Public Assessment Report

Decentralised Procedure

Oxaliplatin 5 mg/ml concentrate for solution for infusion

PL 31750/0048

UK/H/4547/001/DC

Sun Pharmaceutical Industries Europe B.V.
LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Sun Pharmaceutical Industries Europe B.V. a Marketing Authorisation (licence) for the medicinal product Oxaliplatin 5 mg/ml concentrate for solution for infusion (product licence number: PL 31750/0048) on 19 July 2011. This medicine is available on prescription only.

Oxaliplatin is used to treat metastatic (advanced) cancer of the colon (large bowel) or rectum (back passage). It is also used as an additional treatment following surgery to remove a tumour (growth) from the colon. It is used in combination with the other anti-cancer agents, 5-fluorouracil and folinic acid.

The data submitted in support of this application for Oxaliplatin 5 mg/ml concentrate for solution for infusion raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.
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## Module 1

### Information about Decentralised Procedure

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Oxaliplatin 5 mg/ml concentrate for solution for infusion</th>
</tr>
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<tbody>
<tr>
<td>Type of application</td>
<td>Generic (Article 10.1)</td>
</tr>
<tr>
<td>Name of the active substance (INN)</td>
<td>Oxaliplatin</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Other antineoplastic agents, platinum compounds (L01XA 03)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>Concentrate for solution for infusion, 5 mg/ml</td>
</tr>
<tr>
<td>Reference number for the Decentralised Procedure</td>
<td>UK/H/4547/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Germany, Spain, France, Italy, Netherlands</td>
</tr>
<tr>
<td>Start date of Decentralised Procedure</td>
<td>24 September 2010</td>
</tr>
<tr>
<td>End date of Decentralised Procedure</td>
<td>31 August 2011</td>
</tr>
<tr>
<td>Marketing Authorisation number in Reference Member State</td>
<td>PL 31750/0048</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Sun Pharmaceutical Industries Europe B.V.</td>
</tr>
<tr>
<td></td>
<td>Polarisavenue 87</td>
</tr>
<tr>
<td></td>
<td>2132 JH Hoofddorp</td>
</tr>
<tr>
<td></td>
<td>The Netherlands</td>
</tr>
</tbody>
</table>
Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Summaries of Product Characteristics (SmPCs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 3

Patient Information Leaflet

In accordance with Directive 2010/84/EU, the Patient Information Leaflets (PILs) for products that have been granted Marketing Authorisations at a national level are available on the MHRA website.
Module 4

Labelling

10 ml pack label:

![Pack label image]
Oxaliplatin 5 mg/ml concentrate for solution for infusion

Intravenous use
1 vial of 10 ml

**Concentration**
- 1 vial of concentrate contains 5 mg oxaliplatin.
- Each vial contains 50 mg/10 ml of concentrate.
- For dilution, see Dosage and Administration.

**Special Warning**
- This product is a concentrate and must be diluted before use.
- Keep out of reach of children.
- Pregnant women should avoid handling.
- Use gloves when handling.
- Read the package insert for the shelf life of the diluted solution.

**Stability**
- Do not store above 25°C.
- When diluted, store in a refrigerator below 25°C.
- If exposed, reconstitute immediately.

**Packaging Information**
- Type: vial
- Quantity: 1 vial per pack
- Unit: pack carton

**Suppliers**
- MA HOLDER: Sun Pharmaceuticals Europe B.V.
- POLYMERES 87
- 2132 TJ Hooiiddle The Netherlands

**References**
- EUAIS/15266/14
- EUAIS/15266/14
- EUAIS/15266/14
- EUAIS/15266/14
- EUAIS/15266/14

**Packaging and Labelling**
- 10 ml pack carton (1 vial):
20 ml pack label (1 vial):

Oxaliplatin 5 mg/ml concentrate for solution for infusion

Oxaliplatin

Intravenous use

One ml of concentrate contains 5 mg oxaliplatin.

Each vial of 20 ml of concentrate contains 100 mg oxaliplatin.

Excipients: lactose monohydrate, water for injection.

Concentrate for solution for infusion.

Read the package leaflet before use.

1 vial of 20 ml

This product is a concentrate and must be diluted before use. Keep out of the reach and sight of children. Pregnant women should avoid handling cytotoxic agents. Read the package leaflet for the shelf life of the diluted product. Do not store above 25°C. When diluted as directed, use within 24 hours if stored at room temperature (15-25°C) or 48 hours if refrigerated (2-8°C). Cytotoxic. Discard any unused content according to standard practice for cytotoxic agents. In case of contact with skin or mucous membranes, wash immediately and thoroughly with water. Dilute as instructed before administration. To be administered by iv. infusion over 2 to 6 hours.

PL 31750/0048

0448L1568A 0448L1568A
0448L1568A ISS. 07/2011

Sun Pharmaceutical Industries Europe B.V.

Batch No.

Exp.
Oxaliplatin 5 mg/ml concentrate for solution for infusion

Oxaliplatin

Intravenous use

One ml of concentrate contains 5 mg oxaliplatin. Each vial of 40 ml of concentrate contains 200 mg oxaliplatin.

Expiants: lactose monohydrate, water for injection.

Concentrate for solution for infusion. Read the package leaflet before use.

1 vial of 40 ml

This product is a concentrate and must be diluted before use. Keep out of the reach and sight of children. Pregnant women should avoid handling cytotoxic agents. Read the package leaflet for the shelf life of the diluted product. Do not store above 25°C. When diluted as directed, use within 24 hours if stored at room temperature (15-25°C) or 48 hours if refrigerated (2-8°C). Cytotoxic. Discard any unused content according to standard practice for cytotoxic agents. In case of contact with skin or mucous membranes, wash immediately and thoroughly with water. Dilute as instructed before administration. To be administered by i.v. infusion over 2 to 6 hours.
Module 5

Scientific Discussion

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) considers that the application for Oxaliplatin 5 mg/ml concentrate for solution for infusion in the treatment of stage III colon cancer and metastatic colorectal cancer could be approved.

EXECUTIVE SUMMARY
Problem statement
This Decentralised application was submitted under Article 10.1 of Directive 2001/83/EC, as amended. The applicant claims that the proposed product is a generic version of the product Eloxatin 5 mg/ml concentrate for solution for infusion, which has been licensed to Sanofi Aventis in France since 1996. The reference product has, therefore, been authorised in the EEA for at least 10 years and the legal basis of this application is acceptable.

With the UK as the RMS in this Decentralised Procedure, Sun Pharmaceutical Industries Europe B.V. is applying for Marketing Authorisations for Oxaliplatin 5 mg/ml concentrate for solution for infusion in Germany, Spain, France, Italy and the Netherlands.

About the product
Oxaliplatin is an alkylating agent and platinum analogue consisting of platinum bound to oxalate and diaminocyclohexane (DACH) complex. Oxaliplatin forms interstrand and intrastrand cross links with DNA, inhibiting DNA synthesis and resulting in cell death.

The use of oxaliplatin has been investigated in a number of malignancies, including colorectal cancer, ovarian cancer, mesothelioma, breast cancer, non-Hodgkin’s lymphoma, glioblastoma and pancreatic cancer. In patients with colorectal cancer, a synergistic combination of fluorouracil, leucovorin and oxaliplatin (FOLFOX) has emerged as a standard treatment regimen. Common adverse reactions associated with oxaliplatin include neurotoxicity, gastrointestinal disturbances, ototoxicity and myelosuppression.

General comments on the submitted dossier
The submitted documentation in relation to the proposed type of product is considered to be of sufficient quality and is consistent with the current EU regulatory requirements. Satisfactory overall summaries of the dossier regarding the quality, preclinical and clinical parts have been submitted.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles

GMP
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.
For manufacturing sites outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

**GLP**
No new preclinical studies were submitted in support of this application, and none are needed for an application of this type.

**GCP**
No new clinical studies were submitted in support of this application, and none are needed for an application of this type.

**SCIENTIFIC OVERVIEW AND DISCUSSION**

**Quality aspects**

**Drug substance**

rINN: Oxaliplatin  
Chemical names: \((SP)-4-2)-(1R,2R)-Cyclohexane-1,2-diamine-kN, kN']\[(\text{ethanedioato}(2)-kO^1, kO^2]\text{platinum}\)

Structural formula:

![Structural formula of Oxaliplatin]

Molecular formula: \(C_8H_{14}N_2O_4Pt\)  
Molecular weight: 397.3  
Physical characteristics: White or almost white crystalline powder  
Solubility: Slightly soluble in water, very slightly soluble in methanol, practically insoluble in ethanol

The manufacturer of the drug substance holds a valid EDQM Certificate of Suitability. The quality of the substance is suitably controlled in line with the current edition of the Ph. Eur. Monograph.

