Public Assessment Report

Decentralised Procedure

CISPLATIN 1MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

UK/H/2862/001/DC
UK licence no: PL 20075/0123

Accord Healthcare Limited
CISPLATIN 1MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

LAY SUMMARY

On 21st June 2010, Austria, Belgium, Bulgaria, Germany, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden and the UK agreed to grant a marketing authorisation to Accord Healthcare Limited for the medicinal product Cisplatin 1mg/ml Concentrate for Solution for Infusion. The licence was granted via the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 21st June 2010.

This product is a prescription-only medicine (POM), for the treatment of various forms of cancer. Cisplatin forms part of a group of medicines called cytostatics. It can destroy cells in your body that may cause certain types of cancer (tumour of testis, tumour of ovary, tumour of the bladder, head and neck epithelial tumour, lung cancer and for cervical cancer in combination with radiotherapy).

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Cisplatin 1mg/ml Concentrate for Solution for Infusion outweigh the risks, hence a Marketing Authorisation has been granted.
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# Module 1

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<th><strong>Product Name</strong></th>
<th>Cisplatin 1mg/ml Concentrate for Solution for Infusion</th>
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<td><strong>Type of Application</strong></td>
<td>Generic application, Article 10.1</td>
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<td><strong>Active Substance</strong></td>
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<tr>
<td><strong>Form</strong></td>
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<tr>
<td><strong>Strength</strong></td>
<td>1mg/ml</td>
</tr>
<tr>
<td><strong>MA Holder</strong></td>
<td>Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom</td>
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<td><strong>RMS</strong></td>
<td>UK</td>
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<tr>
<td><strong>CMS</strong></td>
<td>Austria, Belgium, Bulgaria, Germany, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/2862/001/DC</td>
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Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Cisplatin 1 mg/ml Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
1 ml of concentrate for solution for infusion contains 1 mg of Cisplatin.
10 ml of concentrate for solution for infusion contains 10 mg of Cisplatin.
25 ml of concentrate for solution for infusion contains 25 mg of Cisplatin.
50 ml of concentrate for solution for infusion contains 50 mg of Cisplatin.

Each ml of solution contains 3.5 mg of sodium. For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion
Clear, colourless to pale yellow solution in an amber glass vial, which is practically free from particles.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Cisplatin is intended for the treatment of:
- advanced or metastasised testicular cancer
- advanced or metastasised ovarian cancer
- advanced or metastasised bladder carcinoma
- advanced or metastasised squamous cell carcinoma of the head and neck
- advanced or metastasised non-small cell lung carcinoma
- advanced or metastasised small cell lung carcinoma.
- Cisplatin is indicated in the treatment of cervical carcinoma in combination with other chemotherapeutics or with radiotherapy.
- Cisplatin can be used as monotherapy and in combination therapy.

4.2 Posology and method of administration
Cisplatin 1 mg/ml concentrate for solution for infusion is to be diluted before administration. For instructions on dilution of the product before administration (see section 6.6).

The diluted solution should be administered only intravenously by infusion (see below). For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided (see section 6.2).

Adults and children:
The cisplatin dosage depends on the primary disease, the expected reaction, and on whether cisplatin is used for monotherapy or as a component of combination chemotherapy. The dosage directions are applicable for both adults and children.

For monotherapy, the following two dosage regimens are recommended:
Single dose of 50 to 120 mg/m² body surface every 3 to 4 weeks;
15 to 20 mg/m²/day for five days, every 3 to 4 weeks.

If cisplatin is used in combination chemotherapy, the dose of cisplatin must be reduced. A typical dose is 20 mg/m² or more once every 3 to 4 weeks.

For treatment of cervical cancer cisplatin is used in combination with radiotherapy. A typical dose is 40 mg/m² weekly for 6 weeks.

For warnings and precautions to be considered prior to the start of the next treatment cycle (see section 4.4).

In patients with renal dysfunction or bone marrow depression, the dose should be reduced adequately (see section 4.3).
The cisplatin solution for infusion prepared according to instructions (see section 6.6.) should be administered by intravenous infusion over a period of 6 to 8 hours.

Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydratation is necessary to cause sufficient diuresis during and after treatment with cisplatin. It is realised by intravenous infusion of one of the following solutions:
- sodium chloride solution 0.9%;
- mixture of sodium chloride solution 0.9% and glucose solution 5% (1:1).

Hydration prior to treatment with cisplatin:
Intravenous infusion of 100 to 200ml/hour for a period of 6 to 12 hours, with a total amount of at least 1L.

Hydration after termination of the administration of cisplatin:
Intravenous infusion of another 2 litres at a rate of 100 to 200 ml per hour for a period of 6 to 12 hours.

Forced diuresis may be required should the urine secretion be less than 100 to 200 ml/hour after hydration. Forced diuresis may be realised by intravenously administering 37.5g mannitol as a 10% solution (375 ml mannitol solution 10%), or by administration of a diuretic if the kidney functions are normal.

The administration of mannitol or a diuretic is also required when the administrated cisplatin dose is higher than 60 mg/m² of body surface.

It is necessary that the patient drinks large quantities of liquids for 24 hours after the cisplatin infusion to ensure adequate urine secretion.

4.3 Contraindications
Cisplatin is contraindicated in patients
- with hypersensitivity to cisplatin or other platinum compounds or to any of the excipients;
- with renal dysfunction (creatinine clearance < 60 ml/min);
- in dehydrated condition (pre- and post-hydration is required to prevent serious renal dysfunction);
- with myelosuppression;
- with a hearing impairment;
- with neuropathy caused by cisplatin
- who are breastfeeding (see section 4.6)
- in combination with live vaccines, including yellow fever vaccine (see section 4.5).
- in combination with phenytoin in prophylactic use (see section 4.5)

4.4 Special warnings and precautions for use
Cisplatin may only be administered under the supervision of a physician qualified in oncology with experience in the use of antineoplastic chemotherapy.

Cisplatin is proven to be cumulative ototoxic, nephrotoxic, and neurotoxic. The toxicity caused by cisplatin may be amplified by the combined use with other medicinal products, which are toxic for the said organs or systems.

Audiograms must be made before starting treatment with cisplatin and always before starting another treatment cycle (see section 4.8).

Nephrotoxicity can be prevented by maintaining adequate hydration before, during and after the intravenous infusion of cisplatin.

Forced diuresis by hydration or by hydration and suitable diuretics before and after the cisplatin administration decreases the risk of nephrotoxicity. Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity.

Before, during and after administration of cisplatin, the following parameters resp. organ functions must be determined:
- renal function;
- hepatic function;
- hematopoiesis functions (number of red and white blood cells and blood platelets);
- serum electrolytes (calcium, sodium, potassium, magnesium).

These examinations must be repeated every week over the entire duration of the treatment with cisplatin.

Repeating administration of cisplatin must be delayed until normal values are achieved for the following parameters:
- Serum creatinine < 130 µmol/l resp. 1.5 mg/dl
- Urea < 25 mg/dl
- White blood cells > 4,000/µl resp. > 4.0 x 10⁹/l
- Blood platelets > 100,000/µl resp. > 100 x 10⁹/l
- Audiogram: results within the normal range.

Anaphylactic-like reactions to cisplatin have been observed. These reactions can be controlled by administration of antihistamines, adrenaline and/or glucocorticoids.

Neurotoxicity secondary to cisplatin administration has been reported and therefore neurological examinations are recommended.

Special caution must be exercised for patients with peripheral neuropathy not caused by cisplatin.

Special care is required for patients with acute bacterial or viral infections.

In cases of extravasation:
- immediately end the infusion of cisplatin;
- do not move the needle, aspirate the extravasate from the tissue, and rinse with sodium chloride solution 0.9% (if solutions with cisplatin concentrations higher than recommended were used; see section 6.6.).

Nausea, vomiting and diarrhoea often occur after administration of cisplatin (see section 4.8). These symptoms disappear in most patients after 24 hours. Less serious nausea and anorexia may continue up to seven days after the treatment.

Prophylactic administration of an anti-emetic may be effective in alleviating or preventing nausea and vomiting.

The liquid loss caused by vomiting and diarrhoea must be compensated.

Cisplatin has been shown to be mutagenic. It may also have an anti-fertility effect. Other anti-neoplastic substances have been shown to be carcinogenic and this possibility should be borne in mind in long term use of cisplatin.

Male and female patients should use effective contraception during and for at least 6 months after the treatment with cisplatin (see section 4.6).

4.5 Interaction with other medicinal products and other forms of interaction

Simultaneous use of myelosuppressives or radiation will boost the effects of cisplatin’s myelosuppressive activity.

The occurrence of nephrotoxicity caused by cisplatin may be intensified by concomitant treatment with antihypertensives containing furosemide, hydralazine, diazoxide, and propranolol.

Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides or Amphotericin B or contrast media) or ototoxic (e.g. aminoglycosides) medicinal products will potentiate the toxic effect of cisplatin on these organs. 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.

It may be required to adjust the dosage of allopurinol, colchicine, probenecid, or sulfinpyrazone if used together with cisplatin, since cisplatin causes an increase in serum uric acid concentration.
Except for patients receiving doses of cisplatin exceeding 60 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.

Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclozine, phenothiazines,
thioxanthenes or trimethobenzamides may mask ototoxicity symptoms (such as dizziness and tinnitus).

Simultaneous use of ifosfamide causes increased protein excretion. The ototoxicity of cisplatin was
reportedly enhanced by concomitant use of ifosfamide, an agent which is not ototoxic when given
alone.

In a randomised trial in patients with advanced ovarian carcinoma the response to therapy was
influenced negatively by concomitant administration of pyridoxine and hexamethylmelamine.

Cisplatin given in combination with bleomycin and vinblastin can lead to a Raynaud-phenomenon.

Evidence has been established that the treatment with cisplatin prior to an infusion with paclitaxel may
reduce the clearance of paclitaxel by 70-75% and therefore can intensify neurotoxicity (in 70% of
patients or more).

In a study of cancer patients with metastatic or advanced tumors, docetaxel in combination with
cisplatin induced more severe neurotoxic effects (doserelated and sensoric) than either drug as a single
agent in similar doses.

Reduction of the blood’s lithium values was noticed in a few cases after treatment with cisplatin
combined with bleomycin and etoposide. It is therefore recommended to monitor the lithium values.

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 (see section 4.3.). Chelating agents like penicillamine may diminish the effectiveness of cisplatin.

The high intra-individual variability of the coagulability during diseases, and the possibility of
interaction between oral anticoagulants and anticancer chemotherapy requires an increased frequency
of the INR (prothrombin time) monitoring.

In concomitant use of cisplatin and ciclosporin the excessive immunosuppression with risk of
lymphoproliferation is to be taken into consideration.

Use of living virus vaccinations is contraindicated given within three months following the end of the
cisplatin treatment.

Yellow fever vaccine is strictly contra-indicated because of the risk of fatal systemic vaccinal disease
(see section 4.3.).

### 4.6 Pregnancy and lactation

#### Pregnancy

There is insufficient data about the use of cisplatin in pregnant women.

However, based on the pharmacological properties, cisplatin is suspected to cause serious birth defects.
Animal studies have shown reproductive toxicity and transplacental carcinogenicity (see section 5.3).
Cisplatin should not be used during pregnancy unless clearly necessary.

Women of childbearing potential and male patients have to use effective contraception during and up to
6 months after treatment.

A preconceptual consult is recommended when patients wish to have children after treatment with
cisplatin. Cisplatin can cause temporary or permanent infertility. Sperm cryopreservation can be
considered (see also section 4.4).

#### Lactation

Cisplatin is excreted in breast milk. Breastfeeding is contra-indicated during treatment with cisplatin.
4.7 Effects on ability to drive and use machines
No studies on the effects on the ability to drive and use machines have been performed.

However, the profiles of undesirable effects (central nervous system and special senses) may lead to minor or moderate influence on the ability to drive and use machines. Patients who suffer from these effects (e.g. sleepy or vomiting) must avoid driving and operating machinery.

4.8 Undesirable effects
Undesirable effects depend on the used dose and may have cumulative effects.
The most frequently reported adverse events (>10%) of cisplatin were haematological (leukopenia, thrombocytopenia and anaemia), gastrointestinal (anorexia, nausea, vomiting and diarrhoea), ear disorders (hearing impairment), renal disorders (renal failure, nephrotoxicity, hyperuricaemia) and fever.

Serious toxic effects on the kidneys, bone marrow and ears have been reported in up to about one third of patients given a single dose of cisplatin; the effects are generally dose-related and cumulative. Ototoxicity may be more severe in children.

Frequencies are defined using the following convention:
Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Infections and infestations

Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Rare: Cisplatin increases the risk of secondary leukaemia. The risk of secondary leukaemia is dose-dependent and not age- and sex-related.

Carcinogenicity is theoretically possible (based on cisplatin’s mechanism of action).

