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# PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

## Vinblastinesulfaat 1 mg/ml PCH, solution for injection
## Pharmachemie B.V., the Netherlands

## vinblastine (as sulphate)

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/1234/001/DC**
**Registration number in the Netherlands: RVG 101349**

**25 November 2009**

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|---|---|
| Pharmacotherapeutic group: | vinca alkaloids and analogues |
| ATC code: | L01CA01 |
| Route of administration: | intravenous |
| Therapeutic indication: | malignant non-Hodgkin's lymphoma; Hodgkin's disease; advanced carcinoma of the testes; recurrent or metastatic breast cancer; (when anthracycline based regimens have failed); langerhans cell histiocytosis (histiocytosis X) |
| Prescription status: | prescription only |
| Date of authorisation in NL: | 6 July 2009 |
| Concerned Member States: | Decentralised procedure with AT, BE, CZ, DE, EE, EL, FR, IT, LT, LU, LV, PL, PT, UK |
| Application type/legal basis: | Directive 2001/83/EC, Article 10(1), Article 10(3) |

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 Vinblastinesulfaat 1 mg/ml PCH, solution for injection, from Pharmachemie B.V. The date of authorisation was on 6 July 2009 in the Netherlands.

The product is indicated in:
- malignant non-Hodgkin's lymphoma
- Hodgkin's disease
- advanced carcinoma of the testes
- recurrent or metastatic breast cancer (when anthracycline based regimens have failed)
- Langerhans cell histiocytosis (histiocytosis X)

Vinblastine can sometimes be administered in monotherapy but is usually administered in combination with other cytostatic drugs and/or radiotherapy.

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

Vinblastine belongs to the vinca-alkaloids, binds to tubulin and disrupts the microtubular function both by preventing polymerisation and by inducing depolymerisation of formed microtubules. This disturbs the normal reorganisation of the microtubule network, which is needed for interphase and mitosis. In addition to an arrest in mitosis vinca-alkaloids also seem to be cytotoxic to non-proliferating cells in the G1- and S-phase.

This decentralised procedure concerns a generic application claiming essential similarity with the historic innovator product Velbe 10 mg, powder for solution for injection (NL license RVG 00543) which was first registered in the Netherlands by Stada Arzneimittel AG in 1966, but has been withdrawn. In addition, reference is made to Velbe 10 mg authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC. In FR and UK, the application is made according to article 10(3) of Directive 2001/83/EC, hybrid application, as in these countries the innovator product Velbe has been registered in a different pharmaceutical form.

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 Vinblastinesulfaat 1 mg/ml PCH, solution for injection is an aqueous 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 these products.

No paediatric development programme has been submitted, as this is not required for a generic medicinal 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 vinblastine sulphate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or slightly yellowish, crystalline powder, which is very hygroscopic. The substance is freely soluble in water and practically insoluble in ethanol.

The CEP procedure is used for the active substance. Under the 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 suitablity 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 Pharmacopoeia, the official handbook in which methods of analysis with specifications for substances are laid down by the authorities of the EU.

Specification
Specifications for the drug substance are in accordance with the Ph.Eur. monograph and additional specifications that are listed on the CEP have been adopted. These additional specifications include several impurities and residual solvents. The MAH has also included a specification on bacterial endotoxins.

Stability
The active substance has a re-test period of 2 years when stored at -20 ºC. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

** 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
Vinblastinesulfaat 1 mg/ml PCH contains as active substance 1 mg/ml of vinblastine sulphate, and is a clear, colourless to light yellow solution.

The excipients are: sodium chloride, water for injection.

Pharmaceutical development
The development of the solution for injection has been satisfactory performed. The drug product does not contain any preservatives. The excipients used are common in the manufacturing of solutions for injections. The packaging materials (glass vials and rubber stoppers) are usual and suitable for the product at issue.

Overfill
The vials are filled with an excess of 0.5 ml. This excess volume is recommended in USP* chapter 1151. This excess is sufficient to permit withdrawal and administration of the labeled volume.

Container closure system
The solution for injection is packed in colourless type I glass injection bottles with a bromobutyl rubber stop and an aluminium seal with a polypropelene “snap-cap” in a carton box.

Detailed information regarding specifications and test methods is given. The rubber stopper and type I glass vial comply to the Ph. Eur. Analysis certificates of the several tests are presented. Tests regarding extractables from the stopper have also been submitted, the (fluorinated) rubber stopper can therefore be regarded as safe. Considering that the product is stored in the vial at 2-8°C, it was demonstrated that the stopper complies to the Ph. Eur.3.2.9 fragmentation test.

