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PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Dilizolen 2 mg/ml, solution for infusion Helm AG, Germany

Linezolid

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2505/001/DC
Registration number in the Netherlands: RVG 111095

27 February 2014

Pharmacotherapeutic group:	Other antibacterials
ATC code:	J01X X08
Route of administration:	intravenous
Therapeutic indication:	community acquired pneumonia and nosocomial Pneumonia and complicated skin and soft tissue infections
Prescription status:	prescription only
Date of authorisation in NL:	25 February 2013
Concerned Member States:	Decentralised procedure with DE
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Dilizolen 2 mg/ml, solution for infusion, from Helm AG, Germany. The date of authorisation was on 25 February 2013 in the Netherlands.

The product is indicated for:

- the treatment of community acquired pneumonia and nosocomial pneumonia when known or suspected to be caused by susceptible Gram positive bacteria. In determining whether Dilizolen 2 mg/ml, solution for infusion is an appropriate treatment, the results of microbiological tests or information on the prevalence of resistance to antibacterial agents among Gram positive bacteria should be taken into consideration (see section 5.1 for the appropriate organisms).
- the treatment of complicated skin and soft tissue infections only when microbiological testing has established that the infection is known to be caused by susceptible Gram positive bacteria.

A comprehensive description of the indications and posology is given in the SPC.

Linezolid is a synthetic, antibacterial agent that belongs to a new class of antimicrobials, the oxazolidinones. It has in vitro activity against aerobic Gram positive bacteria and anaerobic micro-organisms. Linezolid selectively inhibits bacterial protein synthesis via a unique mechanism of action. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex which is an essential component of the translation process.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Zyvoxid 2 mg/ml, solution for infusion (NL License RVG 26567) which has been registered in The Netherlands by Pfizer B.V. since 2001 (original product). In addition, reference is made to Zyvoxid authorisation in the concerned member state (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Dilizolen 2 mg/ml, solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice

The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is linezolid, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is a white to off white crystalline powder, witch is freely soluble in chloroform and sparingly soluble in methanol. The product exhibits polymorphism and the polymorphic form manufactured is Form-III. The product is an optically active compound and exhibits isomerism.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process
The manufacturing process consists of several stages, such as purification and drying.
No class I solvents or heavy metal catalysts are used. The manufacturing process for Linezolid is described in detail in the DMF.

Quality control of drug substance
The drug substance specification has been established in-house by the DMF-holder. The specifications are acceptable in line with the Ph.Eur., the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three batches. In general, the analytical methods are adequately described and validated.

Stability of drug substance
Stability data on the active substance have been provided for six production scaled batches stored at 25°C/60%RH (36 or 6 months) and 40°C/75%RH (6 months). For the tested parameters, no clear trends could be observed under long-term or accelerated conditions. The results remain within the proposed limits. Based on the provided stability data, the proposed retest period of 36 months is justified.
The proposed storage condition "This medicinal product does not require any special temperature storage conditions; keep the polyethylene container in the outer carton in order to protect from light". is justified.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Dilizolen 2 mg/ml is an isotonic, clear colourless solution for infusion.

The solution for infusion is packed in single low-density polyethylene infusion bags containing
300 ml (600mg linezolid) of solution.

The excipients are: citric acid anhydrous (E 330), sodium hydroxide (E 524; for pH-adjustment), glucose monohydrate, sodium citrate (E 331), hydrochloric acid (E 507; for pH-adjustment) and water for injection.

The excipients and packaging are usual for this type of dosage form.

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and their functions explained. All excipients used are well known and are the same as in the reference product. The choices of the packaging and manufacturing process are justified. In accordance with the guideline on bioequivalence the applicant provided adequate justification for not performing bioequivalence studies.

Compatibility with 5% glucose, 0.9% sodium chloride and Ringer-lactate solution for a period of 3 hours at 25 – 26 °C has been demonstrated.

Manufacturing process
The adopted manufacturing process for linezolid 2 mg/ml solution for infusion is a non standard process as aseptic filtration is used. The manufacturing process for Linezolid 2 mg/ml solution for infusion includes dispensing of the raw materials, preparation of the solution, sterile filtration, filling into blow filled seal bags and labelling and packaging.
Adequate in-process controls are laid down. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for three full scale batches.