Blood and lymphatic system disorders
Very common: Dose dependent, cumulative and mostly reversible leukopenia, thrombocytopenia and anaemia are observed in 25-30% of patients treated with cisplatin.

Common: A considerable decrease in the number of white blood cells often occurs approximately 14 days after the use (less than 1.5 × 10^9/l in 5% of the patients). A decrease of the number of platelets is observed after approximately 21 days (less than 10% of the patients showed a total less than 50 × 10^9/l) (the recovery period is approximately 39 days). Anaemia (decreases of greater than 2g haemoglobin) occurs at approximately the same frequency, but generally with a later onset than leukopenia and thrombocytopenia.

Rare: Coombs positive haemolytic anaemia was reported and was reversible if the use of cisplatin was terminated. Literature has been published regarding hemolysis possibly caused by cisplatin. Serious bone marrow failure (including agranulocytosis and/or aplastic anaemia) may occur after high doses of cisplatin.

Very rare: Thrombotic microangiopathy combined with haemolytic uraemic syndrome.

Immune system disorders
Uncommon: Hypersensitivity may present as rash, urticaria, erythema, or pruritus allergic.

Rare:
Anaphylactic reactions have been reported; hypotension, tachycardia, dyspnoea, bronchospasm, face oedema and fever have been reported. Treatment with antihistamines, epinephrine (adrenaline) and steroids may be required.

Immunosuppression has been documented.

**Endocrine disorders**

*Very rare:*

Syndrome of inappropriate antidiuretic hormone secretion.

**Metabolism and nutrition disorders**

*Rare:*

Hypomagnesaemia, hypocalcaemia, hyponatraemia, hypophosphataemia and hypokalaemia with muscle spasms and/or electrocardiogram changes occur as a result of damage to the kidney caused by cisplatin, thus reducing the tubular resorption of cations.

Hypercholesterolemia.

*Very rare:*

Increased blood amylase.

*Very rare:*

Increased blood iron.

**Nervous system disorders**

*Common:*

Neurotoxicity caused by cisplatin is characterised by peripheral neuropathy (typically bilateral and sensory), and rarely by the loss of taste or tactile function, or by optic retrobulbar neuritis with reduced visual acuity and cerebral dysfunction (confusion, disartrhia, individual cases of cortical blindness, loss of memory, paralysis). Lhermitte’s sign, autonomous neuropathy and myelopathy of the spinal cord have been reported.

*Rare:*

Cerebral disorders (including acute cerebrovascular complications, cerebral arteritis, occlusion of the carotid artery, and encephalopathy).

*Very rare:*

Seizures.

The use of cisplatin must be terminated immediately if one of the above mentioned cerebral symptoms occurs. Neurotoxicity caused by cisplatin may be reversible. However, the process is irreversible for 30-50% of the patients, even after discontinuation of the treatment. Neurotoxicity may occur after the first dose of cisplatin, or after a long-term therapy. Severe neurotoxicity may occur in patients who have received cisplatin at high concentrations or for a prolonged period.

**Eye disorders**

*Rare:*

Blindness during a combination treatment with cisplatin. Following high-dose cisplatin application impairment of colour vision and eye movement has been reported.

*Very rare:*

Papilloedema, optic neuritis and cortical blindness have been reported following treatment with cisplatin. One case of unilateral optic neuritis retrobulbar with reduced visual acuity has been reported after combination chemotherapy followed by cisplatin treatment.

**Ear and labyrinth disorders**

*Very common:*

Hearing impairment has been documented in approximately 31% of patients treated with 50 mg/m² cisplatin. The defect is cumulative, may be irreversible, and is sometimes limited to one ear. Ototoxicity manifests itself as tinnitus and/or hearing impairment at higher frequencies (4,000-8,000 Hz). Hearing impairment at frequencies of 250-2000Hz (normal hearing range) was noticed for 10 to 15% of the patients.
**Common:**
Deafness and vestibular toxicity combined with vertigo may occur. Prior or simultaneous cranial radiation increases the risk of hearing loss.

**Rare:**
Patients may lose the ability to conduct a normal conversation. Cisplatin-induced hearing impairment may be serious for children and elderly patients. (See section 4.4.)

**Cardiac disorders**
**Common:**
Arrhythmia including bradycardia, tachycardia and other electrocardiogram changes e.g. ST-segment changes, signs of myocardial ischemia have been observed particularly in combination with other cytotoxics.

