zyvoxid vergessen wurde

Da Sie dieses Arzneimittel unter enger Überwachung erhalten, ist es sehr unwahrscheinlich, dass eine Dosis vergessen wird. Wenn Sie befürchten, dass Sie eine Dosis nicht erhalten haben, dann informieren Sie bitte umgehend Ihren Arzt oder die Krankenschwester.



4. WELCHE NEBENWIRKUNGEN SIND MÖGLICH?

Wie alle Arzneimittel kann Zyvoxid Nebenwirkungen haben, die aber nicht bei jedem auftreten müssen

Wenn Sie bei der Behandlung mit Zyvoxid eine der folgenden Nebenwirkungen bemerken, informieren Sie sofort Ihren Arzt, das Pflegepersonal oder den Apotheker.

- Hautreaktionen, wie eine gerötete, wundte Haut mit Hautablösungen (Dermatitis), Hautausschlag, Juckreiz oder Schwellungen, hauptsächlich im Gesicht und Nacken. Hierbei kann es sich um eine allergische Reaktion handeln und es kann notwendig sein, dass die Anwendung von Zyvoxid beendet werden muss
- Probleme mit Ihren Augen, wie z. B. verschwommenes Sehen, gestörtes Farbsehen, Schwierigkeiten, Details zu erkennen, oder wenn Ihr Sehfeld eingeschränkt ist
- Durchfall, besonders blutiger Durchfall. Dies kann ein Anzeichen für eine Darmentzündung sein, die nach einer Antibiotika-Behandlung auftreten und möglicherweise zu einer Unterbrechung der Behandlung führen kann
- Wiederholte Übelkeit oder Erbrechen, Bauchschmerzen oder schnelles Atmen.

Taubheit, Kribbeln oder verschwommenes Sehen wurden von Patienten berichtet, die Zyvoxid länger als 28 Tage erhalten hatten. Wenn Sie Sehstörungen bei sich bemerken, müssen Sie Ihren Arzt so schnell wie möglich aufsuchen.

Andere Nebenwirkungen sind:

Häufige Nebenwirkungen (die voraussichtlich bei weniger als 1 von 10 Personen auftreten)

- Pilzinfektionen (hauptsächlich der Scheiden- oder Mundschleimhaut)
- Kopfschmerzen
- Metallischer Geschmack im Mund
- Durchfall, Übelkeit oder Erbrechen
- Veränderungen einiger Blutwerte, einschließlich solcher, die Ihre Nieren- oder Leberfunktion betreffen, oder Ihrer Blutzuckerwerte
- Unerklärliche Blutungen oder Blutergüsse durch Veränderungen in der Anzahl bestimmter Blutzellen, was zu einer Beeinflussung der Blutgerinnung oder zu einer Anämie führen kann

Gelegentliche Nebenwirkungen (die voraussichtlich bei weniger als 1 von 100 Personen auftreten)

- Entzündungen der Scheide oder der Genitalregion bei Frauen
- Veränderungen in der Anzahl bestimmter Blutzellen, was Ihre Infektabwehr beeinflussen kann
- Schlafstörungen
- Schwindel, Gefühlsstörungen wie Kribbeln oder Taubheitsgefühl
- Verschwommens Sehen
- Ohrgeräusche (Tinnitus)
- Erhöhter Blutdruck, Venenentzündung
- Verdauungsstörungen, Bauchschmerzen, Verstopfung
- Mundtrockenheit, wundte Mundschleimhaut, geschwollene, wundte oder verfärbte Zunge
- Hautausschlag
- Schmerzen an oder im Bereich der Stelle, an der die Infusion gegeben wurde
- Entzündung der Venen (einschließlich der Stelle, an der die Infusion gegeben wurde)
- Vermehrter Harndrang
- Fieber oder Schüttelfrost, starke Schmerzen



- Müdigkeits- oder Durstgefühl
- Entzündung der Bauchspeicheldrüse
- Vermehrtes Schwitzen
- Veränderungen von Eiweißen, Salzen oder Enzymen im Blut, die Ihre Nieren- oder Leberfunktion betreffen
- Verminderung der Anzahl bestimmter Blutzellen zur Abwehr von Infektionen

Weiterhin wurden Einzelfälle der folgenden Nebenwirkungen beobachtet

- Nierenversagen
- Vorübergehende ischämische Attacken (zeitweise Störung der Blutversorgung des Gehirns, was zu kurzzeitigen Beschwerden wie z. B. Ausfall des Sehvermögens, Schwächegefühl in den Armen und Beinen, undeutliche Sprache und Bewusstseinsverlust führen kann)
- Serotonin-Syndrom (Beschwerden wie Herzrasen, Verwirrtheit, verstärktes Schwitzen, Halluzinationen, unfreiwillige Bewegungen, Schüttelfrost und Zittern)
- Laktatazidose (mit Beschwerden wie wiederholte Übelkeit und Erbrechen, Bauchschmerzen, schnelles Atmen)
- Schwere Hauterkrankungen
- Krämpfe

Informieren Sie bitte Ihren Arzt oder Apotheker, wenn eine der aufgeführten Nebenwirkungen Sie erheblich beeinträchtigt oder Sie Nebenwirkungen bemerken, die nicht in dieser Gebrauchsinformation angegeben sind

5. WIE IST ZYVOXID AUFZUBEWAHREN?

Das Krankenhauspersonal wird sicherstellen, dass die Zyvoxid-Lösung nicht nach dem auf dem Beutel angegebenen Verfallsdatum verwendet wird und dass Sie es umgehend nach dem Öffnen verabreicht bekommen. Sie werden die Lösung darüberhinaus vor der Anwendung kontrollieren und nur eine klare Lösung ohne Partikel wird zum Einsatz kommen. Weiterhin werden sie dafür sorgen, dass die Lösung bis zu ihrer Anwendung zum Schutz vor Sonnenlicht in ihrer Schachtel und Folienverpackung und für Kinder unzugänglich aufbewahrt wird

6. WEITERE INFORMATIONEN

Was Zyvoxid Infusionslösung enthält

- Der Wirkstoff heißt Linezolid. Ein Milliliter der Lösung enthält 2 mg Linezolid.
- Die sonstigen Bestandteile sind Glukose-Monohydrat (Ph.Eur.) (eine Zuckerart), Natriumcitrat (Ph.Eur.)(E 331), wasserfreie Citronensäure (Ph Eur) (E 330), Salzsäure 10 % (E 507) oder Natriumhydroxid (E 524) und Wasser für Injektionszwecke.