The manufacturing process, control of materials, control of critical steps, validation and process development for oxaliplatin were assessed and approved by the EDQM in relation to the granting of the Certificate of Suitability and are, therefore, satisfactory.

Data relevant to the drug substance specification have been assessed in relation to the granting of the Certificate of Suitability by the EDQM and are, therefore, satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging used to store the drug substance. Confirmation has been provided that the primary packaging complies with current guidelines concerning materials in contact with food.
Appropriate stability data have been generated, supporting a suitable retest period when the drug substance is stored in the packaging proposed.

**Drug product**
Each ml of the clear, colourless solution contains 5 mg oxaliplatin and the excipients lactose monohydrate and water for injection.

The excipients comply with their respective Ph. Eur. monograph. Satisfactory Certificates of Analysis are provided. A suitable declaration issued by supplier of the lactose monohydrate confirms compliance with the requirements of the relevant guideline and Directives with regard to TSE.

**Pharmaceutical development**
The objective of the development programme was to develop a formulation similar to the innovator product, Eloxatin 5 mg/ml concentrate for solution for infusion. A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and originator products.

**Manufacturing process**
A satisfactory batch formula has been provided, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

**Finished product specification**
The finished product specification is acceptable. Test methods have been described and have been adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

**Container closure system**
Oxaliplatin 5mg/ml concentrate for solution for infusion is supplied in colourless type I moulded glass vials with 20 mm grey bromobutyl rubber stoppers provided with a 20mm blood-red flip-off aluminium seal (50mg/10ml), a dark blue flip-off aluminium seal (100mg/20ml) or a light yellow flip-off aluminium seal (200mg/40ml) and a tamper proof sleeved cap.

The 50 mg/10 ml and 100 mg/20 ml presentations are available in a 30 ml vial and the 200 mg/40 ml presentation is available in a 50 ml vial. The vials are packaged in cartons containing one or five vials.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with foodstuffs.

**Stability of the product**
Stability studies were performed in accordance with current guidelines on the finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 18 months for this product when the storage precaution ‘Do not store above 25 °C’ is applied. Appropriate advice on the storage of the solution once diluted is given in the SmPC.

**Product literature**
The SmPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups (‘user testing’), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.
Marketing Authorisation Application (MAA) form
The MAA form is pharmaceutically satisfactory.

Expert report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Quality conclusion
There are no objections to the approval of Oxaliplatin 5 mg/ml concentrate for solution for infusion from a quality point of view.

Preclinical aspects

Preclinical overview
The pharmacological, pharmacokinetic and toxicological properties of oxaliplatin are well known. As oxaliplatin is a well known active substance, no further studies are required and the applicant has provided none. An overview based on the literature is thus appropriate.

The preclinical overview has been written by a suitably qualified expert. The overview, dated July 2010, refers to 34 references from the published literature dated up to 2009. In view of the fact that the pharmaco-toxicological properties of oxaliplatin are well known, the overview is acceptable.

Environmental risk assessment
A suitable justification for the absence of a formal environmental risk assessment has been provided, based on the expectation that introduction of this generic product onto the market is unlikely to result in an increase in the combined sales of all oxaliplatin-containing products, which in turn is unlikely to increase exposure of the environment to oxaliplatin.

Product literature
The product literature is acceptable from a preclinical point of view.

Preclinical conclusion
There are no objections to the approval of Oxaliplatin 5 mg/ml concentrate for solution for infusion from a preclinical point of view.

Clinical aspects

Pharmacokinetics and pharmacodynamics
No new data has been submitted and none are required for this generic application.

The pharmacodynamic and pharmacokinetic claims in the SmPC are consistent with the innovator product. The pharmacodynamic and pharmacokinetic properties of oxaliplatin have been extensively studied in the past.

Oxaliplatin 5 mg/ml concentrate for solution for infusion is the generic version of Eloxatin 5 mg/ml concentrate for solution for infusion as both products contain the same quantitative and qualitative composition of the active ingredient, oxaliplatin.

According to the CPMP guidelines, the applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same active substance, in the same concentration as the currently authorised product (CPMP/EWP/1401/98, subpoint 5.1.6, parenteral solutions).

MHRA PAR; OXALIPLATIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION, PL 31750/0048 19
Clinical efficacy and safety
No new data have been submitted and none are required for this generic application.

