Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Cisplatin 1mg/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
100ml of concentrate for solution for infusion contains 100 mg of Cisplatin.

Excipients with known effect:
Each ml of solution contains 3.5 mg of sodium.
For the 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

Posology

Adults and paediatric population

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/m^2 body surface every 3 to 4 weeks;
- 15 to 20 mg/m^2/day for five days, every 3 to 4 weeks.

If cisplatin is used in combination therapy, the dose of cisplatin must be reduced. A typical dose is 20 mg/m^2 or more once every 3 to 4 weeks.

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

For warning 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).

Method of administration
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.
Hydration
Adequate hydration must be maintained from 2 to 12 hours prior to administration until minimum 6 hours after the administration of cisplatin. Hydration is necessary to ensure 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 1 litre.

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 BSA.

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

Cisplatin 1 mg/ml Concentrate for Solution for Infusion is to be diluted before administration. For instructions for dilution of the product before administration see section 4.4 and 6.6.

Although cisplatin is usually administered intravenously, the drug has also been given by intraperitoneal instillation to patients with intraperitoneal malignancies (e.g., ovarian tumours).

For administration, any device containing aluminium that may come in contact with cisplatin (sets for intravenous infusion, needles, catheters, syringes) must be avoided.

4.3 Contraindications

Hypersensitivity to cisplatin or to any of the excipients listed in section 6.1.
or other platinum containing compounds

Cisplatin induces nephrotoxicity which is cumulative. It is therefore contraindicated in patients with pre-existing renal impairment.

Cisplatin has also been shown to be cumulatively neurotoxic (in particular ototoxic) and should not be given to patients with pre-existing hearing impairment.

Cisplatin is also contraindicated in myelosuppressed patients and those who are dehydrated.

Patients receiving cisplatin should not breast feed (see section 4.6).

Concurrent administration of yellow fever vaccine is contraindicated.

4.4 Special warnings and precautions for use

This agent should only be administered under the direction of oncologists in specialist units under conditions permitting adequate monitoring and surveillance. Supportive equipment should be available to control anaphylactic reactions.

Cisplatin reacts with metallic aluminium to form a black precipitate of platinum. All aluminium containing IV sets, needles, catheters and syringes must be avoided. Before administering the solution to the patient, verify the clarity of the solution and the absence of particles.

Cisplatin solution for infusion should not be mixed with other drugs or additives.

Appropriate monitoring and management of the treatment and its complications are only possible if adequate diagnosis and exact treatment conditions are available.

Determine the following parameters and organ functions before, during and after the administration of cisplatin:

- renal function
- hepatic function
- hematopoietic functions (number of red blood cells, white blood cells and blood platelets)
- serum electrolyte levels (calcium, sodium, potassium, magnesium).

These tests should be repeated every week throughout cisplatin treatment.

Repeated administration of cisplatin should be postponed until normal values of the following parameters have been achieved:

- serum creatinine ≤130 µmol/l (1.5mg/100ml)

- urea <25 mg/dl

- white blood cells >4000/µl (>4.0x10^9/l)

- platelets >100000/µl (>100x10^9/l)

- audiogram: results within the normal range

Nephrotoxicity

Cisplatin produces severe cumulative nephrotoxicity which may be potentiated by aminoglycoside antibiotics. Cisplatin should not be given more frequently than once every 3-4 weeks.

To maintain urine output and reduce renal toxicity it is recommended that cisplatin be administered as an intravenous infusion over 6 to 8 hours (see section 4.2).

Repeat courses of cisplatin should not be given unless levels of serum creatinine are below 1.5 mg/100 ml (130 µmol/l) or blood urea below 25 mg/100 ml (9 mmol/l), and circulating blood levels are at an acceptable level. Since the renal toxicity of cisplatin is cumulative, measurement of BUN, serum creatinine or Glomerular Filtration Rate (GFR)/Creatinine Clearance Rate (CCr) should be performed prior to initiating therapy and prior to each subsequent course.

Adequate pre-treatment and 'during treatment' hydration should be ensured to minimise hazards of renal toxicity.

A urine output of 100 ml/hour or greater will tend to minimise cisplatin nephrotoxicity. This can be accomplished by prehydration with 2 litres of an appropriate intravenous solution, and similar post cisplatin hydration treatment (recommended 2,500 mL/m^2 BSA/24 hours). If vigorous hydration is insufficient to maintain adequate urinary output, an osmotic diuretic may be administered (e.g. 10% mannitol solution).

Special care has to be taken when cisplatin-treated patients are given concomitant therapies with other potentially nephrotoxic drugs (see section 4.5).

Bone marrow function
Peripheral blood counts should be monitored frequently in patients receiving cisplatin. Although the hematologic toxicity is usually moderate and reversible, severe thrombocytopenia and leukopenia may occur. In patients who develop thrombocytopenia special precautions are recommended: care in performing invasive procedures; search for signs of bleeding or bruising; test of urine, stools and emesis for occult blood; avoiding aspirin and other NSAIDs. Patients who develop leukopenia should be observed carefully for signs of infection and might require antibiotic support and blood product transfusions (see section 4.8).

Central Nervous System function
Cisplatin is known to induce neurotoxicity. Therefore, neurologic examination at regular intervals is warranted in patients receiving a cisplatin-containing treatment.

Severe cases of neuropathies have been reported.These neuropathies may be irreversible and may manifest by paresthesia, areflexia, proprioceptive loss and a vibration perception. A loss of motor function has also been reported.