Wie Zyvoxid aussieht und Inhalt der Packung

Bei Zyvoxid handelt es sich um eine klare Lösung in einzelnen Infusionsbeuteln zu 300 ml Lösung (600 mg Linezolid).

Packungen mit 1, 2, 5, 10, 20 oder 25 Infusionsbeuteln

Es werden möglicherweise nicht alle Packungsgrößen in den Verkehr gebracht



Gebrauchsinformation Zyvoxid® 2 mg / ml Infusionslösung

Pharmazeutischer Unternehmer

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Fax: 030 / 550054-51000

Hersteller

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Dieses Arzneimittel ist in den Mitgliedsstaaten des Europäischen Wirtschaftsraumes (EWR) unter den folgenden Bezeichnungen zugelassen:

Zyvoxil: Belgien, Dänemark, Deutschland, Estland, Finnland, Frankreich, Griechenland, Island, Italien, Lettland, Litauen, Luxemburg, Niederlande, Norwegen, Polen, Portugal, Slowakei, Slowenien, Spanien, Schweden, Tschechische Republik, Österreich, Zypern.
Zyvox: Irland, Malta, Ungarn.

Diese Gebrauchsinformation wurde zuletzt genehmigt im Oktober 2008.

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About FDA

The Biopharmaceutics Classification System (BCS) Guidance

Purpose of the BCS Guidance:

- Expands the regulatory application of the BCS and recommends methods for classifying drugs.
- Explains when a waiver for in vivo bioavailability and bioequivalence studies may be requested based on the approach of BCS.

Goals of the BCS Guidance:

- To improve the efficiency of drug development and the review process by recommending a strategy for identifying expendable clinical bioequivalence tests.
- To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
- To recommend methods for classification according to dosage form dissolution, along with the solubility and permeability characteristics of the drug substance.

According to the BCS, drug substances are classified as follows:

Class I - High Permeability, High Solubility
Class II - High Permeability, Low Solubility
Class III - Low Permeability, High Solubility
Class IV - Low Permeability, Low Solubility

CLASS BOUNDARIES

- A drug substance is considered HIGHLY SOLUBLE when the highest dose strength is soluble in < 250 ml water over a pH range of 1 to 7.5.
- A drug substance is considered HIGHLY PERMEABLE when the extent of absorption in humans is determined to be > 90% of an administered dose, based on mass-balance or in comparison to an intravenous reference dose.
- A drug product is considered to be RAPIDLY DISSOLVING when > 85% of the labeled amount of drug substance dissolves within 30 minutes using USP apparatus I or II in a volume of < 900 ml buffer solutions.

SOLUBILITY DETERMINATION

- pH-solubility profile of test drug in aqueous media with a pH range of 1 to 7.5.
- Shake-flask or titration method.
- Analysis by a validated stability-indicating assay.

PERMEABILITY DETERMINATION

Extent of absorption in humans:

- Mass-balance pharmacokinetic studies.
- Absolute bioavailability studies.

Intestinal permeability methods:

- *In vivo* intestinal perfusions studies in humans.
- *In vivo* or *In situ* intestinal perfusion studies in animals.
- *In vitro* permeation experiments with excised human or animal intestinal tissue.
- *In vitro* permeation experiments across epithelial cell monolayers.

DISSOLUTION DETERMINATION

- USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 rpm.
- Dissolution media (900 ml): 0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid.
- Compare dissolution profiles of test and reference products using a similarity factor (f_2).

BCS BIOWAIVER

- Rapid and similar dissolution.
- High solubility.
- High permeability.
- Wide therapeutic window.
- Excipients used in dosage form used previously in FDA approved IR solid dosage forms.

REQUEST FOR BIOWAIVERS

Data Supporting Rapid and Similar Dissolution

- A brief description of the IR products used for dissolution testing.
- Dissolution data obtained with 12 individual units of the test and reference products at each specified testing interval for each individual dosage unit. A graphic representation of the mean dissolution profiles for

the test and reference products in the three media.

- Data supporting similarity in dissolution profiles between the test and reference products in each of the three media, using the f_2 metric.

Data supporting High Permeability:

- For human pharmacokinetic studies, information on study design and methods used along with the pharmacokinetic data.
- For direct permeability methods, information supporting method suitability with a description of the study method, criteria for selection of human subjects, animals, or epithelial cell line, drug concentrations, description of the analytical method, method to calculate extent of absorption or permeability, and information on efflux potential (if appropriate).
- A list of selected model drugs along with data on the extent of absorption in humans used to establish method suitability, permeability values and class for each model drug, and a plot of the extent of absorption as a function of permeability with identification of the low/high permeability class boundary and selected internal standard.
- Permeability data on the test drug substance, the internal standards, stability information, data supporting passive transport mechanism where appropriate, and methods used to establish high permeability of the test drug substance.

Data supporting High Solubility:

- Description of test methods (analytical method, buffer composition).
- Information on chemical structure, molecular weight, nature of drug substance, dissociation constants.
- Test results summarized in a table with solution pH, drug solubility, volume to dissolve highest dose strength.
- Graphical representation of mean pH-solubility profile.

For further information visit the BCS guidance "[Waiver of *In-vivo* Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System.](#)"[PDF].

British Pharmacopoeia Volume I & II

British Pharmacopoeia 2009

Published on the recommendation of the Commission on Human Medicines pursuant to the Medicines Act 1968 and notified in draft to the European Commission in accordance with Directive 98/34/EEC

The monographs of the Sixth Edition of the European Pharmacopoeia (2007), as amended by Supplements 6.1 and 6.2 published by the Council of Europe, are reproduced either in this edition of the British Pharmacopoeia or in the associated edition of the British Pharmacopoeia (Veterinary).