Control of excipients
The excipients comply with their Ph.Eur monographs. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance of solution, clarity of solution, pH, extractable volume, visible and sub-visible particles, identification by HPLC and UV, assay, purity tests, sterility test and bacterial endotoxins.
The release and shelf-life limits for the tests are the same except for a impurity at RRT and total impurities.
The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on 3 production scaled batches, demonstrating compliance with the release specifications.

Stability of drug product
Stability data on the product has been provided for one full scale batch and two pilot scale batches stored at 25°C/60% RH (18 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in polyethylene bags which are placed in an outer carton box. Stability results showed an increase in the content of the impurity at RRT and the sum of all impurities which did not differ from the reference product. However all tested parameters remained within the specifications. For the other tested parameters no significant changes or trends were observed.
A photo-stability study on Linezolid 2 mg/ml solution for infusion was conducted according to ICH Q1B guideline. The results showed clear changes in the assay, appearance and impurities for the samples packed in the primary packaging material (PE Bag). The results show that samples packed in the marketing pack (PE bags in cardboard boxes) are stable when irradiated with daylight and UV-light.
The proposed shelf-life of 30 months is justified. The proposed storage condition “This medicinal product does not require any special temperature storage conditions; keep the polyethylene container in the outer carton” is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Zyvoxid 2 mg/ml, solution for infusion, which is available on the European market. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of linezolid released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

Dilizolen 2 mg/ml, solution for infusion is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence "5.1.6 parenteral solutions", which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Dilizolen 2 mg/ml, solution for infusion is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

Risk management plan

The MAH has committed to comply with the following activities, which will be included in an RMP after completion of the DCP:

- closely monitor the following ongoing safety issues and thoroughly discuss them in the PSURs: myelosupression, lactic acidosis, evidence of mitochondrial toxicity and cardiac events, peripheral neuropathy, optic neuropathy, serotonin syndrome and potential for increased blood pressure (potential to inhibit monoamine oxidase); convulsions;
- closely monitor the increased risk of fatal outcome in subsets of patients with chronic renal insufficiency (CRI), especially those with Gram negative organisms.
- provide a separate review of all fatal cases bi-annually. Where possible, the due date of the review can be harmonised with the PSUR.
- ensure that their SmPC is in-line with the innovator SmPC/ CSP.

The MAH has committed to submit an updated RMP within three months of the initial marketing authorization, which is considered acceptable.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Zyvoxid 2 mg/ml, solution for infusion marketed by Pfizer B.V..

Readability test

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questionnaire consisted of 14 questions. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Dilizolen 2mg/ml solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Zyvoxid 2 mg/ml, solution for infusion. Zyvoxid is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other linezolid containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Dilizolen 2mg/ml oplossing voor infusie with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 17 January 2013. Dilizolen 2mg/ml solution for infusion is authorised in the Netherlands on 25 February 2013.

The date for the first renewal will be: 17 January 2018.

The following post-approval commitments have been made during the procedure:

1.

Quality - medicinal product

2. The MAH commits to continue the ongoing stability studies. The results at least up to the proposed shelf life are awaited as soon as available.
3. The MAH commits to perform process validation studies on the first 2 commercial batches with a batch size of 1400 L.

Pharmacovigilance System / Risk Management Plan-

4. The MAH has committed to comply with the following activities:
    - Closely monitor the following ongoing safety issues and thoroughly discuss them in the PSURs: myelosupression, lactic acidosis, evidence of mitochondrial toxicity and cardiac events, peripheral neuropathy, optic neuropathy, serotonin syndrome and potential for increased blood pressure (potential to inhibit monoamine oxidase); convulsions;
    - Closely monitor the increased risk of fatal outcome in subsets of patients with CRI, especially those with Gram negative organisms.
    - Provide a separate review of all fatal cases bi-annually. Where possible, the due date of the review can be harmonised with the PSUR.
5. The MAH commits to submit an updated RMP within three months after the date of initial marketing authorization.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CRI	Chronic Renal Insufficiency
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached