CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Oxalisin 5 mg/ml, concentrate for solution for infusion Pharmachemie B.V., the Netherlands

oxaliplatin

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/820/01/DC
Registration number in the Netherlands: RVG 34033

3 December 2009

Pharmacotherapeutic group:	antineoplastic agents, other
ATC code:	L01XA03
Route of administration:	intravenous
Therapeutic indication:	in combination with 5-fluorouracil (5-FU) and folinic acid (FA): - adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor - treatment of metastatic colorectal cancer.
Prescription status:	prescription only
Date of authorisation in NL:	23 November 2007
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LU, LV, NO, PL, PT, SE, SI, SK and UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) for AT, BE, BG CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, IT, LT, LV, LU, NL, NO, PL, SE, RO, and the UK Directive 2001/83/EC, Article 10(3) for PT, SI and SK

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 Oxalisin 5 mg/ml, concentrate for solution for infusion from Pharmachemie B.V., the Netherlands. The date of authorisation was on 23 November 2007 in the Netherlands. The product is indicated in combination with 5-fluorouracil (5-FU) and folinic acid (FA) for adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor, and for treatment of metastatic colorectal cancer.

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

Oxaliplatin is an antineoplastic drug belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, the Cis- [oxalate (trans-l-1,2- DACH) platinum]. Oxaliplatin exhibits a wide spectrum of both in vitro cytotoxicity and in vivo antitumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrated in vitro and in vivo activity in various cisplatin resistant models. It has been applied in combination with a variety of other chemotherapy agents including fluoropyrimidines, irinotecan, raltitrexed, paclitaxel and cyclophosphamide. The pharmacodynamics, interactions, pharmacokinetics and toxicology of the compound are well known. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil (5-FU) both in vitro and in vivo. The treatment with Oxaliplatin must be part of a combination chemotherapy with 5-fluorouracil and folinic acid

This decentralised recognition procedure concerns a generic application claiming essential similarity with the innovator product Eloxatine 5 mg/ml, powder for solution for infusion (NL License RVG 24195), which has been registered in France by Sanofi-Aventis since 1996. In addition, reference is made to Eloxatine 5 mg/ml authorisations in the individual member states (reference product). Eloxatine has been registered through a mutual recognition procedure in BE, DE, ES, IT, LU, NL, SE and UK.

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC for BE, CZ, DE, DK,EE, EL, ES, FI, FR, IE, IT, LT, LV, LU, NO, SE, and the UK with reference to the medicinal product authorised in the member state where the application is made. In AT, HU and PL reference is made to the European Reference product as registered in the Netherlands which is Eloxatine 5mg/ml, powder for solution for infusion (Sanofi-Aventis Netherlands B.V.).
For PT, SI and SK an Article 10(3) hybrid application was submitted, due to differences in indication. For these hybrid applications, reference is made to the medicinal product authorised in the member state where the application is made.

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 Oxalisin 5 mg/ml, concentrate for solution for infusion, is a product for parenteral use, it is exempted for performing a bioequivalence study (NfG CPMP/EWP/QWP 1401/98). Oxalisin 5 mg/ml is considered to be a generic version of Eloxatine 5 mg/ml for it has the same pharmaceutical form, i.e. the same form of administration as stated in Notice to Applicants.. This application concerns a concentrate for solution for infusion. In the application, reference is made to the Eloxatine powder for solution for infusion. Both these products contain the excipient lactose monohydrate. In contrast, the reference product Eloxatine concentrate for solution for infusion does not contain this excipient. The current product can be used instead of its reference product.

No new preclinical 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.

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 and excipients
The active substance is oxaliplatin, an established active substance described in the European Pharmacopoeia (Ph.Eur.). 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. Oxaliplatin is a white to almost white, crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol. The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur with additional requirements for total mesophilic count and the residual solvents methanol, ethanol and dimethylformamide. Batch analytical data demonstrating compliance with this specification have been provided for 3 pilot batches.

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/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.

Stability data on the active substance have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the active substance over 12 months. Based on the data submitted, a retest period could be granted of 1 year when stored below 25ºC in the original packaging.

Medicinal Product

Composition
Oxalisin 5 mg/ml, concentrate for solution for infusion is a clear, colourless or almost colourless solution.

The concentrate for solution for infusion is packed in a colourless, type I glass vial with bromobutyl rubber stopper, aluminium seal and polypropylene snap-cap. The volume of the concentrate in the vials is either 4 ml, 10 ml or 20 ml. By a type II variation an additional pack size was added of a type I glass vial with 40 ml concentrate (see table Steps taken after the finalisation of the initial procedure on Page 8).

The excipients are: lactose monohydrate and water for injections.

The used excipients are well known and safe in the proposed concentrations. All excipients comply with the requirements in the relevant 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 objective was to develop a product that would be essential similar to the innovator product Eloxatine 5 mg/ml.

Manufacturing process and quality control of the medicinal product
The product is manufactured using conventional manufacturing techniques. Process validation on the product has been presented for 4 pilot-scale batches in accordance with the relevant European guidelines. The MAH committed to submitted to process validation data for full-scale batches post authorisation.

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for appearance, identification, colour of solution, foreign matter, clarity, closure integrity, extractable volume, particulate contamination, pH, related substances, assay, sterility, and bacterial endotoxins. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product.

The majority of the analytical procedures are performed according to the Ph.Eur. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability tests on the finished product
Stability data on the product have been provided for 6 batches in accordance with applicable European guidelines demonstrating the stability of the product over 24 months. On basis of the data submitted, a shelf life was granted of 24 months. From the photostability data it appears that some accelerated degradation occurs under the influence of light. Although no out of specifications results are generated after testing under ICH conditions, the MAH has added an additional storage condition in the SPC: *"Keep the vial in the outer carton in order to protect from light"*.

Chemical and physical in-use stability data have been provided demonstrating that the product remains stable for 24 hours following dilution in 5% glucose, when stored at 2-8°C and 6 hours when stored at 25°C. The stated storage conditions are the following: *"From a microbiological point of view, the infusion preparation should be used immediately. If not used immediately, the in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C unless dilution has taken place in controlled and validated aseptic conditions.*" The MAH committed to place the first industrial scale batch on long-term and accelerated stability testing.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via medicinal products has been satisfactorily demonstrated.

II.2 Non clinical aspects

This product is a generic formulation of Eloxatine 5 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 oxaliplatin 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

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

The indications for Oxalisin 5 mg/ml are analogous to the indications approved for the originator Eloxatine. The SPC is in line with the innovator SPCs FR/H/144/01-02 and MRP SPCs FR/H/284, 285. Section 4.6 has been adapted to the Guideline on risk assessment of medicinal products on human reproduction and lactation.

Oxalisin 5 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. Oxalisin 5 mg/ml, concentrate for solution for infusion is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). Oxalisin 5 mg/ml is a generic of the reference product Eloxatine 5 mg/ml, powder for solution for infusion, which is already on the market in various European countries. Thus, all data regarding to safety and efficacy available of the reference medicinal product also apply to this application.

Risk Management Plan
Oxaliplatin was first approved in 1996, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of oxaliplatin 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.

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. The patient information leaflet has been adapted sufficiently taking into account the test results and the proposals made by the member states. The reference member state concluded that this package leaflet meets the requirements of good readability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Oxalisin 5 mg/ml, concentrate for solution for infusion has a proven chemical-pharmaceutical quality and is a generic form of Eloxatine 5 mg/ml, powder for solution for infusion. Eloxatine 5 mg/ml, 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 SPC is in line with the innovator SPCs FR/H/144/01-02 and MRP SPCs FR/H/284, 285, Section 4.6 has been adapted to the Guideline on risk assessment of medicinal products on human reproduction and lactation and is now more informative.

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.

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 Oxalisin 5 mg/ml with the reference product, and have therefore granted a marketing authorisation.

The decentralised procedure was finished on 28 June 2007. Oxalisin 5 mg/ml, concentrate for solution for infusion was authorised in the Netherlands on 23 November 2007.

A European harmonised birth date has been allocated (12 April 1996) and subsequently the first data lock point for oxaliplatin is April 2009. The first PSUR will cover the period from June 2007 to April 2009, after which the PSUR submission cyclus is 3 years.

The date for the first renewal will be: 28 June 2012

The following post-approval commitments were made during the procedure:

<u>Quality – Medicinal product</u>

- The MAH committed to submitted to process validation data for full-scale batches post authorisation.
- The MAH committed to place the first industrial scale batch on long-term and accelerated stability testing.

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 procedure	Approval/ Non approval	Assessment report attached
Change in the name of the medicinal product in Austria, Finland, Norway, Sweden and Slovenia.	NL/H/0820/ 001/IB/001	IB	15-11-2007	15-11-2007	Approval	N
Change in the name of the medicinal product in Greece.	NL/H/0820/ 001/IB/002	IB	15-11-2007	15-11-2007	Approval	N
Change in the name and/or address of the marketing holder in the Czech Republic.	NL/H/0820/ 001/IA/003	IA	15-11-2007	29-11-2007	Approval	N
Change in the name and/or address of the marketing holder in Denmark, Finland, Sweden and Norway.	NL/H/0820/ 001/IA/004	IA	15-11-2007	29-11-2007	Approval	N
Addition of 40 ml presentation to the existed range of 4, 10 and 20 ml.	NL/H/0820/0 01/II/005	II	26-12-2007	13-5-2008	Approval	N
Submission of a new or updated Ph.Eur. Certificate of Suitability for an active substance or starting/reagent/intermediate in the manufacturing process of the active substance. From a new manufacturer (replacement or addition). Other substances.	NL/H/0820/ 001/IA/006	IA	15-1-2008	29-1-2008	Approval	N
Change in shape or dimensions of the container or closure. Sterile pharmaceutical forms and biological medicinal products.	NL/H/0820/ 001/IB/007	IB	16-1-2008	16-1-2008	Approval	N
Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. Secondary packaging site for all types of the pharmaceutical forms.	NL/H/0820/ 001/IA/008	IA	14-4-2008	28-4-2008	Approval	N
Change in the name and/or address of the marketing holder in Italy.	NL/H/0820/ 001/IA/009	IA	22-7-2008	5-8-2008	Approval	N
Change in the name of the medicinal product in Poland.	NL/H/0820/ 001/IB/010	IB	22-7-2008	22-7-2008	Approval	N
Repeat Use 1 Procedure with CMS BG and RO	NL/H/0820/0 01/E/001	Repeat Use Procedure	30-11-2008	02-03-2009	Approval	Y, Annex I
Inclusion of Section 1.8 Description of the Pharmacovigilance system In the dossier	NL/H/0820/ 001/II/011	II	25-11-2008	02-02-2009	Approval	N
Change in the name and/or adress of MAH for FR	NL/H/0820/ 001/IA/012	IA	02-06-2009	16-06-2009	Approval	N

Annex I – Repeat use procedure (NL/H/0820/001/E/001)

The Repeat use procedure started on 30 November 2008. There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states (BG and RO), on the basis of the data submitted, considered that essential similarity has been demonstrated for Oxalisin 5 mg/ml, concentrate for solution for infusion with the reference product, and have therefore granted a marketing authorisation. The repeat use procedure was finished on 28 February 2009.

The date for the first renewal will be: 28 June 2012

A European harmonised birth date has been allocated (12 April 1996) and subsequently the first data lock point for oxaliplatin is April 2009. The first PSUR will cover the period from June 2007 to April 2009, after which the PSUR submission cyclus is 3 years.

No post-approval commitments haven been made during the procedure.