Safeguarding public health

MHRA

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

Product Name	Cisplatin 1mg/ml Concentrate for Solution for Infusion
Type of Application	Generic application, Article 10.1
Active Substance	Cisplatin
Form	Concentrate for solution for infusion
Strength	1mg/ml
MA Holder	Accord Healthcare Limited, Sage House, 319 Pinner Road, North Harrow, Middlesex, HA1 4HF,United Kingdom
RMS	UK
CMS	Austria, Belgium, Bulgaria, Germany, Denmark, Estonia, Finland, Hungary, Ireland, Italy, Lithuania, Latvia, the Netherlands, Norway, Poland, Portugal, Romania, Slovenia, Spain, Sweden
Procedure Number	UK/H/2862/001/DC
Timetable	Day 210 – 21st June 2010

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/m^2 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/m^2 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 rsp. 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/m^2, 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 ifosphamide 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 carcinogenity (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
Common:
Infections. Sepsis.

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 antiduretic hormone secretion.

Metabolism and nutrition disorders
Rare:
Hypomagnaesaemia, 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.

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, disarthria, 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 carotic 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/m^2 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:
Arrythmia 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/m^2 to < 50 mg/m^2). The use of a single

high dose (50-120 mg/m^2), 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/m^2 of cisplatin. (See section 4.4.)

Hyperuricaemia occurs asymptomatically 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 ($\geq$200 mg/m^2), 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

United Kingdom

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

accord

PACKAGE LEAFLET: INFORMATION FOR THE USER

Cisplatin 1 mg/ml Concentrate for Solution for Infusion

Cisplatin

The name of your medicine is 'Cisplatin 1 mg/ml Concentrate for Solution for Infusion' but in the rest of the leaflet it will be called "Cisplatin Injection".

Read all of this leaflet carefully before you start using this medicine
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

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

Cisplatin forms part of 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.

What is it used for?
Cisplatin 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).
Your doctor will be able to provide you with more information.

2. Before you are given Cisplatin Injection

DO NOT take Cisplatin if:
- you are allergic (hypersensitive) to cisplatin or to any of the other ingredients of Cisplatin
- you are allergic (hypersensitive) to any other medicine that contains platina compounds
- you have kidney problems (renal dysfunction)
- you suffer from dehydration
- you suffer from severe suppression of bone marrow functionality, symptoms may be: extreme tiredness, easy bruising or bleeding, occurrence of infections
- your hearing is impaired
- you suffer from nervous disorders caused by cisplatin
- you are breast-feeding
- combined with live vaccines, including yellow fever vaccine.
- combined with phenytoin in prophylactic use (see "Use of Cisplatin with other medicines" below).

Take special care with Cisplatin:
- Your doctor will carry out tests in order to determine the levels of calcium, sodium, potassium and magnesium in your blood, as well as to check your blood picture and your liver and kidney functionality and neurological function.
- Cisplatin should only be administered under the strict supervision of a specialist doctor experienced in administrating chemotherapy.
- Your hearing will be tested prior to each treatment with Cisplatin.
- If you suffer from a nervous disorder not caused by Cisplatin.
- If you suffer from an infection. Please consult your doctor.
- If you intend to have children (see Pregnancy, breast-feeding and fathering children)
- With spillage of cisplatin the contaminated skin must immediately be washed with water and soap. If cisplatin is injected outside the blood vessels the administration must be stopped immediately. Infiltration of cisplatin in the skin can result in tissue damage (cellulitis, fibrosis and necrosis).

Please consult your doctor, even if these statements were applicable to you at any time in the past.

Taking other medicines
Please note that these statements may also apply to products used some time ago or at some time in the future.
Please inform your doctor or pharmacist if you are taking, of have recently taken, any other medicine – even those not prescribed.
- Simultaneous use of medicines that inhibit the bone marrow function or radiation can potentiate the adverse effects of cisplatin on the bone marrow.
- Cisplatin toxicity may increase when administered simultaneously with other cytostatics (medicine for cancer treatment), such as bleomycin and methotrexate.
- Agents to treat high blood pressure (antihypertensives containing furosemide, hydralazine, diazoxide, and propranolol) may increase the toxic effect of Cisplatin on kidneys.
- Cisplatin toxicity may severely affect the kidneys when administered simultaneously with agents that may cause side effects in the kidneys, such as those for the prevention/ treatment of certain infections (antibiotics: cephalosporins, aminoglycosides, and/or amphotericin B) and contrast agents.
- Cisplatin toxicity may affect hearing faculties when administered simultaneously with agents that may have a side effect on hearing faculties, such as aminoglycosides.
- If you use agents to treat gout during your treatment with cisplatin, then the dosage of such agents may need to be adjusted (e.g. allopurinol, colchicine, probenecid and/or sulfinpyrazone).
- Administration of drugs that elevate your rate of bodily urine excretion (loop diuretics) combined with cisplatin (cisplatin dose: more than 60mg/m², urine secretion: less than 1000 ml per 24 hours) may result in toxic effects on kidneys and hearing.
- The first signs of hearing damage (dizziness and/or tinnitus) may remain hidden when - during your treatment with cisplatin - you are also being administered agents to treat hypersensitivity (antihistamines, such as buclizine, cyclizine, loxapine, meclozine, phenothiazines, thioxanthenes and/or trimethobenzamides).
- Cisplatin given in combination with ifosphamide may result in hearing impairment.
- The effects of treatment with cisplatin can be reduced through simultaneous administration of pyridoxine and hexamethylmelamine.
- Cisplatin given in combination with bleomycin and vinblastine may result in paleness or blue coloration of the fingers and/or toes (Raynaud's phenomenon).
- Administration of cisplatin prior to treatment with paclitaxel or in combination with docetaxel may result in severe nerve damage.
- The combined use of cisplatin with bleomycin and etoposide may decrease lithium levels in the blood. Therefore, lithium levels should be checked on a regular basis.
- Cisplatin reduces the effects of phenytoin on the treatment of epilepsy.
- Penicillamine may reduce the effectiveness of Cisplatin.
- Cisplatin may have an adverse impact on the effectivity of agents preventing coagulation (anticoagulants). Therefore, coagulation should be checked more often during combined use.
- Concomitant use of cisplatin with ciclosporin can weaken the immune system, with the risk of increased production of white blood cells (lymphocytes)
- You should not receive any vaccinations containing live viruses within three months after the end of treatment with cisplatin.
- When undergoing treatment with cisplatin, you should not receive yellow fever vaccinations (also see "Do not take Cisplatin").

Pregnancy, breast-feeding and fathering children
Ask your doctor or pharmacist for advice before you begin to use, or are administered, Cisplatin.

Cisplatin must not be used during pregnancy unless clearly indicated by your doctor.
You must use effective contraception during and at least 6 months after treatment with Cisplatin.
You must not breastfeed while you are treated with Cisplatin.

Male patients treated with Cisplatin are advised not to father a child during treatment and for up to 6 months after treatment. Further, men are advised to seek counseling on sperm preservation before starting treatment.

Driving and using machines
Cisplatin may cause side effects such as feeling sleepy and/or vomiting. If you suffer from either of these conditions, then you should not operate any machines that require your full attention.

Important information about some of the ingredients of Cisplatin
Cisplatin contains 3.5 mg sodium per ml. This should be considered if you have to keep to a low sodium diet.

3. How you are given Cisplatin Injection

Dosage and method of administration
Cisplatin should only be given by a specialist in cancer treatment.
The concentrate is diluted with a sodium chloride solution that contains glucose.
Cisplatin is only given by injection into a vein (an intravenous infusion).
Cisplatin should not come into contact with any materials that contain aluminium.
The recommended dosage of Cisplatin depends on your well-being, the anticipated effects of the treatment, and whether or not cisplatin is given on its own (monotherapy) or in combination with other agents (combination chemotherapy).

Cisplatin (monotherapy):
The following dosages are recommended:
- A single dosage of 50 to 120 mg/m² body surface, every 3 to 4 weeks.
- 15 to 20 mg/m² per day over a 5-day period, every 3 to 4 weeks

Cisplatin in combination with other chemotherapeutical agents (combination chemotherapy):
- 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.
In order to avoid, or reduce, kidney problems, you are advised to drink copious amounts of water for a period of 24 hours following treatment with Cisplatin.

If you believe you have received more Cisplatin than you should
Your doctor will ensure that the correct dose for your condition is given. In case of overdose, you may experience increased side effects. Your doctor may give you symptomatic treatment for these side effects. If you think you received too much Cisplatin, immediately contact your doctor.

(Please note this is a Prescriber Information Leaflet NOT the SPC for full details regarding this product please refer to the SPC)

The following information is intended for medical or healthcare professionals only:

Preparation and handling of the product
Like with all anti-neoplastic products caution is needed with the processing of cisplatin. 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. 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 below "Special precautions for storage".

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. Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

If you have any further questions on the use of this product, ask your doctor.

4. Possible side effects

Like all medicines, Cisplatin can cause side effects.
If you experience any side effect it is important that you inform your doctor before your next treatment.

Tell your doctor immediately, if you notice any of the following:
- persistent or severe diarrhoea or vomiting
- stomatitis/mucositis (sore lips or mouth ulcer)
- swelling of the face, lips mouth or throat
- unexplained respiratory symptoms such as non-productive cough, difficulty in breathing or crackles
- difficulty in swallowing
- numbness or tingling in your fingers or toes
- extreme tiredness
- abnormal bruising or bleeding
- signs of infection, such as sore throat and high temperature
- sensation of discomfort close to or at the injection site during the infusion.

