Public Assessment Report

Decentralised Procedure

Cisplatin 1 mg/ml concentrate for solution for infusion

(Cisplatin)

Procedure No: UK/H/5712/001/DC

UK Licence No: PL 36390/0182

Cipla (EU) Limited
LAY SUMMARY

Cisplatin 1 mg/ml concentrate for solution for infusion
(cisplatin, concentrate for solution for infusion, 1 mg/ml)

This is a summary of the Public Assessment Report (PAR) for Cisplatin 1 mg/ml concentrate for solution for infusion (PL 36390/0182; UK/H/5712/001/DC). It explains how Cisplatin 1 mg/ml concentrate for solution for infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Cisplatin 1 mg/ml concentrate for solution for infusion.

For practical information about using Cisplatin 1 mg/ml concentrate for solution for infusion, patients should read the package leaflet or contact their doctor or pharmacist.

This product will be referred to as Cisplatin Injection throughout the remainder of this public assessment report.

What is Cisplatin Injection and what is it used for?
Cisplatin Injection is a ‘generic medicine’. This means that Cisplatin Injection is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Platinol 1 mg/ml concentrate for solution for infusion (Bristol-Myers Squibb AB, Sweden).

Cisplatin Injection contains the active ingredient cisplatin which belongs to a group of medicines called cytostatics which are used in the treatment of cancer. Cisplatin can be used alone but more commonly cisplatin is used in combination with other cytostatics. Cisplatin is used to treat cancers of the testis, ovary, urinary bladder, head and neck, and lung. Cisplatin is used to treat cervical cancer in combination with radiotherapy.

How does Cisplatin Injection work?
Cisplatin belongs to a group of medicines called cytostatics. Cytostatic medicines work by stopping the cancer cells from multiplying; so they stop the cancer from growing.

How is Cisplatin Injection used?
The pharmaceutical form of this medicine is a concentrate for solution for infusion which is diluted before administration. The route of administration of this medicine is an injection into the patient’s vein (an intravenous infusion).

Cisplatin Injection must only be given by a specialist in cancer treatment.

The recommended dosage of Cisplatin Injection depends on the patient’s well-being, the anticipated effects of the treatment, and whether or not Cisplatin Injection is given on its own (monotherapy) or in combination with other agents (combination therapy).

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.
What benefits of Cisplatin Injection have been shown in studies?
No additional studies were needed as Cisplatin Injection is a generic medicine that is given by infusion and contains the same active substance as the reference medicine, Platinol 1 mg/ml concentrate for solution for infusion (Bristol-Myers Squibb AB, Sweden).

What are the possible side effects of Cisplatin Injection?
Because Cisplatin Injection is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Cisplatin Injection, see section 4 of the package leaflet available on the MHRA website.

Why was Cisplatin Injection approved?
It was concluded that, in accordance with EU requirements, Cisplatin Injection has been shown to have comparable quality and to be comparable to Platinol 1 mg/ml concentrate for solution for infusion. Therefore, the MHRA decided that, as for Platinol 1 mg/ml concentrate for solution for infusion, the benefits are greater than its risk and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Cisplatin Injection?
A risk management plan (RMP) has been developed to ensure that Cisplatin Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Cisplatin Injection including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Cisplatin Injection
Cyprus, Germany, France, Malta, Romania and the UK agreed to grant a Marketing Authorisation for Cisplatin Injection on 10 February 2015. A Marketing Authorisation was granted in the UK on 06 March 2015.

The full PAR for Cisplatin Injection follows this summary.

For more information about treatment with Cisplatin Injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2015.
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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Cisplatin Injection (PL 36390/0182; UK/H/5712/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for the treatment of:

- advanced or metastatic testicular cancer
- advanced or metastatic ovarian cancer
- advanced or metastatic bladder carcinoma
- advanced or metastatic squamous cell carcinoma of the head and neck
- advanced or metastatic non-small cell lung carcinoma
- advanced or metastatic small cell lung carcinoma

Cisplatin is indicated in combination with radiotherapy in the treatment of cervical carcinoma.

Cisplatin can be used as monotherapy and in combination therapy

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Cyprus, Germany, France, Malta, Romania as Concerned Member States (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Platinol 1 mg/ml concentrate for solution for infusion, which was originally granted to Bristol-Myers Squibb AB, Sweden on 21 February 1992. The UK reference product is Platinex concentrate for solution for infusion which was authorised to the same Marketing Authorisation Holder (MAH), Bristol-Myers Squibb Holdings Limited (PL 00125/0213) on 14 June 1996. The reference medicinal product has now been withdrawn from the UK market since 08 February 2007.

Cisplatin is an inorganic compound which contains a heavy metal [cis-diamminedichlorido(platinum(II)]. It inhibits DNA-synthesis by the formation of DNA cross-links. Protein and RNA synthesis are inhibited to a lesser extent.

Although the most important mechanism of action seems to be inhibition of DNA synthesis, other mechanisms can also contribute to the antineoplastic activity of cisplatin, including the increase of tumour immunogenicity. The oncolytic properties of cisplatin are comparable to other alkylating agents.

Cisplatin also has immunosuppressive, radiosensitising, and antibacterial properties. Cisplatin seems to be cell-cycle non-specific. The cytotoxic action of cisplatin is caused by binding to all DNA-bases, with a preference for the N-7 position of guanine and adenosine.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release 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 as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 10 February 2015. After a subsequent national phase, a licence was granted in the UK on 06 March 2015.
II QUALITY ASPECTS

II.1 Introduction
Each ml of concentrate for solution for infusion contains 1 mg of cisplatin.
One vial of 10 ml of concentrate for solution for infusion contains 10 mg of cisplatin.
One vial of 50 ml of concentrate for solution for infusion contains 50 mg of cisplatin
One vial of 100 ml of concentrate for solution for infusion contains 100 mg of cisplatin
Other ingredients consist of the pharmaceutical excipients sodium chloride, sodium hydroxide (for pH adjustment), hydrochloric acid (for pH adjustment) and water for injections. The finished product is packed into 10 ml, 50 ml and 100 ml type I amber glass vials with a 20 mm rubber stopper (Teflon coated), sealed with a 20 mm flip off tear off aluminium seal. Not all pack sizes may be marketed. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2 Drug Substance
INN: Cisplatin
Chemical name: Cis-diaminedichloroplatinum (II)

Structural formula:

\[
\begin{align*}
\text{Cl} & \quad \text{Pt} & \quad \text{NH}_3 \\
\text{Cl} & \quad \text{Pt} & \quad \text{NH}_3
\end{align*}
\]

Molecular formula: \( \text{Cl}_2\text{H}_6\text{N}_2\text{Pt} \)
Molecular mass: 300.0
Appearance: A yellow powder or yellow or orange-yellow crystals.
Solubility: Slightly soluble in water, sparingly soluble in dimethyl formamide, practically insoluble in alcohol.

Cisplatin is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, concentrate for solution for infusion containing 1 mg cisplatin per ml that was comparable to the originator product Platinol 1 mg/ml concentrate for solution for infusion (Bristol-Myers Squibb AB, Sweden). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results. The Marketing Authorisation Holder (MAH) has committed to carry out additional process validation on future commercial-scale batch sizes.

Finished Product Specification

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

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened vial with the storage conditions ‘Do not store above 25°C. Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.’

Storage conditions of the reconstituted medicinal product are included in section 6.3 of the SmPC. These are:

Shelf-life after dilution of the medicinal product:
Chemical and physical in-use stability has been demonstrated after dilution with infusion fluids described in section 6.6 of the SmPC for 24 hours at 25°C, protected from light.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.
Do not store diluted solutions in the refrigerator or freezer.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of cisplatin are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The MAH’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Cisplatin Injection is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
As per the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), “bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product.”

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of cisplatin.

Based on the data provided, Cisplatin Injection can be considered a generic of Platinol 1 mg/ml concentrate for solution for infusion (Bristol-Myers Squibb AB, Sweden).
IV.2  Pharmacokinetics
In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3  Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4  Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5  Clinical safety
No new safety data were submitted and none were required for this application.

IV.6  Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Cisplatin Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

| Important identified risks                           | • Hypersensitivity reactions including anaphylactoid reactions |
|                                                    | • Nephrotoxicity                                               |
|                                                    | • Myelosuppression                                             |
|                                                    | • Ototoxicity                                                  |
|                                                    | • Neuropathies                                                 |
|                                                    | • Drug interactions with live vaccines, including yellow fever vaccine |
|                                                    | • Drug interaction with phenytoin                             |
|                                                    | • Sepsis                                                      |
|                                                    | • Use in breast feeding                                        |

| Important potential risks                          | • Secondary carcinoma including acute leukaemia                |
|                                                    | • Risk of use during pregnancy including teratogenicity       |
|                                                    | • Irreversible infertility                                    |
|                                                    | • Optic neuritis                                              |
|                                                    | • Overdose                                                    |

| Missing information                                | None                                                         |
Summary table of risk minimisation measures:

**Important Identified Risks**

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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tr>
<td>Hypersensitivity reactions including anaphylactoid reactions</td>
<td>Cisplatin is contraindicated in patients with known hypersensitivity to cisplatin or other platinum compounds or to any of the excipients. These reactions can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids. This safety concern has been mentioned in Section 4.3 “Contraindications”, Section 4.4 “Special warnings and precautions for use”, Section 4.8 “Undesirable effects” of the SPC and Section 2 “What you need to know before you are given Cisplatin Injection” and Section 4 “Possible side effects” of the PIL. Close supervision must also be carried out with regard to anaphylactic reactions. Other routine risk minimisation measures: This product is available only as prescription</td>
<td>None</td>
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<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
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<td>only medicine.</td>
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<td>Nephrotoxicity</td>
<td>Concomitant administration of nephrotoxic medicinal products (e.g. cephalosporins, aminoglycosides or Amphotericin B or contrast media) will potentiate the toxic effect of cisplatin on the kidneys and should be avoided. During or after treatment with cisplatin caution is advised with predominantly renally eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination. The use of cisplatin in combination with docetaxel should be initiated based on benefit-risk evaluation. A urine output of 100 mL/hour or greater will tend to minimize cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration (recommended 2,500 mL/m²/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. mannitol). Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity. This safety concern has been mentioned in Section 4.3 “Contraindications”, Section 4.4 “Special warnings and precautions for use” and</td>
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<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
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<td></td>
<td>Section 4.8 “Undesirable effects” of the SPC and Section 2 “What you need to know before you are given Cisplatin injection” of the PIL. Pre- and post-hydration is required to prevent serious renal dysfunction. Before, during and after administration of cisplatin serum electrolytes (calcium, sodium, potassium, magnesium) levels should be determined in patients. These examinations must be repeated every week over the entire duration of the treatment with cisplatin. This has been mentioned in Section 4.4. “Special Warnings and Precautions for Use” of the SPC. Dehydration can occur as a result of damage to the kidney caused by cisplatin, thus reducing the tubular resorption of cations. Generally, normal serum electrolyte levels should be restored by administering supplemental electrolytes and discontinuing cisplatin. This has been mentioned in Section 4.8 “Undesirable effects” of the SPC. Cisplatin is contraindicated in patients with dehydrated condition. This safety concern has been mentioned in Section 4.3 Contraindications of the SPC and Section 2 “What you need to know before you are given Cisplatin injection” of the PIL.</td>
<td>Other routine risk minimisation measures: This product is available only as prescription</td>
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<td>Safety concern</td>
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<td>only medicine.</td>
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<td>Myelosuppression</td>
<td>Cisplatin is contraindicated in patients with myelosuppression. This safety concern has been mentioned in Section 4.3 “Contraindications” and Section 4.8 “Undesirable effects” of the SPC. Simultaneous use of myelosuppressives or radiation will boost the effects of cisplatin’s myelosuppressive activity. This safety concern has been mentioned in Section 4.5, “Interaction with other medicinal products and other forms of interaction” of the SPC. If any symptoms such as extreme tiredness, increased bruising or bleeding or occurrence of infections are observed, medical attention should be sought. Before, during and after administration of cisplatin, hematopoiesis functions (number of red and white blood cells and blood platelets) should be determined. Repeating administration of cisplatin must be delayed until normal values (White blood cells &gt; 4.000/µl resp. &gt; 4.0 x 10⁹/l and Blood platelets &gt; 100.000/µl resp. &gt; 100 x 10⁹/l ) are achieved. This has been mentioned in Section 4.4. “Special Warnings and Precautions for Use” of the SPC. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
<td>None</td>
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<td>Safety concern</td>
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<td>Ototoxicity</td>
<td>Cisplatin is contraindicated in patients with pre-existing hearing impairment due to the fact that cisplatin is nephrotoxic and neurotoxic (in particular ototoxic). These toxicities may be cumulative if disorders of this type pre-exist. This safety concern has been mentioned in Section 4.3 “Contraindications” of the SPC. Careful monitoring by audiometry should be performed prior to initiation of therapy and prior to subsequent doses of cisplatin. This safety concern has been mentioned in Section 4.4, “Special Warnings and Precautions for Use” of the SPC. Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function. Except for patients receiving doses of cisplatin exceeding 50 mg/m², whose urine secretion is less than 1000 ml per 24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity. Ifosfamide may increase hearing loss due to cisplatin. Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus).</td>
<td>None</td>
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<td>Safety concern</td>
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<td>This safety concern has been mentioned in Section 4.5, “Interaction with other medicinal products and other forms of interaction” and Section 4.8 “Undesirable effects of the SPC. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
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<tr>
<td>Neuropathies</td>
<td>Cisplatin is contraindicated in patients with neuropathy caused by cisplatin. This safety concern has been mentioned in Section 4.3 “Contraindications” of the SPC. A neurologic examination must be carried out at regular intervals. Special caution must be exercised for patients with peripheral neuropathy not caused by cisplatin. This has been mentioned in Section 4.4, “Special Warnings and Precautions for Use” of the SPC. The use of cisplatin in combination with docetaxel should be initiated based on benefit-risk evaluation. Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity. This safety concern has been mentioned in Section 4.5, “Interaction with other medicinal products and other forms of interaction” of the SPC. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
<td>None</td>
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<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tr>
<td>Drug interactions with live vaccines, including yellow fever vaccine</td>
<td>The use of cisplatin is contraindicated in combination with live vaccines; including yellow fever vaccine. This has been mentioned in Section 4.3 &quot;Contraindications&quot; of the SPC. Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease. In view of the risk of generalised illness, it is advisable to use an inactive vaccine if available. This has been mentioned in Section 4.5, “Interaction with other medicinal products and other forms of interaction” of the SPC and Section 2, “What you need to know before you are given Cisplatin injection” of the PIL. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
<td>None</td>
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<tr>
<td>Drug interaction with phenytoin</td>
<td>The use of cisplatin is contraindicated for use in combination with phenytoin in prophylactic use. This has been mentioned in Section 4.3 “Contraindications” of the SPC. Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment. During cisplatin therapy starting a new anticonvulsivant treatment with phenytoin is strictly contraindicated. This has been mentioned in Section 4.5,</td>
<td>None</td>
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<td>Safety concern</td>
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<td>“Interaction with other medicinal products and other forms of interaction” of the SPC</td>
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<td>Other routine risk minimisation measures:</td>
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<td></td>
<td>This product is available only as prescription only medicine.</td>
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<tr>
<td>Sepsis</td>
<td>Sepsis is known to occur at a frequency of ≥1/100 to &lt;1/10 (common) while on</td>
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<td>cisplatin treatment. Infectious complications have led to death in some patients. This</td>
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<td>safety concern has been mentioned in Section 4.8 “Undesirable effects” of the SPC.</td>
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<td>Other routine risk minimisation measures:</td>
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<td>This product is available only as prescription only medicine.</td>
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<td>Use in breast feeding</td>
<td>Cisplatin is excreted in breast milk. Breastfeeding is contraindicated during treatment with</td>
<td>None</td>
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<td>cisplatin. The risk is mentioned in section 4.6 (Fertility, pregnancy and lactation) of the</td>
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<td>SPC. Other routine risk minimisation measures:</td>
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<td>This product is available only as prescription only medicine.</td>
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**Important Potential Risks**

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<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<tr>
<td>Secondary carcinoma</td>
<td>In humans, in rare cases, the appearance of acute leukaemia has coincided with use of</td>
<td>None</td>
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<td>Safety concern</td>
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<td>including acute leukaemia’</td>
<td>Cisplatin, which was, in general, associated with other leukaemogenic agents. Cisplatin is a bacterial mutagen and causes chromosome aberrations in cultures on animal cells. Carcinogenicity is possible but has not been demonstrated. This has been mentioned in Section 4.4, “Special Warnings and Precautions for Use” of the SPC. Cisplatin is mutagenic in numerous <em>in vitro</em> and <em>in vivo</em> tests (bacterial test systems, chromosomal disorders in animal cells and in tissue cultures). In long-term studies it has been shown that cisplatin is carcinogenic in mice and rats. This has been mentioned in Section 5.3 “Preclinical safety data” of the SPC. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
<td>None</td>
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<td>Risk of use during pregnancy including teratogenicity</td>
<td>Cisplatin may be toxic to the foetus when administered to a pregnant woman. Animal studies have shown reproductive toxicity and transplacental carcinogenicity. During treatment with Cisplatin and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy: this applies to patients of both sexes. Genetic consultation is recommended if the patient wishes to have children after ending the treatment. Male and female patients have to</td>
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<td>Safety concern</td>
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<td>use effective contraception during and for at least 6 months after the treatment with cisplatin. This has been mentioned in Section 4.3 “Contraindications”, Section 4.4 “Special warnings and Precautions for Use” and Section 4.6 “Fertility, pregnancy and lactation” of the SPC and Section 2 “What you need to know before you are given Cisplatin injection” of the PIL. Studies in rats have shown that exposure during pregnancy can cause tumours in adult offspring. Cisplatin is embryotoxic in mice and rats, and in both species deformities have been reported. This has been mentioned in Section 5.3 “Preclinical safety data” of the SPC. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
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</table>
| Irreversible infertility | Treatment with cisplatin may cause irreversible infertility; therefore it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryoconservation of their sperm prior to treatment. In mice, gonadal suppression, resulting in amenorrhea or azoospermia has been observed, which can be irreversible and result in infertility. In female rats cisplatin induced morphological changes in the ovaries, causing partial and reversible
<p>|                      | None                                                                                                                                                                                                                                                                                                                                                                                      |</p>
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Routine risk minimisation measures</th>
<th>Additional risk minimisation measures</th>
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<td>infertility. This has been mentioned in section 4.6 “Fertility, pregnancy and lactation” and Section 5.3 “Preclinical safety data” of the SPC and Section 2 “What you need to know before you are given Cisplatin injection” of the PIL. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
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<td>Optic neuritis Optic neuritis is known to occur at an unknown frequency with cisplatin. This has been mentioned in Section 4.8 “Undesirable effects” of the SPC and Section 4 Possible side effects of PIL. Other routine risk minimisation measures: This product is available only as prescription only medicine.</td>
<td>None</td>
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<td>Overdose Symptoms of overdose involve several side effects in an excessive manner. Efficient hydration and osmotic diuresis can aid in reduction of toxicity, provided this is applied immediately after overdose. In case of overdose (≥200 mg/m³), direct effects on the respiratory centre are possible, which might result in life threatening respiratory disorders and acid base equilibrium disturbance due to passage of the blood brain barrier. An acute overdose of Cisplatin may result in renal failure, liver failure, deafness, ocular toxicity</td>
<td>None</td>
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<tr>
<td>Safety concern</td>
<td>Routine risk minimisation measures</td>
<td>Additional risk minimisation measures</td>
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<td>(including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. An overdose may be fatal. There is no specific antidote in the event of an overdose of Cisplatin. Even if haemodialysis is initiated 4 hours after the overdose it has little effect on the elimination of cisplatin from the body following a strong and rapid fixation of Cisplatin to proteins. Treatment in the event of an overdose consists of general support measures. Convulsions may be treated with appropriate anticonvulsants. Renal function, cardiovascular function and blood counts should be monitored daily in order to assess the potential toxicity to these systems. Serum magnesium and calcium levels should be carefully monitored as should symptoms and signs of voluntary muscle irritability. If symptomatic tetany develops, electrolyte supplements should be administered. Serum liver enzymes and uric acid should also be monitored daily after an acute overdose. If fever develops during prolonged myelosuppression, appropriate presumptive antibiotic coverage should be instilled after cultures have been obtained. This has been mentioned in Section 4.8 “Overdose” of the SPC and Section 3 “How you are given Cisplatin Injection- If you</td>
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</tbody>
</table>
The RMP for Cisplatin Injection adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of cisplatin and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

**IV.7 Discussion on the clinical aspects**

No new clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application.

**V User consultation**

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 language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

**VI Overall conclusion, benefit/risk assessment and recommendation**

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with cisplatin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels**

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 approved labelling for Cisplatin Injection is presented below:
Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin 1 mg/ml Concentrate for Solution for Infusion contains 100 mg of Cisplatin.

Sodium chloride, Sodium hydroxide (for pH adjustment) Hydrochloric acid (for pH adjustment) Water for injections

To be diluted before use.

Read the package leaflet before use.

Keep out of the sight and reach of children.

Do not store above 25°C.
PAR Cisplatin 1 mg/ml concentrate for solution for infusion

UK/H/5712/001/DC

Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin

50 ml of concentrate for solution for infusion contains 50 mg of Cisplatin

100 ml of concentrate for solution for infusion contains 100 mg of Cisplatin

Sodium chloride, Sodium hydroxide (for pH adjustment), Hydrochloric acid (for pH adjustment)

Water for Injection

See leaflet for further information

To be diluted before use

Read the package leaflet before use. Keep out of the sight and reach of children. Read the leaflet for the shelf life of the medicinal product. Do not store above 30°C. Keep tightly closed in the original packaging in order to protect from light. Do not refrigerate or freeze. Shakes or foams should not be used. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required.

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Unregistered Art.