**Rare:**
Hypertension and myocardial infarction may occur, even some years after chemotherapy. Severe coronary artery disease.

**Very rare:**
Cardiac arrest has been reported after treatment with cisplatin combined with other cytotoxics.

**Vascular disorders**
**Common:**
Phlebitis may occur in the area of the injection after intravenous administration.

**Very rare:**
Vascular disorders (cerebral or myocardial ischaemia, impairment of the peripheral circulation related to the Raynaud’s syndrome) were linked to cisplatin chemotherapy.

**Respiratory, thoracic and mediastinal disorders**
**Common:**
Dyspnoea, pneumonia and respiratory failure.

**Gastrointestinal disorders**
**Very common:**
Anorexia, nausea, vomiting and diarrhoea occur between 1 and 4 hours after the use of cisplatin. (See section 4.4.)

**Uncommon:**
Metallic setting on the gums.

**Rare:**
Stomatitis, diarrhoea.

**Hepatobiliary disorders**
**Common:**
Abnormal hepatic function with increased transaminases and blood bilirubin are reversible.

**Rare:**
Reduced blood albumin levels were noticed and may be linked to the treatment with cisplatin.

**Skin and subcutaneous tissue disorders**
**Common:**
Erythema and skin ulcer may occur in the area of the injection after intravenous administration.

**Uncommon:**
Alopecia.

**Renal and urinary disorders**
**Very common:**
Renal failure after single or multiple doses of cisplatin. A mild, reversible renal dysfunction may be observed after a single intermediary dose of cisplatin (20 mg/m² to < 50 mg/m²). The use of a single
high dose (50-120 mg/m²), or repeated daily use of cisplatin, may cause renal failure with tubular renal necrosis presenting as uraemia or anuria. Renal failure may be irreversible. The nephrotoxicity is cumulative and may occur 2-3 days, or two weeks after the first dose of cisplatin. Serum creatinine and urea concentrations may increase. Nephrotoxicity was observed in 28-36% of patients without sufficient hydration after a single dose of 50 mg/m² of cisplatin. (See section 4.4.)

Hyperuricaemia occurs asymptptomatically or as gout. Hyperuricaemia has been reported in 25-30% of patients in conjunction with nephrotoxicity.

Hyperuricaemia and hyperalbuminaemia may predispose to cisplatin-induced nephrotoxicity.

Reproductive system and breast disorders

Uncommon:
Abnormal spermatogenesis and ovulation, and painful gynaecomastia.

General disorders and administration site conditions

Very common:
Fever.

Common:
Localised oedema and pain may occur in the area of the injection after intravenous administration.

Uncommon:
Hiccups, asthenia, malaise

4.9 Overdose

Symptoms of overdose involve above mentioned 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/m²), 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, Platinum compounds, ATC code: L01XA01

Cisplatin is an inorganic compound which contains a heavy metal [cis-diamminedichloridoplatinum (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 the 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.

5.2 Pharmacokinetic properties

After intravenous administration cisplatin quickly distributes across all tissues; cisplatin badly penetrates in the central nervous system. The highest concentrations are reached in the liver, kidneys, bladder, muscle tissue, skin, testes, prostate, pancreas and spleen.

After intravenous administration the elimination of filterable, non-protein bound cisplatin runs biphasic, with an initial and terminal half life of 10-20 minutes and 32-53 minutes, respectively. The elimination of the total quantity of platinum runs triphasic with half lives of 14 minutes, and 274 minute and 53 days respectively.

Cisplatin is bound to plasma proteins for 90%.
The excretion primarily takes place via the urine: 27-43% of the administered dose is recovered in the urine in the first five days after the treatment. Platinum is also excreted in the bile.

5.3 Preclinical safety data

Chronic toxicity
In chronic toxicity models indications for renal damage, bone marrow depression, gastro-intestinal disorders and ototoxicity have been observed.

Mutagenicity en carcinogenity
Cisplatin is mutagenic in numerous in vitro and in vivo 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.

Reproductive toxicity
In mice, gonadal suppression, resulting in amenorrhoea 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 infertility.