Side effects may appear **very common** (in more than 1 in 10 patients); **common** (in more than 1 in 100, but less than 1 in 10 patients); **uncommon** (in more than 1 in 1,000, but less than 1 in 100 patients); **rarely** (in more than 1 in 10,000, but less than 1 in 1,000 patients); **very rarely** (in less than 1 in 10,000 patients).

The following side effects may occur:
Very common
Blood and lymphatic system: reduction in the number of white blood cells, which makes infections more likely (leukopenia), reduction in blood platelets, which increases the risk of bruising and bleeding (thrombocytopenia), as well as reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness (anaemia).
Hearing and balance function: loss of hearing combined with tinnitus.
Gastrointestinal tract: loss of appetite (anorexia), nausea, vomiting, diarrhoea.
Kidneys and urinary tracts: renal dysfunction, such as failure to produce urine (anuria) and urine poisoning of the blood (uraemia), and excessive uric acid levels (hyperuricaemia) in the blood (e.g. gout).
General symptoms: fever.

Common
Infections: Infections and blood-poisoning (sepsis).
Blood and lymphatic system: reduction in the number of white blood cells (leukopenia; approximately 14 days after use), reduction in blood platelets (thrombocytopenia; approximately 21 days after use) and reduction in red blood cells (later onset than leukopenia and thrombocytopenia).
Nervous system: peripheral neuropathy of the sensory nerves (bilateral, sensory neuropathy), characterised by tickling, itching or tingling without cause and sometimes characterised by a loss of taste, touch, sight, as well as brain dysfunction (confusion, slurred speech, sometimes blindness, memory loss, and paralysis); sudden shooting pains from the neck through the back into the legs when bending forwards, spinal disease.
Hearing and balance function: deafness and dizziness.
Heart: arrhythmia, including reduced heartbeat (bradycardia), accelerated heartbeat (tachycardia).
Blood vessels: inflammation of a vein (phlebitis).
Respiratory disorders: difficulty of breathing (dyspnoea), inflammation of the lungs (pneumonia) and respiratory failure.
Liver and bile: liver dysfunction.
Skin: redness and inflammation of the skin (erythema, skin ulcer) in the area of the injection.
General symptoms: swelling (oedema), pain at the area of injection.

Uncommon
Immune system: hypersensitivity reactions, including rash, eczema with severe itching and lump formation (urticaria), redness and inflammation of the skin (erythema) or itching (pruritus).
Gastrointestinal tract: metallic setting on the gums.
Skin: loss of hair (alopecia).
Reproductive system and breasts: dysfunctional spermatogenesis and ovulation, and painful breast growth in men (gynaecomastia).
General symptoms: hiccups, weakness (asthenia), malaise.

Rare
Blood: haemolytic anaemia, suppression of the bone marrow characterised by a severe decrease of white blood cells, combined with high fever, severe sore throat and mouth ulcers (agranulocytosis), as well as anaemia as a result of decreased blood cell production.
Immune system: severe hypersensitivity (anaphylactic reactions) with low blood pressure (hypotension), accelerated heartbeat (tachycardia), breathing difficulties (dyspnoea), distress as a result of muscle cramps in the airways (bronchospasms), swelling of the face and fever; suppression of the immune system (immunosuppression).

Nutrition and metabolism: reduced level of electrolytes (magnesium, calcium, sodium, phosphate, potassium) in the blood with muscle cramping and/or changes in an electrocardiogram (ECG). Excessive cholesterol levels in the blood. Increased blood amylase (enzyme) levels.
Nervous system: loss of certain types of brain function, including brain dysfunction characterised by spasms and reduced levels of consciousness (encephalopathy), as well as closure of the carotid artery.

Eyes: loss of sight (blindness), difficulties in colour perception and eye movement dysfunction.
Hearing: unable to hold normal conversation, loss of hearing (in particular among children and elderly patients).
Heart: increased blood pressure levels, coronary artery disease and heart attacks.
Gastrointestinal tract: inflammation of mucous membranes of the mouth (stomatitis), diarrhoea.
Liver and bile: reduced blood protein levels (albumin).
General: Cisplatin, like other similar medicines, increases the risk of leukaemia (secondary leukaemia).
Very rare
Hormones: insufficient production of the vasopressin hormone in the brain (SIADH).
Nutrition and metabolism: increased iron levels in the blood.
Nervous system: attacks (seizures).
Eyes: swelling (papilloedema), inflammation of the eye nerve combined with pain and reduced nerve function (optic neuritis), blindness as a result of brain dysfunction.
Heart: heart arrest.
Blood vessels: blood flow dysfunction, e.g. in the brain, but also in the fingers and toes (Raynaud's syndrome).
Skin and dermis: baldness due to hair loss.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. How to store Cisplatin injection

Keep Cisplatin out of the reach and sight of children.
Keep the vial in the outer carton (to avoid exposure of Cisplatin to light).

Concentrate for solution for infusion 1 mg/ml
Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.