See General Notices

Effective date: 1 January 2009

see Notices

London: The Stationery Office

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In respect of Northern Ireland:

THE DEPARTMENT OF HEALTH, SOCIAL SERVICES AND PUBLIC SAFETY

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First Published 2008

ISBN 978 0 11 322799 0

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British Pharmacopoeia Volume I & II
General Notices

Part II

General Notices Part II

The following general notices apply to the statements made in the monographs of the British Pharmacopoeia other than those reproduced from the European Pharmacopoeia and to the statements made in the Appendices of the British Pharmacopoeia other than when a method, test or other matter described in an appendix is invoked in a monograph reproduced from the European Pharmacopoeia.

Official Standards

The requirements stated in the monographs of the Pharmacopoeia apply to articles that are intended for medicinal use but not necessarily to articles that may be sold under the same name for other purposes. An article intended for medicinal use that is described by means of an official title must comply with the requirements of the relevant monograph. A formulated preparation must comply throughout its assigned shelf-life (period of validity). The subject of any other monograph must comply throughout its period of use.

A monograph is to be construed in accordance with any general monograph or notice or any appendix, note or other explanatory material that is contained in this edition and that is applicable to that monograph. All statements contained in the monographs, except where a specific general notice indicates otherwise and with the exceptions given below, constitute standards for the official articles. An article is not of pharmacopoeial quality unless it complies with all of the requirements stated. This does not imply that a manufacturer is obliged to perform all the tests in a monograph in order to assess compliance with the Pharmacopoeia before release of a product. The manufacturer may assure himself that a product is of pharmacopoeial quality by other means, for example, from data derived from validation studies of the manufacturing process, from in-process controls or from a combination of the two. Parametric release in appropriate circumstances is thus not precluded by the need to comply with the Pharmacopoeia. The general notice on Assays and Tests indicates that analytical methods other than those described in the Pharmacopoeia may be employed for routine purposes.

Requirements in monographs have been framed to provide appropriate limitation of potential impurities rather than to provide against all possible impurities. Material found to contain an impurity not detectable by means of the prescribed tests is not of pharmacopoeial quality if the nature or amount of the impurity found is incompatible with good pharmaceutical practice.

The status of any statement given under the headings Definition, Production, Characteristics, Storage, Labelling or Action and use is defined within the general notice relating to the relevant heading. In addition to any exceptions indicated by one of the general notices referred to above, the following parts of a monograph do not constitute standards: (a) a graphic or molecular formula given at the beginning of a monograph; (b) a molecular weight; (c) a Chemical Abstracts Service Registry Number; (d) any information given at the end of a monograph concerning impurities known to be limited by that monograph; (e) information in any annex to a monograph. Any statement containing the word 'should' constitutes non-mandatory advice or recommendation.

The expression 'unless otherwise justified and authorised' means that the requirement in question has to be met, unless a competent authority authorises a modification or exemption where justified in a particular case. The term 'competent authority' means the national, supranational or international body or organisation vested with the authority for making decisions concerning the issue in question. It may, for example, be a licensing authority or an official control laboratory. For a formulated preparation that is the subject of monograph in the British Pharmacopoeia any justified and authorised modification to, or exemption from, the requirements of the relevant general monograph of the European Pharmacopoeia is stated in the individual monograph. For example, the general monograph for Tablets requires that Uncoated Tablets, except for chewable tablets, disintegrate within 15 minutes; for Calcium Lactate Tablets a time of 30 minutes is permitted.

Many of the general monographs for formulated preparations include statements and requirements additional to those of the European Pharmacopoeia that are applicable to the individual monographs of the British Pharmacopoeia. Such statements and requirements apply to all monographs for that dosage form included in the Pharmacopoeia unless otherwise indicated in the individual monograph.

Where a monograph on a biological substance or preparation refers to a strain, a test, a method, a substance, etc., using

the qualifications 'suitable' or 'appropriate' without further definition in the text, the choice of such strain, test, method, substance, etc., is made in accordance with any international agreements or national regulations affecting the subject concerned.

Definition of Terms

Where the term "about" is included in a monograph or test it should be taken to mean approximately (fairly correct or accurate; near to the actual value).

Where the term "corresponds" is included in a monograph or test it should be taken to mean similar or equivalent in character or quantity

Where the term "similar" is included in a monograph or test it should be taken to mean alike though not necessarily identical.

Further qualifiers (such as numerical acceptance criteria) for the above terms are not included in the BP. The acceptance criteria for any individual case is set based on the range of results obtained from known reference samples, the level of precision of the equipment or apparatus used and the level of accuracy required for the particular application. The user should determine the variability seen in his/her own laboratory and set in-house acceptance criteria that he/she judges to be appropriate based on the local operating conditions.

Expression of Standards

Where the standard for the content of a substance described in a monograph is expressed in terms of the chemical formula for that substance an upper limit exceeding 100% may be stated. Such an upper limit applies to the result of the assay calculated in terms of the equivalent content of the specified chemical formula. For example, the statement 'contains not less than 99.0% and not more than 101.0% of $C_{20}H_{24}N_2O_2 \cdot HCl$ ' implies that the result of the assay is not less than 99.0% and not more than 101.0%, calculated in terms of the equivalent content of $C_{20}H_{24}N_2O_2 \cdot HCl$.

Where the result of an assay or test is required to be calculated with reference to the dried, anhydrous or ignited substance, the substance free from a specified solvent or to the peptide content, the determination of loss on drying, water content, loss on ignition, content of the specified solvent or peptide content is carried out by the method prescribed in the relevant test in the monograph.

Temperature

The Celsius thermometric scale is used in expressing temperatures.

Weights and Measures

The metric system of weights and measures is employed; SI Units have generally been adopted. Metric measures are required to have been graduated at 20°C and all measurements involved in the analytical operations of the Pharmacopoeia are intended, unless otherwise stated, to be made at that temperature. Graduated glass apparatus used in analytical operations should comply with Class A requirements of the appropriate International Standard issued by the International Organization for Standardization.

Atomic Weights

The atomic weights adopted are the values given in the Table of Relative Atomic Weights 2001 published by the International Union of Pure and Applied Chemistry (Appendix XXV)

Constant Weight

The term 'constant weight', used in relation to the process of drying or the process of ignition, means that two consecutive weighings do not differ by more than 0.5 mg, the second weighing being made after an additional period of drying or ignition under the specified conditions appropriate to the nature and quantity of the residue (1 hour is usually suitable).