Microbiological attributes
Integrity of the container closure system to prevent microbial contamination have been tested with several batches, furthermore closure integrity is tested at release.

Manufacturing process
The drug product is manufactured by sterile filtration followed by aseptic processing. The description and validation of the manufacturing process were adequate. The MAH committed to validate the first batch at maximum production size.

Product specification
The drug product specification includes tests for appearance, particulate contamination, identification, extractable volume, closure integrity, pH, related substances, assay, sterility and bacterial endotoxins.
The analytical methods used are generally based on Ph. Eur. and/or BP methods and have been sufficiently validated according to the applicable guidelines. The relevant methods are sufficiently stability indicating, and therefore also suitable for the stability studies. HPLC methods are used as well, and are based on those for the drug substance. Batch analytical data have been provided for two batches, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data has been obtained during storage at 2-8 ºC and 25 ºC/60% RH. The drug product was packaged in the proposed commercial package. The product was not stable regarding related substances at accelerated conditions. Based on the stability data, a shelf-life of 2 years could be granted. The shelf-life has been changed into 3 years by a post-approval variation, see variation NL/H/1234/001/IB/001 in the "*steps taken after finalisation of the initial procedure*" table on page 8. The in-use stability testing showed that the product is stable for a period of 6 hours at 15–25°C and ambient light in the proposed dilutions. The storage conditions will be *'store and transport refrigerated (2-8°C). Do not freeze. Keep container in the outer carton.'*
The MAH made several post-approval commitments regarding stability studies on the finished product; these can be found on page 6 of this report.

Compatibility with diluents
Compatibility and stability for the product is demonstrated when diluted in 0.9% sodium chloride solution or 5% glucose solution for a concentration of 0.5 mg/ml in infusion bags, stored 6 hours at room temperature (15–25 °C) in ambient light.
The MAH committed to perform in-use stability testing on samples near the expiration data and submit the obtained results.

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.

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

## II.2 Non clinical aspects

This product is a generic formulation of Velbe 10 mg, powder for solution for injection 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 this type of 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 vinblastine sulphate 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

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

Vinblastinesulfaat 1 mg/ml PCH 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 Vinblastinesulfaat 1 mg/ml PCH 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
Vinblastine sulphate has been used in the EU for several decades, and there is extensive post-authorisation experience with the active substance. The safety profile of vinblastine sulphate can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation 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.

**Product information**

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 two rounds with 10 participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability.
In the first round, a total of four sections for attention were identified (scoring below 80%), i.e. the sections '*Possible side effects', 'Take special care with Vinblastine', 'Do not take Vinblastine', 'Taking other medicines'.* These sections were amended in order to improve findability, comprehensibility and applicability.
In the second round the overall result was succesful, although two sections ('*Taking other medicines'*, and *'Possible side effects'*) still did not meet the requirement of 80%. However, due to the the legal requirements regarding content, heading location and lay-out defined by the applicable templates, no room for further improvement could be identified. The readability test has been sufficiently performed.

## III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Vinblastinesulfaat 1 mg/ml PCH, solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Velbe 10 mg, powder for solution for injection. Velbe 10 mg 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, package leaflet and labelling are in the agreed templates and are in agreement with other vinblastine sulphate 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 Vinblastinesulfaat 1 mg/ml PCH with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 4 November 2008. Vinblastinesulfaat 1 mg/ml PCH, solution for injection was authorised in the Netherlands on 6 July 2009.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from November 2008 to November 2011.

The date for the first renewal will be: 4 November 2013

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

Quality - medicinal product

- The MAH committed to validate the first production size batch and to submit the results as soon as available.
- The MAH committed to perform in-use stability testing on samples near the expiration data and submit the obtained results.
- The MAH committed to place one additional production scaled batch on long term stability studies through the proposed shelf life and on accelerated studies for six months.
- The MAH committed to submit results of the stability studies covering the complete shelf life as soon as these become available.

## List of abbreviations

| | |
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| 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 |
| 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 |
|---|---|---|---|---|---|---|
| Change in the shelf life of the finished product (as packaged for sale) from 2 years to 3 years | NL/H/1234/ 001/IB/001 | IB | 23-2-2009 | 26-3-2009 | Approval | N |