CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Vinorelbine Sandoz 10 mg/ml, concentrate for solution for infusion Sandoz B.V., the Netherlands

vinorelbine tartrate

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/1032/001/DC
Registration number in the Netherlands: RVG 35140

30 September 2009

Pharmacotherapeutic group:	Antineoplastic and immunomodulating agents, vinca alkaloids and analogues
ATC code:	L01CA04
Route of administration:	Parenteral
Therapeutic indication:	treatment of non-small cell lung cancer (stage 3 or 4) and as single agent in patients with metastatic breast cancer (stage 4), where treatment with anthracycline- and taxane containing chemotherapy has failed or is not appropriate.
Prescription status:	prescription only
Date of authorisation in NL:	1 December 2008
Concerned Member States:	Decentralised procedure with AT, CZ, DK, ES, FI, FR, IT, PL, PT, SE, SK and UK.
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 Vinorelbine Sandoz 10 mg/ml, concentrate for solution for infusion from Sandoz B.V., Almere, the Netherlands. The date of authorisation was on 1 December 2008 in the Netherlands.

The product is indicated for treatment of non-small cell lung cancer (stage 3 or 4) and as single agent in patients with metastatic breast cancer (stage 4), where treatment with anthracycline- and taxane containing chemotherapy has failed or is not appropriate.

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

Vinorelbine tartrate inhibits tubulin polymerisation and binds preferentially to mitotic microtubules, only affecting axonal microtubules at high concentration thus hampering the formation of microtubuli, which is a process essential for mitosis. Vinorelbine blocks mitosis at G2-M, causing cell death in interphase or at the following mitosis.

This mutual recognition procedure concerns a generic application in accordance with Article 10(1) of Directive 2001/83/EC. The innovator product is Navelbine 10mg /ml, concentrate for solution for infusion, marketed by Pierre Fabre, United Kingdom since 1996 (NL RVG 18020). The oldest registration in the EU was on 11 April 1989 in France. Formally, this registration should have been chosen as reference product. However, the MAH indicated that the originator and/or reference medicinal product is more than 6/10 years on the EU market. Several countries where found for which above mentioned statement is applicable, and from these countries UK was randomly chosen. The argumentation provided by the MAH was deemed acceptable. In addition, reference is made to Navelbine 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 Vinorelbine Sandoz 10 mg/ml is an aqueous solution for intravenous 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.

No paediatric development programme has been submitted.

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 vinorelbine tartrate, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). It is a white or almost white hygroscopic powder. It is freely soluble in water and methanol, and practically insoluble in hexane. The substance is chiral and has a specific optical rotation of +20º ± 5º.

The Active Substance Master File (ASMF) procedure is used for both manufacturers of 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/EMEA 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
The synthesis of vinorelbine tartrate of the first manufacturer can be divided into three steps. A reaction scheme, flow chart and sufficient description of the synthetic route have been provided.
The manufacturing process of the second manufacturer can be divided into six steps. A flow diagram and a sufficient description of the manufacturing process have been provided.

Specification
The drug substance specification and methods are in line with the Ph.Eur., with additional requirements for residual solvents and microbiological purity. The specification is acceptable in view of the route of synthesis, the Ph.Eur. and ICH guidelines.

Stability of drug substance
Stability data has been obtained during storage at -20 ºC, 2-8 ºC and/or 25 ºC/60% RH. The drug substance was packaged in the proposed commercial package. Vinorelbine tartrate was stable during long-term conditions. The substance is sensitive to light and heat. The proposed re-test periods of 1 or 3 years (depending on the ASM) were granted. The drug substance should be stored at -20 ºC and protected from light.

** 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
Vinorelbine Sandoz is formulated as concentrate for solution for infusion containing 10 mg/ml or 50 mg/5 ml vinorelbine (as vinorelbine tartrate) in water for injections.

As the drug substance is sensitive to light, the product is packaged in amber glass type I vials with bromobutyl stoppers and an aluminium cap. Nitrogen is added as head-space gas.

The only excipient used is water for injection. The excipient is common in the manufacture of parental formulations, and of Ph.Eur. quality.

Pharmaceutical development

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The packaging materials (amber glass bottles) are suitable for the products at issue as it is light sensitive. An overfill of 0.2 ml is employed for both presentations.

The objective was to develop a product that would be essentially similar to the innovator product Navelbine 10 mg/ml.

Manufacturing process and quality control of the medicinal product

The manufacturing process has been validated according to relevant European/ICH guidelines. Adequate in-process controls have been implemented and the process has been adequately validated for the smallest size commercial scale batches (three of each presentation). Validation protocols for the validation of the process of the largest size commercial scale batches have been provided and are acceptable. The MAH committed to validate the production process for the largest commercial scale for both presentations (10 mg/ml and 50 mg/ml) according to the provided protocol.

Microbiological attributes

The drug products are manufactured by aseptic processing. All relevant GMP regulations are met. During aseptic processing, the following items are controlled: particle count, microbiological monitoring of the people and the surfaces, and microbiological control of the air. Bioburden of the solution was tested during validation of the full-scale production batches and results showed that the manufacturing process is appropriate.

Compatibilities

The compatibility of the product with the solutions for reconstitution mentioned in the SPC (0.9% sodium chloride, 5.0% dextrose) is demonstrated by means of in-use stability studies. The reconstituted solution proved to be stable over the recommended in-use shelf-life of 48 h at +2-8 ºC.

Quality control of the drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, extractable volume, pH, relative density, assay, related substances, sterility, bacterial endotoxins and particulate contamination.

Batch analysis data from the manufacturing site have been provided on 5 production scale batches of each presentation, demonstrating compliance with the release specifications.

Satisfactory validation data for the analytical methods have been provided.

Stability tests on the finished product

Stability data has been obtained during storage at 2-8 ºC and 25 ºC/60% RH for 18 months for the 10 mg/ml product and 12 months for the 50 mg/5 ml product. The drug product was packaged in the proposed commercial package, i.e. amber glass bottles with bromobutyl rubber stoppers and an aluminium crimp cap. Based on the stability data, the proposed shelf-life of 18 months can be granted for the 10 mg/ml. A shelf-life of 12 months can be granted for the 50 mg/5 ml presentation. The special storage conditions of “Protect from light. Store in a refrigerator at 2-8 ºC” apply. Stability data has been provided demonstrating that the product remains stable for 48 hours after dilution when stored at 2-8 ºC and protected from light. The MAH committed to place the first three batches of the larger batch sizes on stability studies according to the stability protocol.

Photostability

The photostability study was performed on the vinorelbine 10 mg/ml product according to the applicable ICH guidelines. UV and visible light conditions were used, as well was controls. No changes in appearance, assay or degradation products was observed. However, as the drug substance is light sensitive, the storage condition of *protect from light* 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 Navelbine 10 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 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 vinorelbine tartrate 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

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

The content of the SPC approved during the decentralised procedure is harmonised with that accepted for another generic product Vinorelbine Mimer (SE/H/0577/001/MR).

Vinorelbine Sandoz 10 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 Vinorelbine Sandoz 10 mg/ml is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). Vinorelbine Sandoz 10 mg/ml is a generic of the reference product Navelbine 10 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
Vinorelbine was first approved in 1989, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of vinorelbine 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 MAH provided reports on readability tests for Gemcitabine Sandoz 200 mg powder for solution for infusion and Irinotecan HCL Sandoz 20 mg/ml concentrate for infusion, proposing a waiver for conduction of a readability on the current package leaflet. As the content and format of the proposed PIL is sufficiently similar to the content and format of the successfully user tested PILs, no separate readability test was deemed necessary.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Vinorelbine Sandoz 10 mg/ml, concentrate for solution for infusion, has a proven chemical-pharmaceutical quality and is a generic form of Navelbine 10 mg/ml, concentrate for solution for infusion. Navelbine® 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 harmonised with that accepted for another generic product Vinorelbine Mimer (SE/H/0577/001/MR). The SPC, package leaflet and labelling are in agreed templates.

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.

There was no discussion in the CMD(h). Agreement between member states was reached during the written procedure. The member states on the basis of the data submitted, considered that essential similarity has been demonstrated for Vinorelbine Sandoz 10 mg/ml with the reference product, and have therefore granted a marketing authorization. The product was authorized in the Netherlands on 1 December 2008.

A European harmonised birth date has been allocated (11 April 1989) and subsequently the first data lock point for vinorelbine is April 2009. The first PSUR is therefore expected in June 2009, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 30 December 2009.

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

Quality - medicinal product

- The MAH committed to validate the production process for the largest commercial scale for both presentations (10 mg/ml and 50 mg/ml) according to the provided protocol.
- The MAH committed to place the first three batches of the larger batch sizes on stability studies according to the stability protocol.

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
Withrawal of marketing authorisation in Czech Republic	NL/H/1032/001/DC	Withdrawal	-	14-1-2009	-	N
Change in the shelf life of the finished product: 10 mg/ml: from 18 months to 24 months; 50 mg/ml: from 12 months to 24 months	NL/H/1032/001/IB/001	IB	18-3-2009	17-4-2009	Approval	N
Withdrawal of marketing authorisation in Portugal	NL/H/1032/001/DC	Withdrawal	-	29-5-2009	-	N