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. Cisplatin is excreted in the breast milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Sodium chloride,
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

6.2 Incompatibilities
Do not bring in contact with aluminium. Cisplatin reacts with metal aluminium to form a black precipitate of platinum. All aluminium-containing IV sets, needles, catheters and syringes should be avoided. Cisplatin decomposes with solution in media with low chloride content; the chloride concentration should at least be equivalent to 0.45% of sodium chloride.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.
Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulfates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.

Cisplatin should only be used with those diluents specified in section 6.6.

6.3 Shelf life
Before opening
2 years

After dilution
Chemical and physical in-use stability after dilution with infusion fluids described in section 6.6, indicate that after dilution with recommended intravenous fluids, Cisplatin Injection remains stable for 24 hours at 20-25°C room temperature. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.

From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Undiluted solution:
Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.

For the storage conditions of the diluted medicinal product (see section 6.3).
6.5 Nature and contents of container
For 10 ml
10 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal

For 25 ml
30 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal

For 50 ml
50 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal.

Not all pack sizes may be marketed

6.6 Special precautions for disposal
Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of cisplatin. Must be diluted before use. Dilution should take place under aseptic conditions by trained personnel in an area specifically intended for this. Protective gloves should be worn for this. Precautions should be taken to avoid contact with the skin and mucous membranes. If skin contact did occur anyway, the skin should be washed with soap and water immediately. With skin contact tingling, burns and redness have been observed. In case of contact with the mucous membranes they should be copiously rinsed with water. After inhalation dyspnoea, pain in the chest, throat irritation and nausea have been reported.

Pregnant women must avoid contact with cytostatic drugs.

Bodily waste matter and vomit should be disposed with care.
If the solution is cloudy or a deposit that does not dissolve is noticed, the bottle should be discarded.

A damaged bottle must be regarded and treated with the same precautions as contaminated waste. Contaminated waste must be stored in waste containers specifically marked for this. See section “Disposal”.

Preparation of the intravenous administration
Take the quantity of the solution that is needed from the bottle and dilute with at least 1 litre of the following solutions:
- sodium chloride 0.9%
- mixture of sodium chloride 0.9% / glucose 5% (1:1), (resulting final concentrations: sodium chloride 0.45%, glucose 2.5%)
- sodium chloride 0.9% and 1.875% mannitol, for injection
- sodium chloride 0.45%, glucose 2.5% and 1.875% mannitol for injection

Always look at the injection before use. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used. Only a clear solution, free from particles should be administered.

DO NOT bring in contact with injection material that contains aluminium
DO NOT administer undiluted

With respect to microbiological, chemical and physical stability with use of the undiluted solutions (see section 6.3).

Disposal
All materials that have been used for the preparation and administration, or which have been in contact with cisplatin in any way, must be disposed of according to local cytotoxic guidelines. These measures will help to protect the environment.

7 MARKETING AUTHORISATION HOLDER
Accord Healthcare Limited
Sage House, 319, Pinner Road,
North Harrow, Middlesex,
HA1 4HF
8 MARKETING AUTHORISATION NUMBER(S)
PL 20075/0123

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
21/06/2010

10 DATE OF REVISION OF THE TEXT
21/06/2010
PAR Cisplatin 1mg/ml Concentrate for Solution for Infusion

UK/H/2862/001/DC

1. What Cisplatin Injection is and what it is used for

Cisplatin forms part of a group of medicines called cytotoxics, which are used in the treatment of cancer. Cisplatin can be used alone or in combination with other cytotoxic medicines.

What is it used for?

Cisplatin can destroy cells in your body that may cause certain types of cancer. Common uses include:

- Swelling of the prostate, lymph nodes and the cervix.
- Swelling of the rectum, bladder and the prostate.
- Swelling of the breast.
- Swelling of the kidneys.
- Swelling of the liver.
- Swelling of the spleen.
- Swelling of the blood vessels.
- Swelling of the heart.
- Swelling of the lungs.
- Swelling of the spinal cord.
- Swelling of the brain.
- Swelling of the muscles.
- Swelling of the bones.
- Swelling of the joints.
- Swelling of the tendons.
- Swelling of the skin.
- Swelling of the nerves.
- Swelling of the eyes.
- Swelling of the ears.
- Swelling of the mouth.
- Swelling of the throat.
- Swelling of the nose.
- Swelling of the gums.
- Swelling of the fingers.
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Module 4
Labelling

Cisplatin 1 mg/ml Concentrate for Solution for Infusion

**Cytotoxic Drug**

Keep out of the reach and sight of children.

Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

PL 2007/0123

PA 1390/XXX/2014

POM

Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin

1 ml of concentrate for solution for infusion contains 1 mg of Cisplatin.

One vial of 10 ml contains 10 mg of Cisplatin.

Contains:

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

Affix dispensing label here

1 X 10 ml vial

1 X 10 ml vial

For intravenous infusion use only. This product is a concentrate.

**Must Be Diluted Before Use.**

Read the package leaflet before use.

After first opening the product should be used immediately.

Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze. For storage conditions of the diluted medicinal product please see the package leaflet.
Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin
For intravenous infusion use only.
This product is a concentrate.
MUST be diluted before use.
Read the package leaflet before use.

10 mg/10 ml
PL 20075/0123
PA 1390/XXXXX

accord
Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin
For intravenous infusion use only.
This product is a concentrate.
**MUST be diluted before use.**
Read the package leaflet before use.

25 mg/25 ml
PL 20075/0123
PA 1390/XXX/XXX
Module 5

Scientific discussion during initial procedure

I INTRODUCTION

On 21st June 2010, Austria, Belgium, Bulgaria, Germany, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden and the UK agreed to grant a marketing authorisation to Accord Healthcare Limited for the medicinal product Cisplatin 1mg/ml Concentrate for Solution for Infusion. The licence was granted via the Decentralised Procedure (UK/H/2862/01/DC), with the UK as Reference Member State (RMS). After the national phase, a licence was granted in the UK on 21st June 2010 (PL 20075/0123).

This application was made under Article 10.1 of Directive 2001/83 EC for Cisplatin 1mg/ml Concentrate for Solution for Infusion, containing the active substance cisplatin. The reference medicinal product for this application is Platinol 1mg/ml konsentrat til infusjonsvæske (Bristol-Myers Squibb, Norway), which has been registered in at least one European member state for over 10 years.

Cisplatin (cis-diaminedichloroplatinum) is a platinum-based anti-neoplastic agent. Platinum-based agents cause intrastrand and interstrand crosslinks between purine bases of DNA, resulting in contortion of the DNA molecule. It is widely accepted that this DNA damage induces apoptosis, but there may also be other mechanisms involved in the cytotoxic effects of cisplatin. Cisplatin is given intravenously for the treatment of a wide range of solid tumours. Treatment may be complicated by severe nausea and vomiting. Toxic effects include nephrotoxicity, ototoxicity, peripheral neuropathy, hypomagnesaemia and myelosuppression.

The proposed product is developed using an approved drug substance that is to be administered as an aqueous intravenous solution, containing the same drug substance in the same concentration as the reference product. Therefore, a bioequivalence study is not required in support of this application.

A formal Environmental Risk Assessment has not been performed as the product is intended for generic substitution. Hence, no increase in environmental risk is to be expected.

The pharmacovigilance system, as described by the applicant, fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance, and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country. An acceptable justification for not submitting a European Risk Management Plan has been provided.

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 outside the Community, the RMS has accepted copies of current GMP certificates of satisfactory inspection summary reports or ‘close-out letters’ issued by the inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those non-Community sites.
II. ABOUT THE PRODUCT

| Name of the product in the Reference Member State | Cisplatin 1mg/ml Concentrate for Solution for Infusion |
| Name(s) of the active substance(s) (USAN) | Cisplatin |
| Pharmacotherapeutic classification (ATC code) | Platinum compounds, ATC code L01XA01 |
| Pharmaceutical form and strength(s) | 1mg/ml Concentrate for Solution for Infusion |
| Reference number for the Mutual Recognition Procedure | UK/H/2862/001/DC |
| Reference Member State | United Kingdom |
| Member States concerned | Austria, Belgium, Bulgaria, Germany, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden |
| Marketing Authorisation Number(s) | PL 20075/0123 |
| Name and address of the authorisation holder | Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF, United Kingdom |
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Cisplatin
Chemical Names: cis-diamminedi-chloroplatinum (II)
Structure:

\[
\text{Molecular formula: } [\text{PtCl}_2(\text{NH}_3)_2] \\
\text{Molecular weight: } 300.0 \\
\text{Physical form: A yellow powder or yellow or orange-yellow crystals, slightly soluble in water, sparingly soluble in dimethylformamide, practically insoluble in alcohol.}
\]

Cisplatin is the subject of a European Pharmacopoeia monograph. Cisplatin does not exhibit any polymorphism.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

Satisfactory specifications have been provided for all packaging used for the active substance. Confirmation has been provided that the primary packaging complies with EC Directive 2002/72/EC, concerning materials in contact with foodstuff.