Do not use Cisplatin injection after the expiry date which is stated on the vial and the outer carton after 'EXP'. The expiry date refers to the last day of that month. Do not use Cisplatin if you notice visible signs of deterioration.

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

If you find the solution cloudy or a deposit that does not dissolve is noticed, the bottle should be discarded.

6. Further information

What Cisplatin Injection contains:
Cisplatin Injection contains the active ingredient cisplatin.
Each millilitre (ml) of solution contains 1 milligram (mg) of cisplatin. This medicine is presented in amber glass containers called vials.

Presentations	10 ml	25 ml	50 ml
Amount of cisplatin	10 mg	25 mg	50 mg

It is available in packs containing a single vial (not all the presentations mentioned may be marketed).

The other ingredients include water for injections, sodium chloride, dilute hydrochloric acid (for pH adjustment) and/or dilute sodium hydroxide (for pH adjustment).

What Cisplatin Injection looks like and content of the pack:
Cisplatin Injection is clear, colourless to pale yellow solution in an amber glass vial practically free from particles with flip off transparent seal.

Packaging with 1 injection vial of 10 ml, each injection vial containing 10 mg cisplatin.
Packaging with 1 injection vial of 25 ml, each injection vial containing 25 mg cisplatin.
Packaging with 1 injection vial of 50 ml, each injection vial containing 50 mg cisplatin.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and manufacturer:
Accord Healthcare Limited
Sage House, 319, Pinner Road, North Harrow, Middlesex, HA1 4HF,
United Kingdom

The leaflet was last approved in 06/2010.

Incompatibilities
Do not bring in contact with aluminium. Cisplatin may interact 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.

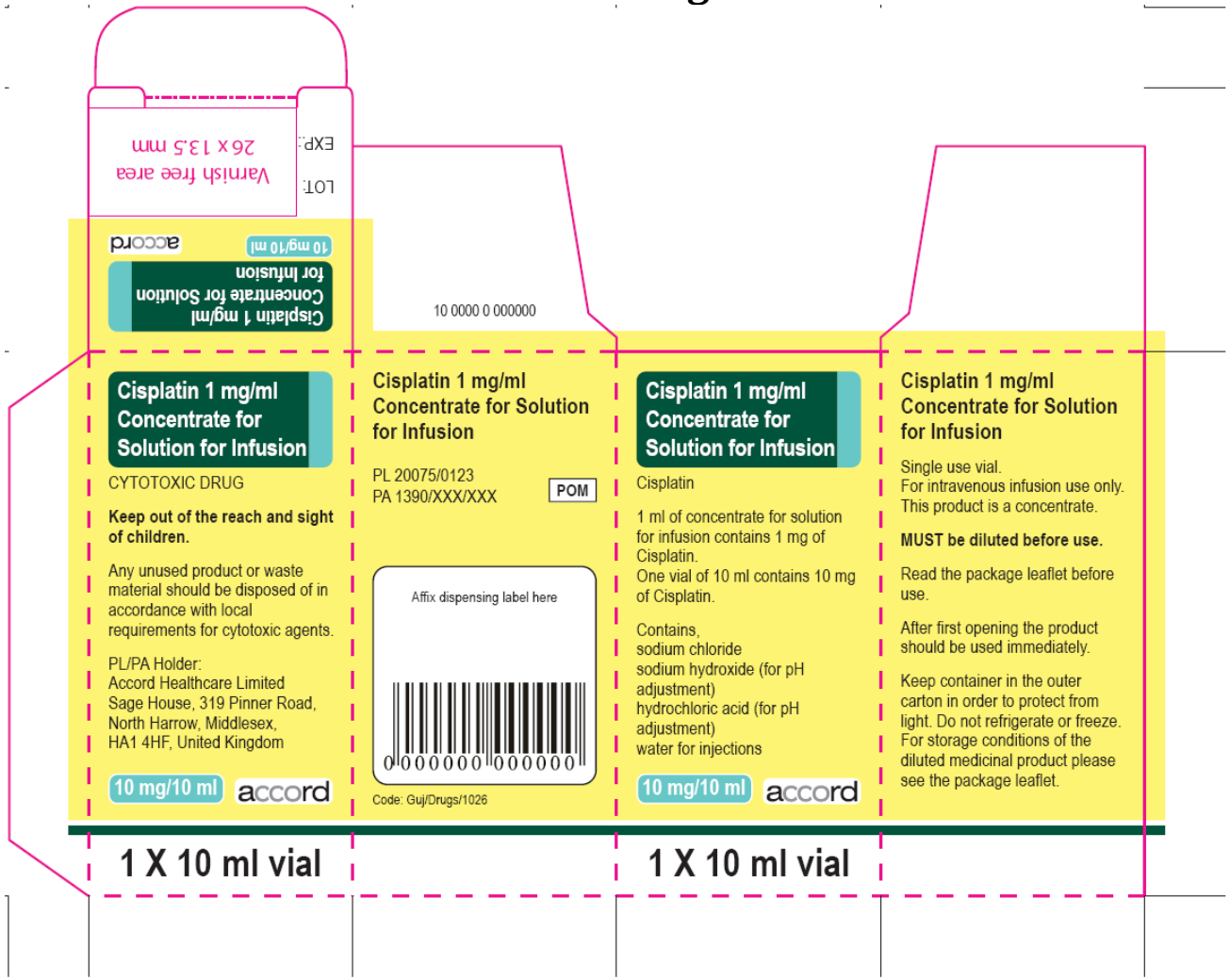
Antioxidants (such as sodium metabisulphite), bicarbonates (sodium bicarbonate), sulfates, fluorouracil and paclitaxel may inactivate cisplatin in infusion systems.

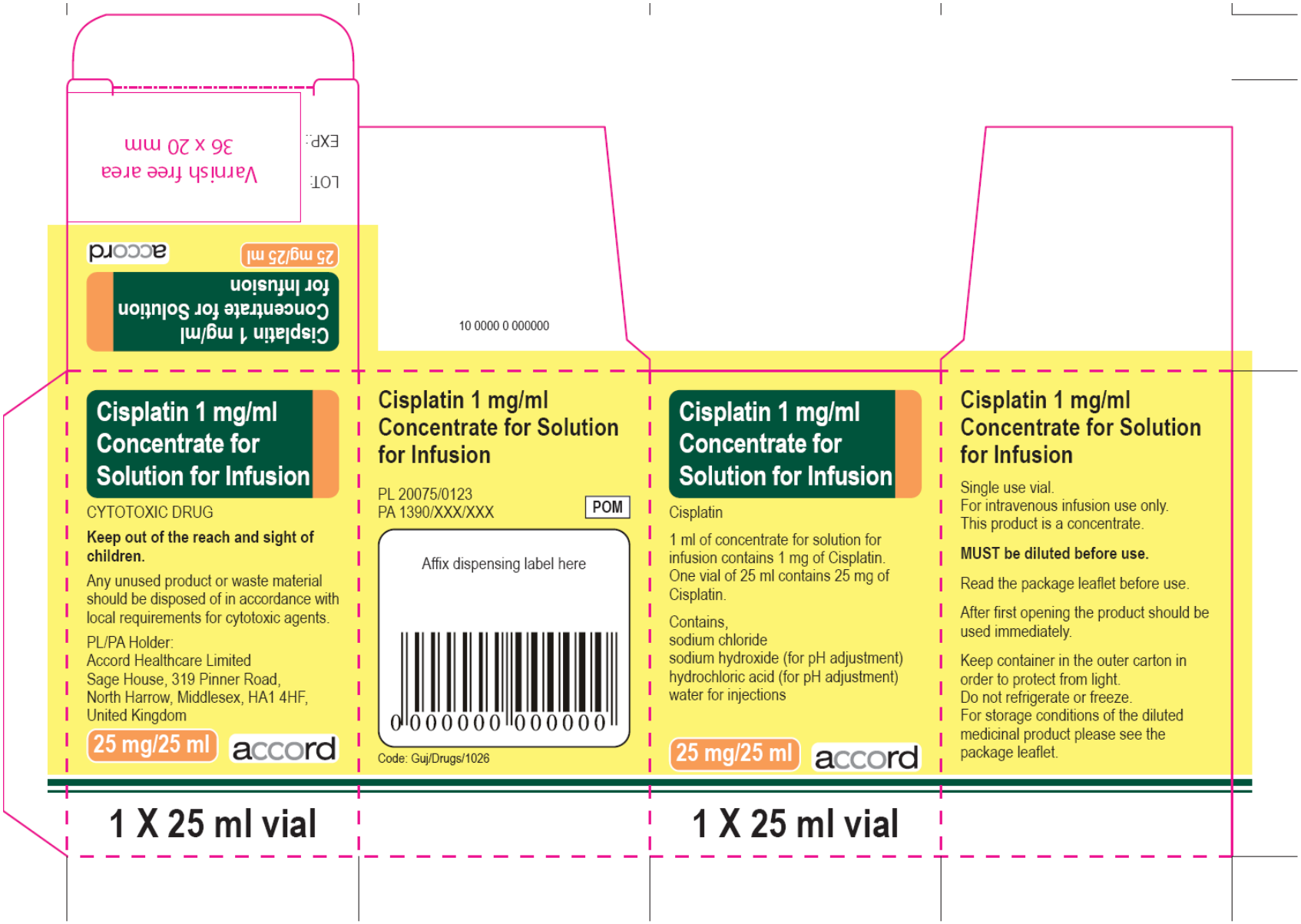
Special precautions for storage
Medicinal product as packaged for sale:

Concentrate for solution for infusion 1 mg/ml
Undiluted solution: Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze. If the solution is not clear or an undissolvable precipitate is formed the solution must not be used.
Diluted solution:
For the storage condition of the diluted medicinal product: see below "Concentrate for solution for infusion after dilution".
Do not refrigerate or freeze.

Concentrate for solution for infusion after dilution:
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.
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.

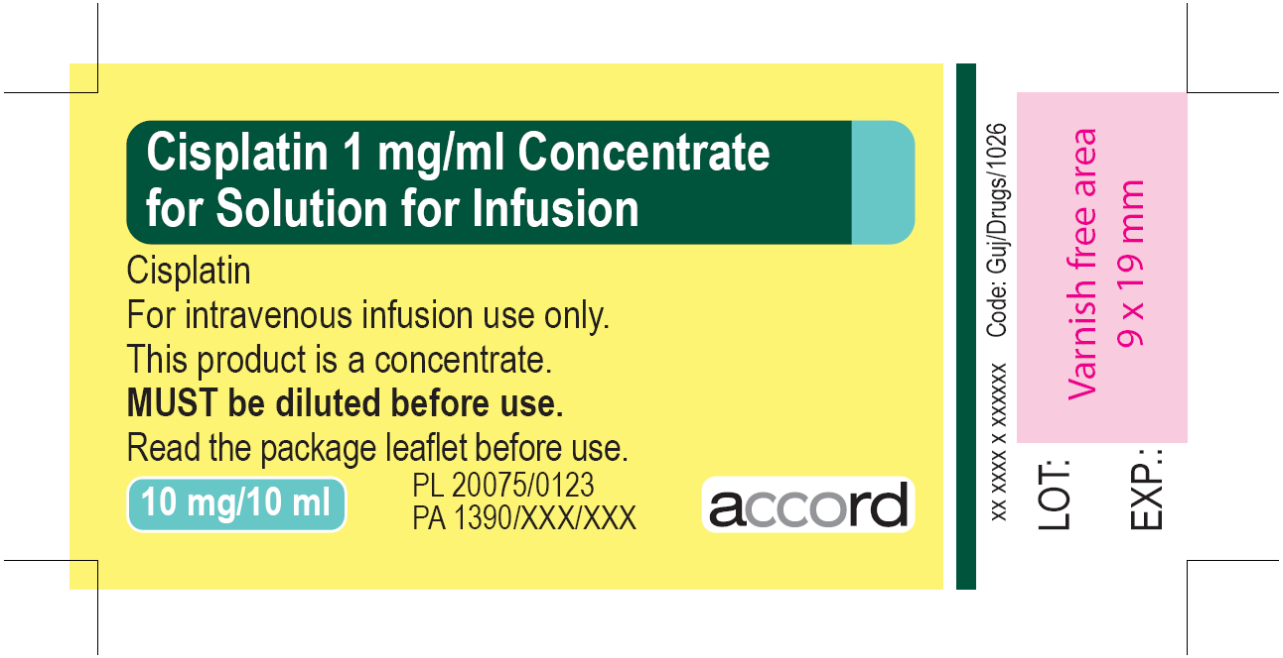
Module 4
Labelling



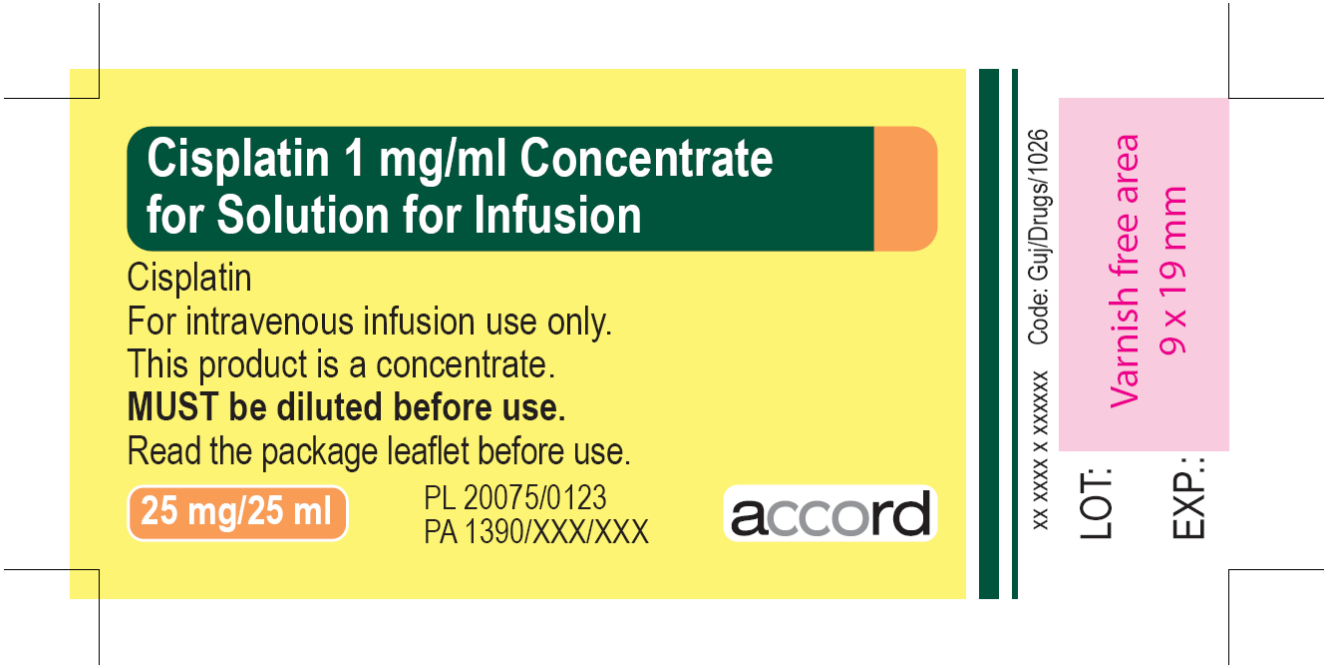

Varnish free area
36 x 20 mm
EXP:
LOT:
10 0000 0 000000
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
25 mg/25 ml
accord
Cisplatin 1 mg/ml
Concentrate for
Solution for Infusion
CYTOTOXIC DRUG
Keep out of the reach and sight of children.
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.
PL/PA Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
25 mg/25 ml
accord
1 X 25 ml vial
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
PL 20075/0123
PA 1390/XXX/XXX
POM
Affix dispensing label here
0000000 000000
Code: Guj/Drugs/1026
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 25 ml contains 25 mg of Cisplatin.
Contains,
sodium chloride
sodium hydroxide (for pH adjustment)
hydrochloric acid (for pH adjustment)
water for injections
25 mg/25 ml
accord
1 X 25 ml vial
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
Single use 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.

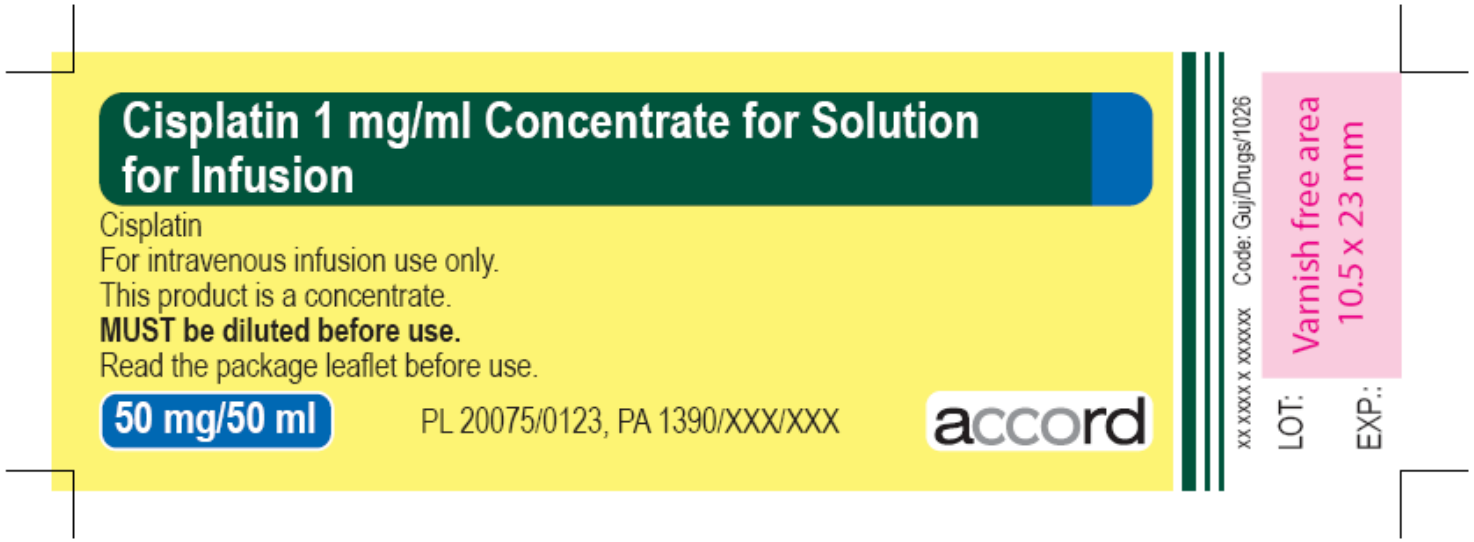

Varnish free area
38 x 20 mm
EXP:
LOT:
10 0000 0 000000
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
50 mg/50 ml
accord
Cisplatin 1 mg/ml
Concentrate for
Solution for Infusion
CYTOTOXIC DRUG
Keep out of the reach and sight of children.
Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.
PL/PA Holder:
Accord Healthcare Limited
Sage House, 319 Pinner Road,
North Harrow, Middlesex, HA1 4HF,
United Kingdom
50 mg/50 ml
accord
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
PL 20075/0123
PA 1390/XXX/XXX
POM
Affix dispensing label here
5 060149 313404
Code: Guj/Drugs/1026
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 50 ml contains 50 mg of Cisplatin
Contains,
sodium chloride
sodium hydroxide (for pH adjustment)
hydrochloric acid (for pH adjustment)
water for injections
50 mg/50 ml
accord
Cisplatin 1 mg/ml
Concentrate for Solution
for Infusion
Single use 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.
1 X 50 ml vial
1 X 50 ml vial

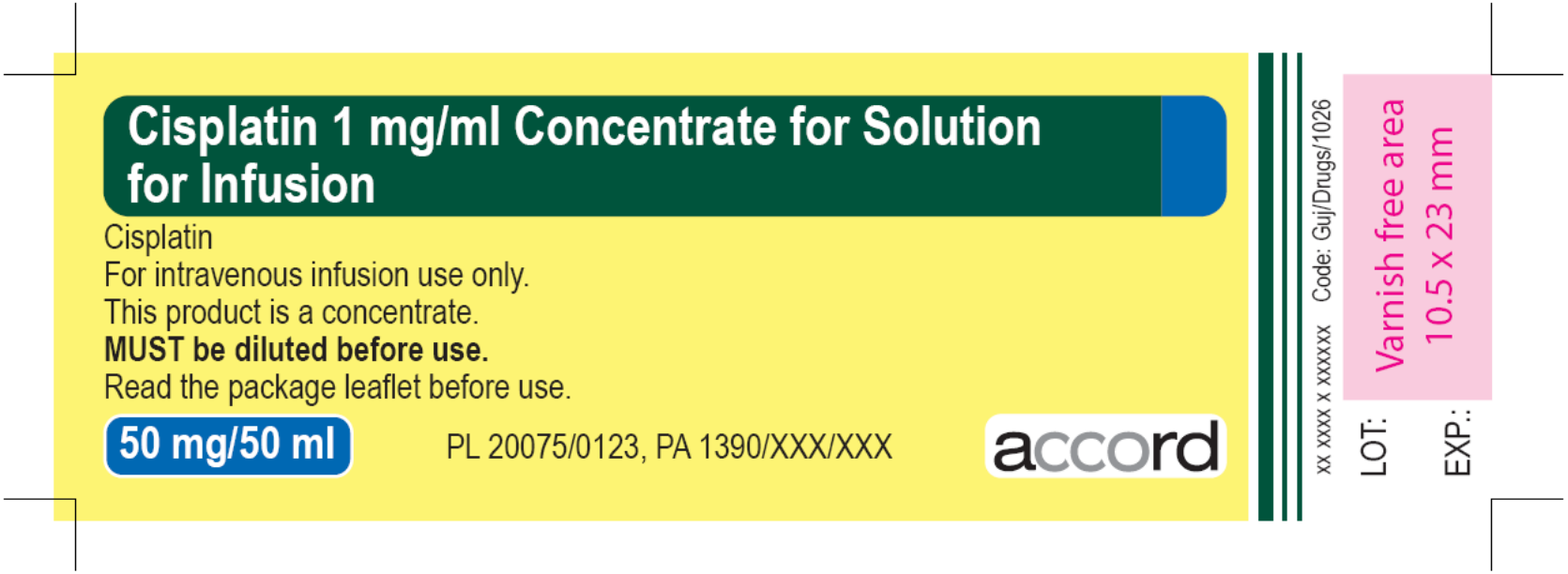

Cisplatin 1 mg/ml Concentrate for Solution for Infusion
Cisplatin
For intravenous infusion use only.
This product is a concentrate.
MUST be diluted before use.
Read the package leaflet before use.
10 mg/10 ml
PL 20075/0123
PA 1390/XXX/XXX
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
9 x 19 mm


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/XXX/XXX
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
9 x 19 mm


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
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
9 x 19 mm


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
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
9 x 19 mm


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.
50 mg/50 ml
PL 20075/0123, PA 1390/XXX/XXX
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
10.5 x 23 mm


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.
50 mg/50 ml
PL 20075/0123, PA 1390/XXX/XXX
accord
xx xxxx x xxxxxx Code: Guj/Drugs/1026
LOT:
EXP.:
Varnish free area
10.5 x 23 mm

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 Cisplatin1mg/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 L01X A01
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

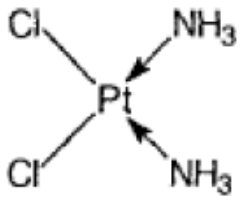
III.1 QUALITY ASPECTS

DRUG SUBSTANCE

INN: Cisplatin

Chemical Names: *cis*-diamminedi-chloroplatinum (II)

Structure:



Molecular formula: $[PtCl_2(NH_3)_2]$

Molecular weight: 300.0

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 charateristics 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 guidelinesin 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 arerequired 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

Date submitted	Application type	Scope	Outcome