Satisfactory evidence to support combination and adjuvant therapy has been provided in the clinical overview.

Oxaliplatin has an acceptable adverse events profile. No novel safety data are supplied or required for this generic application. Oxaliplatin has a well established side-effect profile and is generally well tolerated. The applicant has provided a review of clinical trials published in the literature, confirming the safety of oxaliplatin.

Pharmacovigilance system
The RMS considers that the pharmacovigilance system fulfils the requirements. The applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the collection and notification of any adverse reaction suspected of occurring in the Community or in a third country.

Risk management plan
No safety concerns requiring additional risk minimization activities have been identified. A detailed RMP is not considered necessary for this application.

Expert report
A clinical overall summary, written by an appropriately qualified physician, has been provided and is a satisfactory summary of the clinical part of the dossier.

Product literature
All product literature (SmPC, PIL and labelling) is medically satisfactory.

Clinical conclusion
There are no objections to the approval of Oxaliplatin 5 mg/ml concentrate for solution for infusion from a clinical point of view.
OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Oxaliplatin 5 mg/ml concentrate for solution for infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of these type.

EFFICACY AND SAFETY
No new clinical data were submitted and none are required for applications of these type.
No new or unexpected safety concerns arise from this application.

The SmPC and PIL are satisfactory and consistent with that of the reference product. Satisfactory product labelling has also been submitted.

BENEFIT: RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with oxaliplatin is considered to have demonstrated the therapeutic value of the compound. The benefit: risk ratio is, therefore, considered to be acceptable. A Marketing Authorisation should be granted.
### Module 6

**STEPS TAKEN AFTER INITIAL PROCEDURE – SUMMARY**

The following table lists a non-safety update to the Marketing Authorisation for this product that has been approved by the MHRA since the product was first licensed. The table includes updates that have been incorporated into the text of this Public Assessment Report (PAR) or added as an annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to this Marketing Authorisation.

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>21 January 2013</td>
<td>Type II</td>
<td>To update sections 2, 3, 4.2, 4.3, 4.4, 4.6, 4.8, 5.1, 6.4, 6.5, 6.6, and 9 of the Summary of Product Characteristics (SmPC), the labelling and leaflet in line with the Quality Review of Documents (QRD) template following comments during the Repeat use procedure UK/H/4567/001/E/001.</td>
<td>Approved 31 July 2013</td>
</tr>
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</table>
Annex 1

Reference: PL 31750/0048, Application 0007
Product(s): Oxaliplatin 5 mg/ml concentrate for solution for infusion
Marketing Authorisation Holder: Sun Pharmaceutical Industries Europe BV
Active Ingredient(s): Oxaliplatin
EU Procedure Number: UK/H/4547/001/II/003

Reason:
To update sections 2, 3, 4.2, 4.3, 4.4, 4.6, 4.8, 5.1, 6.4, 6.5, 6.6, and 9 of the Summary of Product Characteristics (SmPC), the labelling and leaflet in line with the Quality Review of Documents (QRD) template following comments during the Repeat use procedure UK/H/4567/001/E/001.

Supporting Evidence
Revised SmPC, leaflet and labelling have been provided.

Evaluation
Adequate clinical information has been provided.

The updated sections of the SmPC, the updated labelling and the leaflet are satisfactory.

Conclusion
The amendments to the SmPC, labelling and leaflet are acceptable and there are no objections to approval.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website. The revised labelling is presented below:
Oxaliplatin 5 mg/ml concentrate for solution for infusion

Oxaliplatin

Intravenous use

5 vials of 10 ml
20 ml pack carton (1 vial):

This product is a concentrate and must be diluted before use. Keep out of the sight and reach of children.
Cytotoxic
Do not store above 25°C
Read the package leaflet for the storage conditions and for
the shelf life of the diluted product.
Discard any unused content according to standard practice for
cytotoxic agents.

Minimum PRINT details

Mylan Pro
5.5 µl

Concentration

- Each vial of 20 ml concentrate contains 100 mg oxaliplatin.

Dosage

- Read the package leaflet before use.

Special Warning

- The product is an amber solution and must be
diluted for use.
- Keep out of the sight and reach of children.
- Do not store above 25°C
- Read the package leaflet for the storage conditions and for
  the shelf life of the diluted product.
- Cytotoxic.
- Discard any unused content according to standard practice for
cytotoxic agents.
40 ml pack carton (5 vials):

Decision – Approved 31 July 2013