PUBLIC ASSESSMENT REPORT
of the Medicines Evaluation Board
in the Netherlands

Etomedac 20 mg/ml, concentrate for solution for infusion
Medac Gesellschaft für klinische Spezialpräparate mbH, Germany

etoposide

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/1157/001/MR
Registration number in the Netherlands: RVG 30845

Date of first publication: 23 October 2008
Last revision: 16 August 2010

Pharmacotherapeutic group:	Antineoplastic and immunomodulating agents, podophyllotoxin derivatives
ATC code:	L01CB01
Route of administration:	intravenous
Therapeutic indication:	Treatment of small-cell lung cancer, resistant non-seminomatous testicular carcinoma, acute myelomonocytic and monocytic leukaemia (AML, FAB subtype M4 or M5) as part of combination therapy after failure of induction chemotherapy.
Prescription status:	prescription only
Date of first authorisation in NL:	12 May 2004
Concerned Member States:	Mutual recognition 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 concerned member state has granted a marketing authorisation for Etomedac 20 mg/ml, concentrate for solution for infusion, from Medac Gesellschaft für klinische Spezialpräparate mbH. The date of authorisation was on 12 May 2004 in the Netherlands.
The product is indicated for treatment of small-cell lung cancer, resistant non-seminomatous testicular carcinoma, acute myelomonocytic and monocytic leukaemia (AML, FAB subtype M4 or M5) as part of combination therapy after failure of induction chemotherapy.

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

Etomedac 20 mg/ml is a semisynthetic derivative of podophyllotoxin with a significant cytotoxic activity and dosage-scheme-dependent properties. Etoposide affects the function of topoisomerase II (DNA opening enzyme) and inhibits DNA-synthesis in the terminal phase. This results in cleavage of single and double stranded DNA. Cell death occurs in relation to the concentration of etoposide and duration of exposure. Etoposide is phase specific with cell stop in S and early G_2 -phases of the cell cycle but differs from other known podophyllcompounds through the fact that it doesn't cause accumulation in the metaphase, but prevents the cell from mitosis or destroys cells that prepare mitosis.

This mutual recognition procedure concerns a generic application in accordance with Article 10(1) of Directive 2001/83/EC. The innovator product is Vepesid 20 mg/ml, concentrate for solution for infusion, marketed by Brystol Myers Squibb/NL since 1981 in the Netherlands (NL RVG 08542). In addition, reference is made to Vepesid authorisations in the individual member states (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 Etomedac 20 mg/ml 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 new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to this product.

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 etoposide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white crystalline powder, practically insoluble in water, sparingly in methanol, slightly in alcohol and in methylene chloride.

The drug substance specification and methods are in line with the Ph.Eur., with additional requirements for residual solvents, particle size, bulk density, bioburden and bacterial endotoxins. This specification is acceptable in view of the route of synthesis, the Ph.Eur. and ICH guidelines. Batch analytical data of six commercial-scale batches, demonstrating compliance with the drug substance specification, have been provided.

The CEP procedure is used for the active substance. Under this official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopeia.

Stability data has been obtained during storage at 25°C/60%RH (36 months) and 40°C/75%RH (12 months) in accordance with applicable European guidelines. On basis of the data submitted, a retest period could be granted of 2 years without specific temperature or humidity in amber glass bottles.

** 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
The primary packaging is type I tube glass vials in three (nominal volumes): 100 mg: 5 ml; 500mg: 25 ml; 1000 mg: 50 ml, with bromobutyl stoppers and flip-off aluminium caps. The product is a clear and yellowish liquid. The headspace of the ampoule concerns nitrogen.

The excipients used are:
- citric acid (anhydrous) (E330)
- polysorbate 80
- macrogol 300
- ethanol (262 mg/ml)

The excipients are common in the manufacture of parental formulations. In contrast with the innovator no benzylalcohol as preservative (compensated for by adding more ethanol) was added. Other generics without benzylalcohol are registered. All excipients comply with the requirements laid down in their respective Ph.Eur. monographs

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packagings are usual and suitable for the product at issue.