Expression of Concentrations

The term 'per cent' or more usually the symbol '%' is used with one of four different meanings in the expression of concentrations according to circumstances. In order that the meaning to be attached to the expression in each instance is clear, the following notation is used:

Per cent w/w (% w/w) (percentage weight in weight) expresses the number of grams of solute in 100 g of product.

Per cent w/v (% w/v) (percentage weight in volume) expresses the number of grams of solute in 100 ml of product.

Per cent v/v (% v/v) (percentage volume in volume) expresses the number of millilitres of solute in 100 ml of product.

Per cent v/w (% v/w) (percentage volume in weight) expresses the number of millilitres of solute in 100 g of product.

Usually the strength of solutions of solids in liquids is expressed as percentage weight in volume, of liquids in liquids as percentage volume in volume and of gases in liquids as percentage weight in weight.

When the concentration of a solution is expressed as parts per million (p.p.m.), it means weight in weight, unless otherwise specified.

When the concentration of a solution is expressed as parts of dissolved substance in parts of the solution, it means parts by weight (g) of a solid in parts by volume (ml) of the final solution; or parts by volume (ml) of a liquid in parts by volume (ml) of the final solution; or parts by weight (g) of a gas in parts by weight (g) of the final solution.

When the concentration of a solution is expressed in molarity designated by the symbol M preceded by a number, it denotes the number of moles of the stated solute contained in sufficient Purified Water (unless otherwise stated) to produce 1 litre of solution.

Water Bath

The term 'water bath' means a bath of boiling water, unless water at some other temperature is indicated in the text. An alternative form of heating may be employed providing that the required temperature is approximately maintained but not exceeded.

Reagents

The reagents required for the assays and tests of the Pharmacopoeia are defined in appendices. The descriptions set out in the appendices do not imply that the materials are suitable for use in medicine.

Indicators

Indicators, the colours of which change over approximately the same range of pH, may be substituted for one another but in the event of doubt or dispute as to the equivalence of indicators for a particular purpose, the indicator specified in the text is alone authoritative.

The quantity of an indicator solution appropriate for use in acid-base titrations described in assays or tests is 0.1 ml unless otherwise stated in the text.

Any solvent required in an assay or test in which an indicator is specified is previously neutralised to the indicator, unless a blank test is prescribed.

Caution Statements

A number of materials described in the monographs and some of the reagents specified for use in the assays and tests of the Pharmacopoeia may be injurious to health unless adequate precautions are taken. The principles of good laboratory practice and the provisions of any appropriate regulations such as those issued in the United Kingdom in accordance with the Health and Safety at Work etc. Act 1974 should be observed at all times in carrying out the assays and tests of the Pharmacopoeia.

Attention is drawn to particular hazards in certain monographs by means of an italicised statement; the absence of such a statement should not however be taken to mean that no hazard exists.

Titles

Subsidiary titles, where included, have the same significance as the main titles. An abbreviated title constructed in accordance with the directions given in Appendix XXI A has the same significance as the main title.

Titles that are derived by the suitable inversion of words of a main or subsidiary title, with the addition of a preposition if appropriate, are also official titles. Thus, the following are all official titles: Aspirin Tablets, Tablets of Aspirin; Ginger

Tincture, Tincture of Ginger; Atropine Injection, Injection of Atropine.

A title of a formulated preparation that includes the full nonproprietary name of the active ingredient or ingredients, where this is not included in the title of the monograph, is also an official title. For example, the title Promethazine Hydrochloride Oral Solution has the same significance as Promethazine Oral Solution and the title Brompheniramine Maleate Tablets has the same significance as Brompheniramine Tablets.

Where the English title at the head of a monograph in the European Pharmacopoeia is different from that at the head of the text incorporated into the British Pharmacopoeia, an Approved Synonym has been declared in accordance with section 65(8) of the Medicines Act 1968. The titles and subsidiary titles, if any, are thus official titles. A cumulative list of such Approved Synonyms is provided in Appendix XXI B.

Where the names of pharmacopoeial substances, preparations and other materials occur in the text they are printed with capital initial letters and this indicates that materials of Pharmacopoeial quality must be used. Words in the text that name a reagent or other material, a physical characteristic or a process that is described or defined in an appendix are printed in italic type, for example, *methanol*, *absorbance*, *gas chromatography*, and these imply compliance with the requirements specified in the appropriate appendix.

Chemical Formulae

When the chemical composition of an official substance is known or generally accepted, the graphic and molecular formulae, the molecular weight and the Chemical Abstracts Service Registry Number are normally given at the beginning of the monograph for information. This information refers to the chemically pure substance and is not to be regarded as an indication of the purity of the official material. Elsewhere, in statements of standards of purity and strength and in descriptions of processes of assay, it is evident from the context that the formulae denote the chemically pure substances.

Where the absolute stereochemical configuration is specified, the International Union of Pure and Applied Chemistry (IUPAC) *R/S* and *E/Z* systems of designation have been used. If the substance is an enantiomer of unknown absolute stereochemistry the sign of the optical rotation, as determined in the solvent and under the conditions specified in the monograph, has been attached to the systematic name. An indication of sign of rotation has also been given where this is incorporated in a trivial name that appears on an IUPAC preferred list.

All amino acids, except glycine, have the *L*-configuration unless otherwise indicated. The three-letter and one-letter symbols used for amino acids in peptide and protein sequences are those recommended by the Joint Commission on Biochemical Nomenclature of the International Union of Pure and Applied Chemistry and the International Union of Biochemistry.

In the graphic formulae the following abbreviations are used:

Me	-CH ₃	Bu ^s -	CH(CH ₃)CH ₂ CH ₃
Et	-CH ₂ CH ₃	Bu ⁿ -	CH ₂ CH ₂ CH ₂ CH ₃
Pr ⁱ	-CH(CH ₃) ₂	Bu ^t -	C(CH ₃) ₃
Pr ⁿ	-CH ₂ CH ₂ CH ₃	Ph-	C ₆ H ₅
Bu ⁱ	-CH ₂ CH(CH ₃) ₂	Ac-	COCH ₃

Definition

Statements given under the heading Definition constitute an official definition of the substance, preparation or other article that is the subject of the monograph. They constitute instructions or requirements and are mandatory in nature.

Certain medicinal or pharmaceutical substances and other articles are defined by reference to a particular method of manufacture. A statement that a substance or article *is* prepared or obtained by a certain method constitutes part of the official definition and implies that other methods are not permitted. A statement that a substance *may be* prepared or obtained by a certain method, however, indicates that this is one possible method and does not imply that other methods are proscribed.

Additional statements concerning the definition of formulated preparations are given in the general notice on Manufacture of Formulated Preparations.

Production

Statements given under the heading Production draw attention to particular aspects of the manufacturing process but are not necessarily comprehensive. They constitute mandatory instructions to manufacturers. They may relate, for example, to source materials, to the manufacturing process itself and its validation and control, to in-process testing or to testing that is to be carried out by the manufacturer on the final product (bulk material or dosage form) either on selected batches or on each batch prior to release. These statements cannot necessarily be verified on a sample of the final product by an independent analyst. The competent authority may establish that the instructions have been followed, for example, by examination of data received from the manufacturer, by inspection or by testing appropriate samples.

The absence of a section on Production does not imply that attention to features such as those referred to above is not required. A substance, preparation or article described in a monograph of the Pharmacopoeia is to be manufactured in accordance with the principles of good manufacturing practice and in accordance with relevant international agreements and supranational and national regulations governing medicinal products.

Where in the section under the heading Production a monograph on a vaccine defines the characteristics of the vaccine strain to be used, any test methods given for confirming these characteristics are provided as examples of suitable methods. The use of these methods is not mandatory.

Additional statements concerning the production of formulated preparations are given in the general notice on Manufacture of Formulated Preparations.

Manufacture of Formulated Preparations

Attention is drawn to the need to observe adequate hygienic precautions in the preparation and dispensing of pharmaceutical formulations. The principles of good pharmaceutical manufacturing practice should be observed.

The Definition in certain monographs for pharmaceutical preparations is given in terms of the principal ingredients only. Any ingredient, other than those included in the Definition, must comply with the general notice on Excipients and the product must conform with the Pharmacopoeial requirements.

The Definition in other monographs for pharmaceutical preparations is presented as a full formula. No deviation from the stated formula is permitted except those allowed by the general notices on Colouring Agents and Antimicrobial Preservatives. Where additionally directions are given under the heading Extemporaneous Preparation these are intended for the extemporaneous preparation of relatively small quantities for short-term supply and use. When so prepared, no deviation from the stated directions is permitted. If, however, such a pharmaceutical preparation is manufactured on a larger scale with the intention that it may be stored, deviations from the stated directions are permitted provided that the final product meets the following criteria:

- (1) compliance with all of the requirements stated in the monograph;
- (2) retention of the essential characteristics of the preparation made strictly in accordance with the directions of the Pharmacopoeia.

Monographs for yet other pharmaceutical preparations include both a Definition in terms of the principal ingredients and, under the side-heading Extemporaneous Preparation, a full formula together with, in some cases, directions for their preparation. Such full formulae and directions are intended for the extemporaneous preparation of relatively small quantities for short-term supply and use. When so prepared, no deviation from the stated formula and directions is permitted. If, however, such a pharmaceutical preparation is manufactured on a larger scale with the intention that it may be stored, deviations from the formula and directions stated under the heading Extemporaneous Preparation are permitted provided that any ingredient, other than those included in the Definition, complies with the general notice on Excipients and that the final product meets the following criteria:

- (1) accordance with the Definition stated in the monograph;
- (2) compliance with all of the requirements stated in the monograph;
- (3) retention of the essential characteristics of the preparation made strictly in accordance with the formula and directions of the Pharmacopoeia.

In the manufacture of any official preparation on a large scale with the intention that it should be stored, in addition to

following any instruction under the heading Production, it is necessary to ascertain that the product is satisfactory with respect to its physical and chemical stability and its state of preservation over the claimed shelf-life. This applies irrespective of whether the formula of the Pharmacopoeia and any instructions given under the heading Extemporaneous Preparation are followed precisely or modified. Provided that the preparation has been shown to be stable in other respects, deterioration due to microbial contamination may be inhibited by the incorporation of a suitable antimicrobial preservative. In such circumstances the label states appropriate storage conditions, the date after which the product should not be used and the identity and concentration of the antimicrobial preservative.

Freshly and Recently Prepared

The direction, given under the heading Extemporaneous Preparation, that a preparation must be freshly prepared indicates that it must be made not more than 24 hours before it is issued for use. The direction that a preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15°C to 25°C.

Methods of Sterilisation

The methods of sterilisation used in preparing the sterile materials described in the Pharmacopoeia are given in Appendix XVIII. For aqueous preparations, steam sterilisation (heating in an autoclave) is the method of choice wherever it is known to be suitable. Any method of sterilisation must be validated with respect to both the assurance of sterility and the integrity of the product and to ensure that the final product complies with the requirements of the monograph.

Water

The term water used without qualification in formulae for formulated preparations means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled Purified Water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation.

Excipients

Where an excipient for which there is a pharmacopoeial monograph is used in preparing an official preparation it shall comply with that monograph. Any substance added in preparing an official preparation shall be innocuous, shall have no adverse influence on the therapeutic efficacy of the active ingredients and shall not interfere with the assays and tests of the Pharmacopoeia. Particular care should be taken to ensure that such substances are free from harmful organisms.

Colouring Agents

If in a monograph for a formulated preparation defined by means of a full formula a specific colouring agent or agents is prescribed, suitable alternatives approved in the country concerned may be substituted.

Antimicrobial Preservatives

When the term 'suitable antimicrobial preservative' is used it is implied that the preparation concerned will be effectively preserved according to the appropriate criteria applied and interpreted as described in the test for *efficacy of antimicrobial preservation* (Appendix XVI C). In certain monographs for formulated preparations defined by means of a full formula, a specific antimicrobial agent or agents may be prescribed; suitable alternatives may be substituted provided that their identity and concentration are stated on the label.

Characteristics

Statements given under the heading Characteristics are not to be interpreted in a strict sense and are not to be regarded as official requirements. Statements on taste are provided only in cases where this property is a guide to the acceptability of the material (for example, a material used primarily for flavouring). The status of statements on solubility is given in the general notice on Solubility.

Solubility Statements on solubility given under the heading Characteristics are intended as information on the approximate solubility at a temperature between 15°C and 25°C, unless otherwise stated, and are not to be considered as official requirements.

Statements given under headings such as Solubility in ethanol express exact requirements and constitute part of the standards for the substances under which they occur.

The following table indicates the meanings of the terms used in statements of approximate solubilities.

Descriptive term	Approximate volume of solvent in millilitres per gram of solute
very soluble	less than 1
freely soluble	from 1 to 10
soluble	from 10 to 30
sparingly soluble	from 30 to 100
slightly soluble	from 100 to 1000
very slightly soluble	from 1000 to 10 000
practically insoluble	more than 10 000

The term 'partly soluble' is used to describe a mixture of which only some of the components dissolve.

Identification

The tests described or referred to under the heading Identification are not necessarily sufficient to establish absolute proof of identity. They provide a means of verifying that the identity of the material being examined is in accordance with the label on the container.

Unless otherwise prescribed, identification tests are carried out at a temperature between 15°C and 25°C.

Reference spectra Where a monograph refers to an infrared reference spectrum, this spectrum is provided in a separate section of the Pharmacopoeia. A sample spectrum is considered to be concordant with a reference spectrum if the transmission minima (absorption maxima) of the principal bands in the sample correspond in position, relative intensities and shape to those of the reference. Instrumentation software may be used to calculate concordance with a previously recorded reference spectrum.

When tests for infrared absorption are applied to material extracted from formulated preparations, strict concordance with the specified reference spectrum may not always be possible, but nevertheless a close resemblance between the spectrum of the extracted material and the specified reference spectrum should be achieved.

Assays and Tests

The assays and tests described are the official methods upon which the standards of the Pharmacopoeia depend. The analyst is not precluded from employing alternative methods, including methods of micro-analysis, in any assay or test if it is known that the method used will give a result of equivalent accuracy. Local reference materials may be used for routine analysis, provided that these are calibrated against the official reference materials. In the event of doubt or dispute, the methods of analysis, the reference materials and the reference spectra of the Pharmacopoeia are alone authoritative.

Where the solvent used for a solution is not named, the solvent is Purified Water.

Unless otherwise prescribed, the assays and tests are carried out at a temperature between 15°C and 25°C.

A temperature in a test for Loss on drying, where no temperature range is given, implies a range of $\pm 2^\circ\text{C}$ about the stated value.

Visual comparative tests, unless otherwise prescribed, are carried out using identical tubes of colourless, transparent, neutral glass with a flat base. The volumes of liquid prescribed are for use with tubes 16 mm in internal diameter; tubes with a larger internal diameter may be used but the volume of liquid examined must be increased so that the depth of liquid in the tubes is not less than that obtained when the prescribed volume of liquid and tubes 16 mm in internal diameter are used. Equal volumes of the liquids to be compared are examined down the vertical axis of the tubes against a white background or, if necessary, against a black background. The examination is carried out in diffuse light.

Where a direction is given that an analytical operation is to be carried out 'in subdued light', precautions should be taken to avoid exposure to direct sunlight or other strong light. Where a direction is given that an analytical operation is to be

carried out 'protected from light', precautions should be taken to exclude actinic light by the use of low-actinic glassware, working in a dark room or similar procedures

For preparations other than those of fixed strength, the quantity to be taken for an assay or test is usually expressed in terms of the active ingredient. This means that the quantity of the active ingredient expected to be present and the quantity of the preparation to be taken are calculated from the strength stated on the label.

In assays the approximate quantity to be taken for examination is indicated but the quantity actually used must not deviate by more than 10% from that stated. The quantity taken is accurately weighed or measured and the result of the assay is calculated from this exact quantity. Reagents are measured and the procedures are carried out with an accuracy commensurate with the degree of precision implied by the standard stated for the assay.

In tests the stated quantity to be taken for examination must be used unless any divergence can be taken into account in conducting the test and calculating the result. The quantity taken is accurately weighed or measured with the degree of precision implied by the standard or, where the standard is not stated numerically (for example, in tests for Clarity and colour of solution), with the degree of precision implied by the number of significant figures stated. Reagents are measured and the procedures are carried out with an accuracy commensurate with this degree of precision.

The limits stated in monographs are based on data obtained in normal analytical practice; they take account of normal analytical errors, of acceptable variations in manufacture and of deterioration to an extent considered acceptable. No further tolerances are to be applied to the limits prescribed to determine whether the article being examined complies with the requirements of the monograph.

In determining compliance with a numerical limit, the calculated result of a test or assay is first rounded to the number of significant figures stated, unless otherwise prescribed. The last figure is increased by 1 when the part rejected is equal to or exceeds one half-unit, whereas it is not modified when the part rejected is less than a half-unit.

In certain tests, the concentration of impurity is given in parentheses either as a percentage or in parts per million by weight (ppm). In chromatographic tests such concentrations are stated as a percentage irrespective of the limit. In other tests they are usually stated in ppm unless the limit exceeds 500 ppm. In those chromatographic tests in which a secondary spot or peak in a chromatogram obtained with a solution of the substance being examined is described as corresponding to a named impurity and is compared with a spot or peak in a chromatogram obtained with a reference solution of the same impurity, the percentage given in parentheses indicates the limit for that impurity. In those chromatographic tests in which a spot or peak in a chromatogram obtained with a solution of the substance being examined is described in terms other than as corresponding to a named impurity (commonly, for example, as any (other) *secondary spot or peak*) but is compared with a spot or peak in a chromatogram obtained with a reference solution of a named impurity, the percentage given in parentheses indicates an impurity limit expressed in terms of a nominal concentration of the named impurity. In chromatographic tests in which a comparison is made between spots or peaks in chromatograms obtained with solutions of different concentrations of the substance being examined, the percentage given in parentheses indicates an impurity limit expressed in terms of a nominal concentration of the medicinal substance itself. In some monographs, in particular those for certain formulated preparations, the impurity limit is expressed in terms of a nominal concentration of the active moiety rather than of the medicinal substance itself. Where necessary for clarification the terms in which the limit is expressed are stated within the monograph.

In all cases where an impurity limit is given in parentheses, the figures given are approximations for information only; conformity with the requirements is determined on the basis of compliance or otherwise with the stated test.

The use of a proprietary designation to identify a material used in an assay or test does not imply that another equally suitable material may not be used.

Biological Assays and Tests

Methods of assay described as Suggested methods are not obligatory, but when another method is used its precision must be not less than that required for the Suggested method.

For those antibiotics for which the monograph specifies a microbiological assay the potency requirement is expressed in the monograph in International Units (IU) per milligram. The material is not of pharmacopoeial quality if the upper fiducial limit of error is less than the stated potency. For such antibiotics the required precision of the assay is stated in the monograph in terms of the fiducial limits of error about the estimated potency.

For other substances and preparations for which the monograph specifies a biological assay, unless otherwise stated, the

precision of the assay is such that the fiducial limits of error, expressed as a percentage of the estimated potency, are within a range not wider than that obtained by multiplying by a factor of 10 the square roots of the limits given in the monograph for the fiducial limits of error about the stated potency.

In all cases fiducial limits of error are based on a probability of 95% ($P = 0.95$).

Where the biological assay is being used to ascertain the purity of the material, the stated potency means the potency stated on the label in terms of International Units (IU) or other Units per gram, per milligram or per millilitre. When no such statement appears on the label, the stated potency means the fixed or minimum potency required in the monograph. This interpretation of stated potency applies in all cases except where the monograph specifically directs otherwise.

Where the biological assay is being used to determine the total activity in the container, the stated potency means the total number of International Units (IU) or other Units stated on the label or, if no such statement appears, the total activity calculated in accordance with the instructions in the monograph.

Wherever possible the primary standard used in an assay or test is the respective International Standard or Reference Preparation established by the World Health Organization for international use and the biological activity is expressed in International Units (IU).

In other cases, where Units are referred to in an assay or test, the Unit for a particular substance or preparation is, for the United Kingdom, the specific biological activity contained in such an amount of the respective primary standard as the appropriate international or national organisation indicates. The necessary information is provided with the primary standard.

Unless otherwise directed, animals used in an assay or a test are healthy animals, drawn from a uniform stock, that have not previously been treated with any material that will interfere with the assay or test. Unless otherwise stated, guinea-pigs weigh not less than 250 g or, when used in systemic toxicity tests, not less than 350 g. When used in skin tests they are white or light coloured. Unless otherwise stated, mice weigh not less than 17 g and not more than 22 g.

Certain of the biological assays and tests of the Pharmacopoeia are such that in the United Kingdom they may be carried out only in accordance with the Animals (Scientific Procedures) Act 1986. Instructions included in such assays and tests in the Pharmacopoeia, with respect to the handling of animals, are therefore confined to those concerned with the accuracy and reproducibility of the assay or test.

Reference Substances and Reference Preparations

Certain monographs require the use of a reference substance, a reference preparation or a reference spectrum. These are chosen with regard to their intended use as prescribed in the monographs of the Pharmacopoeia and are not necessarily suitable in other circumstances.

Any information necessary for proper use of the reference substance or reference preparation is given on the label or in the accompanying leaflet or brochure. Where no drying conditions are stated in the leaflet or on the label, the substance is to be used as received. No certificate of analysis or other data not relevant to the prescribed use of the product are provided. The products are guaranteed to be suitable for use for a period of three months from dispatch when stored under the appropriate conditions. The stability of the contents of opened containers cannot be guaranteed. The current lot is listed in the BP Laboratory website catalogue. Additional information is provided in Supplementary Chapter III E.

Chemical Reference Substances The abbreviation BPCRS indicates a Chemical Reference Substance established by the British Pharmacopoeia Commission. The abbreviation CRS or EPCRS indicates a Chemical Reference Substance established by the European Pharmacopoeia Commission. Some Chemical Reference Substances are used for the microbiological assay of antibiotics and their activity is stated, in International Units, on the label or on the accompanying leaflet and defined in the same manner as for Biological Reference Preparations.

Biological Reference Preparations The majority of the primary biological reference preparations referred to are the appropriate International Standards and Reference Preparations established by the World Health Organisation. Because these reference materials are usually available only in limited quantities, the European Pharmacopoeia has established Biological Reference Preparations (indicated by the abbreviation BRP or EPBRP) where appropriate. Where applicable, the potency of the Biological Reference Preparations is expressed in International Units. For some Biological Reference Preparations, where an international standard or reference preparation does not exist, the potency is expressed in European Pharmacopoeia Units.

Storage

Statements under the side-heading Storage constitute non-mandatory advice. The substances and preparations described in the Pharmacopoeia are to be stored under conditions that prevent contamination and, as far as possible, deterioration. Unless otherwise stated in the monograph, the substances and preparations described in the Pharmacopoeia are kept in well-closed containers and stored at a temperature not exceeding 25°. Precautions that should be taken in relation to the effects of the atmosphere, moisture, heat and light are indicated, where appropriate, in the monographs. Further precautions may be necessary when some materials are stored in tropical climates or under other severe conditions.

The expression 'protected from moisture' means that the product is to be stored in an airtight container. Care is to be taken when the container is opened in a damp atmosphere. A low moisture content may be maintained, if necessary, by the use of a desiccant in the container provided that direct contact with the product is avoided.

The expression 'protected from light' means that the product is to be stored either in a container made of a material that absorbs actinic light sufficiently to protect the contents from change induced by such light or in a container enclosed in an outer cover that provides such protection or stored in a place from which all such light is excluded.

The expression 'tamper-evident container' means a closed container fitted with a device that reveals irreversibly whether the container has been opened, whereas, the expression 'tamper-proof container' means a closed container in which access to the contents is prevented under normal conditions of use. The two terms are considered to be synonymous by the European Pharmacopoeia Commission.

Labelling

The labelling requirements of the Pharmacopoeia are not comprehensive, and the provisions of regulations issued in accordance with the requirements of the territory in which the medicinal product is to be used should be met.

Licensed medicines intended for use within the United Kingdom must comply with the requirements of the Medicines Act 1968 and EU Directive 2001/83/EC, Title V (as amended) in respect of their labelling and package leaflets, together with those regulations for the labelling of hazardous materials.