A suitable retest period has been determined, based on stability data from batches of active substance stored in the proposed packaging under standard conditions.

DRUG PRODUCT

Other ingredients
Other ingredients consist of pharmaceutical excipients sodium chloride, sodium hydroxide, hydrochloric acid and water for injections. All excipients are controlled to their European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients are sourced from animal/human origin or from genetically modified sources.

Pharmaceutical development
The objective of the pharmaceutical development programme was to produce a concentrate for solution for infusion that could be considered a generic medicinal product of Platinol 1mg/ml konsentrat til infusjonsvæske (Bristol-Myers Squibb, Norway).

Suitable pharmaceutical development data have been provided for this application.

Manufacture
A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory based on process validation data and controls on the finished
product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished product specification**
The finished product specification is satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

**Container Closure System**
The finished product is supplied in 10ml, 30ml and 50ml Type I amber glass vials, containing 10ml, 25ml and 50ml of product, respectively. The vials are sealed with a grey chlorobutyl stopper and a white, transparent aluminium flip-off seal.

Specifications and certificates of analysis for the primary packaging material have been provided. These are satisfactory. All primary packaging is controlled to European Pharmacopoeia standards and complies with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years has been set when the product is unopened, with the storage conditions “Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.”

The following instructions are also given concerning storage of the product after dilution:

*Chemical and physical in-use stability after dilution with infusion fluids, indicate that after dilution with recommended intravenous fluids, Cisplatin Injection remains stable for 24 hours at 20-25°C room temperature. The diluted solution should be protected from light. Do not store diluted solutions in the refrigerator or freezer.*

*From a microbiological point of view, the diluted solution should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and dilution should take place in controlled and validated aseptic conditions.*

**Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and Labelling**
The SPC, PIL and labelling are pharmaceutically satisfactory.

The applicant has submitted results of PIL user testing. The results indicate that the PIL 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.

**MAA Form**
The MAA form is pharmaceutically satisfactory.

**Expert Report**
The pharmaceutical expert report is written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.
Conclusion
It is recommended that a Marketing Authorisation is granted for this application.

III.2 PRE-CLINICAL ASPECTS
The pharmacological, pharmacokinetic and toxicological properties of cisplatin are well-known. As cisplatin is a well-known active substance, no further studies are required.

A pre-clinical overview, based on a literature review, has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

The summary of product characteristics is satisfactory from a preclinical viewpoint.

The grant of a marketing authorisation is recommended.

III.3 CLINICAL ASPECTS

Pharmacokinetics
No new data are required for an application of this type.

According to CPMP guidelines in force at the time of application, 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).

Based on the data provided, Cisplatin 1mg/ml Concentrate for Solution for Infusion can be considered a generic medicinal product of Platinol 1mg/ml konsentrat til infusjonsvæske (Bristol-Myers Squibb, Norway).

Pharmacodynamics
No new data have been submitted and none are required for an application of this type.

Clinical efficacy
No new data have been submitted and none are required for an application of this type.

Clinical safety
No new safety data have been submitted or are required for this generic application.

Summary of Product Characteristics (SPC), Patient Information Leaflet (PIL) and labelling
The SPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product.

Clinical Expert Report
The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA Form is satisfactory from a clinical perspective.

Clinical Conclusion
The grant of a marketing authorisation is recommended.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Cisplatin 1mg/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 ratio.

PRE-CLINICAL
The pre-clinical data submitted have not revealed any evidence of potential risks to human health from treatment with Cisplatin 1mg/ml Concentrate for Solution for Infusion beyond those already described.

EFFICACY
No new data have been submitted and none are required for an application of this type.

Cisplatin 1mg/ml Concentrate for Solution for Infusion is the generic version of Platinol 1mg/ml konsentrat til infusjonsvæske (Bristol-Myers Squibb, Norway). The use of the reference product is well-established in the EU. Both products contain the same quantitative and qualitative composition of the active ingredient, cisplatin.

According to CPMP guidelines in force at the time of application, 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).

No new safety data are supplied or required for this generic application. Cisplatin has a well-established side-effect profile.

The SPC, PIL and labelling are satisfactory.

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable, and no new pre-clinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with cisplatin is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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