The objective was to develop a product that would be essentially similar to the innovator product Vepesid 20 mg/ml.

Manufacturing process and quality control of the medicinal product
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three pilot-scale batches in accordance with the relevant European guidelines. As the equipment is independent of the actual batch size this validation is also acceptable for production scale batches.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, pH, assay, ethanol content, related substances, bacterial endotoxins, sterility, extractable volume and particles. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) has been provided for 3 full-scale scale batches of each vial volume demonstrating compliance with the specification.

Stability tests on the finished product
Stability data has been obtained during storage at 25ºC/60%RH and 40ºC/75%RH for three commercial batches of each size (5, 25 en 50 ml) in accordance with applicable European guidelines. On basis of the data submitted, a shelf life was granted of 2 years without refrigerating or freezing. The labelled storage conditions are “Do not refrigerate or freeze”.
In-use stability study was performed showing stability of the concentrate covering 120 hours and that the concentrate remains sterile and the purity does not deteriorate when the stoppers are perforated according to the normal use i.e. after being pierced every day with a sterile needle and after removing in each piercing the necessary volume for its application. The applicant´s claim that the larger vials of the product can be used as a multi-use product was accepted.

Stability data has been provided demonstrating that the diluted product (0.4 mg/ml) remains stable for 24 hours at 25ºC. The diluted product (0.2 mg/ml) should be used immediately.

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 Vepesid 20 mg/ml, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for a generic application.

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 etoposide 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

Etomedac is a well-known active substance with established efficacy and tolerability.

The content of the SPC approved during the mutual recognition procedure is in accordance with that accepted for the reference product Vepesid 20 mg/ml,

Etomedac 20 mg/ml is administered as an aqueous solution intended for intravenous injection containing the same active substance in the same concentration as the currently authorised reference medicinal product. As Etomedac 20 mg/ml is a product for parenteral use, it is exempted for biostudy (NfG

CPMP/EWP/QWP 1401/98). Etomedac 20 mg/ml is a generic of the reference product Vepesid 20 mg/ml, concentrate for solution for infusion, which is already on the European market. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

Risk Management Plan

Etoposide was first approved in 1981, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of etoposide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

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. An initial test was performed with 2 participants, followed by two test rounds with 10 participants each. The distribution of age, gender and educational background was acceptable and the study population is deemed adequately representative of the target population. The results were considered supportive of the proposed package leaflet. The readability test has been adequately performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Etomedac 20 mg/ml, concentrate for solution for infusion, has a proven chemical-pharmaceutical quality and is a generic form of Vepesid 20 mg/ml, concentrate for solution for infusion. Vepesid 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 content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Vepesid 20 mg/ml, although more detailed and better formulated. The SPC, package leaflet and labelling are in agreed templates. The applicant gave an adequate statement for the request to provide an adequate statement in Module 1.3.6 regarding a waiver for the Braille requirements, as etoposide is a concentrate for solution for IV injection, to be used in hospital setting only.

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

The Board followed the advice of the assessors. The product was authorized in the Netherlands on 12 May 2004.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member state on the basis of the data submitted, considered that essential similarity has been demonstrated for Etomedac 20 mg/ml with the reference product, and has therefore granted a marketing authorization. The mutual recognition procedure was finished on 31 January 2008.

A European harmonised birth date has been allocated (17 February 1976) and subsequently the first data lock point for etoposide is February 2010. The first PSUR is therefore expected in April 2010 after which a PSUR should be submitted every 3 years.

The date for the first renewal will be: January 31st, 2013.

There were no post-approval commitments made during the procedure.

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
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
PL	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
Change in the name of the medicinal product.	NL/H/1157/001/ IB/001	IB	24-7-2008	23-8-2008	Approval	N