Best practice guidance on the labelling and packaging of medicines for use in the United Kingdom advises that certain items of information are deemed critical for the safe use of the medicine (see MHRA Guidance Note No. 25: Best Practice Guidance on Labelling and Packaging of Medicines). Further information and guidance on the labelling of medicinal products can be found in Supplementary Chapter I G.

Such matters as the exact form of wording to be used and whether a particular item of information should appear on the primary label and additionally, or alternatively, on the package or exceptionally in a leaflet are, in general, outside the scope of the Pharmacopoeia. When the term 'label' is used in Labelling statements of the Pharmacopoeia, decisions as to where the particular statement should appear should therefore be made in accordance with relevant legislation.

The label of every official formulated preparation other than those of fixed strength also states the content of the active ingredient or ingredients expressed in the terms required by the monograph. Where the content of active ingredient is required to be expressed in terms other than the weight of the official medicinal substance used in making the formulation, this is specifically stated under the heading Labelling. Unless otherwise stated in the monograph, the content of the active ingredient is expressed in terms of the official medicinal substance used in making the formulation.

These requirements do not necessarily apply to unlicensed preparations supplied in accordance with a prescription. For requirements for unlicensed medicines see the general monograph on Unlicensed Medicines.

Action and Use

The statements given under this heading in monographs are intended only as information on the principal pharmacological actions or the uses of the materials in medicine or pharmacy. It should not be assumed that the substance has no other action or use. The statements are not intended to be binding on prescribers or to limit their discretion.

Crude Drugs; Traditional Herbal and Complementary Medicines

Herbal and complementary medicines are classed as medicines under European Directive 2001/83/EC as amended. It is emphasised that, although requirements for the quality of the material are provided in the monograph to assist the registration scheme by the UK Licensing Authority, the British Pharmacopoeia Commission has not assessed the safety or

efficacy of the material in traditional use

Monograph Title For traditional herbal medicines, the monograph title is a combination of the established English name together with a description of use. Monographs for the material that has not been processed (the herbal drug) and the processed material (the herbal drug preparation) are published where possible. To distinguish between the two, the word 'Processed' is included in the relevant monograph title. The acronym 'THM' is used in the title to indicate 'Traditional Herbal Medicine'. This refers to the general use of the material that has not been processed. Where the acronym 'THMP' is used, this indicates the use of the processed herb in a 'Traditional Herbal Medicinal Product'.

Definition Under the heading Definition, the botanical name together with any synonym is given. Where appropriate, for material that has not been processed, information on the collection/harvesting and/or treatment/drying of the whole herbal drug may be given. For processed materials, the method of processing, where appropriate, will normally be given in a separate section.

Characteristics References to odour are included only where this is highly characteristic. References to taste are not included.

Control methods Where applicable, the control methods to be used in monographs are:

- (a) macroscopical and microscopical descriptions and chemical/chromatographic tests for identification
- (b) tests for absence of any related species
- (c) microbial test to assure microbial quality
- (d) tests for inorganic impurities and non-specific purity tests, including extractive tests, sulphated ash and heavy metals where appropriate
- (e) test for Loss on drying or Water
- (f) wherever possible, a method for assaying the active constituent(s) or suitable marker constituent(s).

The macroscopical characteristics include those features that can be seen by the unaided eye or by the use of a hand lens. When two species/subspecies of the same plant are included in the Definition, individual differences between the two are indicated where possible.

The description of the microscopical characteristics of the powdered drug includes information on the dominant or the most specific characters. Where it is considered to be an aid to identification, illustrations of the powdered drug may be provided.

The following aspects are controlled by the general monograph for Herbal Drugs, that is, they are required to be free from moulds, insects, decay, animal matter and animal excreta. Unless otherwise prescribed the amount of foreign matter is not more than 2% w/w. Microbial contamination should be minimal.

In determining the content of the active principle(s) or the suitable marker principle(s) measurements are made with reference to the dried or anhydrous herbal drug. In the tests for Acid-insoluble ash, Ash, Extractive soluble in ethanol, Loss on drying, Sulphated ash, Water, Water-soluble ash and Water-soluble extractive of herbal drugs, the calculations are made with reference to the herbal drug that has not been specifically dried unless otherwise prescribed in the monograph.

Homoeopathic Medicines

Homoeopathic medicines are classed as medicines under European Directive 2001/83/EC as amended. It is emphasised that, although requirements for the quality of the material are provided in the monograph to assist the simplified registration scheme by the UK Licensing Authority, the British Pharmacopoeia Commission has not assessed the safety or efficacy of the material in use.

The statements under Crude Drugs; Traditional Herbal and Complementary Medicines are also applicable to homoeopathic stocks and mother tinctures.

Specific BP monographs for homoeopathic medicines only apply to homoeopathic stocks and mother tinctures. These monographs also include general statements on the methods of preparation of homoeopathic stocks and mother tinctures. Specifications have not been set for final homoeopathic products due to the high dilution used in their preparation and the subsequent difficulty in applying analytical methodology.

Identification tests rely predominantly on macroscopical description and thin-layer chromatography. Tests for foreign matter are included when there is the hazard of contamination.

Unlicensed Medicines

The General Monograph for Unlicensed Medicines applies to those formulations used in human medicine that are prepared under a manufacturing special licence or prepared extemporaneously under the supervision of a pharmacist, whether or not there is a published monograph for the specific dosage form.

An article intended for medicinal use that is described by means of an official title must comply with the requirements of the relevant monograph. A formulated preparation must comply throughout its assigned shelf-life (period of validity). The subject of any other monograph must comply throughout its period of use.

Unlicensed medicines that are prepared under a manufacturing special licence comply with the requirements of the general monograph and, where applicable, the requirements of the individual monograph for the specific dosage form.

Unlicensed medicines prepared extemporaneously under the supervision of a pharmacist comply with the requirements of the general monograph and, where applicable, the requirements of the individual monograph for the specific dosage form. While it is expected that extemporaneous preparations will demonstrate pharmacopoeial compliance when tested, it is recognised that it might not be practicable to carry out the pharmacopoeial tests routinely on such formulations. In the event of doubt or dispute, the methods of analysis, the reference materials and the reference spectra of the Pharmacopoeia are alone authoritative.

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