Ototoxicity
Cisplatin may produce cumulative ototoxicity, which is more likely to occur with high-dose regimens. Audiometry should be performed prior to initiating therapy, and repeated audiograms should be performed when auditory symptoms occur or clinical hearing changes become apparent. Clinically important deterioration of auditive function may require dosage modifications or discontinuation of therapy. Vestibular toxicity has also been reported (see section 4.8).

Ototoxicity has been observed in up to 31% of patients treated with a single dose of cisplatin 50mg/m2, and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally. Ototoxic effect may be more pronounced in children receiving cisplatin.

Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; however, deafness after initial dose of cisplatin has been reported rarely. Ototoxicity may be enhanced with prior simultaneous cranial irradiation and may be related to peak plasma concentration of cisplatin. It is unclear whether cisplatin induced ototoxicity is reversible.

Close supervision must also be carried out with regard to ototoxicity, myelodepression and anaphylactic reactions (see section 4.8).

Allergic phenomena
As with other platinum-based products, hypersensitivity reactions may occur, appearing in most cases during perfusion necessitate discontinuation of the perfusion and an appropriate symptomatic treatment. Cross reactions, sometimes fatal, have been reported with all the platinum compounds (see sections 4.3 and 4.8).

Hepatic function and haematological formula
The haematological formula and hepatic function must be monitored at regular intervals.

Carcinogenic potential
In humans, in rare cases the appearance of acute leukaemia has coincided with the use of cisplatin, which was in general associated with other leukaemogenic agents.

Cisplatin is carcinogenic in mice and rats (see section 5.3).

Injection site reactions
Injection site reactions may occur during the administration of cisplatin. Given the possibility of extravasation, it is recommended to closely monitor the infusion site for possible infiltration during drug administration. A specific treatment for extravasation reactions is unknown at this time.

Gastrointestinal effects
Nausea and vomiting may be intense and require adequate antiemetic treatment.

Immunosuppressant effects/ Increased susceptibility to infections.
Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including cisplatin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving

cisplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished. Yellow fever vaccine is strictly contraindicated because of the risk of fatal systemic vaccinal disease (see section 4.3.)

Excipient(s) warning

This medicinal product contains 3.5 mg sodium per ml, equivalent to 0.18% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

Cisplatin may be further prepared for administration with sodium-containing solutions (see section 6.6) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

4.5 Interaction with other medicinal products and other forms of interaction

Cisplatin can be used in combination with other cytostatics with corresponding mechanisms of action. Additive toxicity might occur in such cases.

Myelosuppression induced by cisplatin will be additive to existent impairment or to the similar toxicity of other agents such as cephaloridine, furosemide, aminoglycosides, etc., administered concurrently.

Nephrotoxic substances
Concomitant administration of nephrotoxic (e.g. cephalosporins, aminoglycosides, amphotericin B or contrast media) medicinal products will potentiate the toxic effect of cisplatin on the kidneys. *Nephrotoxicity*might be exacerbated by aminoglycoside antibiotics, administered simultaneously or 1-2 weeks after treatment with cisplatin. The concomitant use of other potentially nephrotoxic drugs (e.g. amphotericin B) is not recommended during treatment with cisplatin.

Renally excreted drugs
During or after treatment with cisplatin caution is advised with predominantly renal eliminated substances, e.g. cytostatic agents such as bleomycin and methotrexate, because of potentially reduced renal elimination.

The renal toxicity of ifosfamide may be greater when used with cisplatin or in patients who have previously been given cisplatin.

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.

Ototoxic substances
Concomitant and/or sequential administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function, especially in the presence of renal impairment. Except for patients receiving doses of cisplatin exceeding 60 mg/m^2 BSA, whose urine secretion is less than 1000 ml per 24 hours,no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

Ifosfamide may increase hearing loss due to cisplatin.

Oral anticoagulants
In the event of simultaneous use of oral anticoagulants, it is advisable to regularly check the INR.

Antihistamines, Phenothiazines and others
Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclizine, phenothiazines, thioxanthenes or trimethobenzamines may mask ototoxicity symptoms (such as dizziness and tinnitus).

Pyroxidine + altretamine combination
During a randomised study of the treatment of advanced ovarian cancer, the response time was unfavourably affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

Paclitaxel
Treatment with cisplatin prior to an infusion with paclitaxel may reduce the clearance of paclitaxel by 33% and therefore can intensify neurotoxicity.

Anticonvulsive substances/Anti-epileptics

Serum concentrations of anticonvulsive medicines may remain at subtherapeutic levels during treatment with cisplatin. For example; in patients receiving cisplatin and phenytoin, the serum level of phenytoin might be reduced. This is probably due to reduced absorption and/or increased metabolism. One should monitor the levels of phenytoin in plasma, and adjust the dose accordingly.

Antigout agents
Cisplatin may raise the concentration of blood uric acid, thus, in patients concurrently receiving antigout agents such as allopurinol, colchicine, probenecid or sulfinpyrazone, dosage adjustment of these drugs may be necessary to control hyperuricaemia and gout.

Cisplatin may interact with aluminium (see section 4.2).

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data from the use of cisplatin in pregnant women, but based on its pharmacological properties cisplatin is suspected to cause serious birth defects. Studies in animals have shown reproductive toxicity (see section 5.3). Cisplatin should not be used during pregnancy unless the clinician considers the risk to the individual patient to be justified.

Women of childbearing potential / Contraception in males and females
During treatment with cisplatin and for a minimum of the following 6 months, appropriate measures must be taken to avoid pregnancy this applies to patients of both sexes.

Genetic consultation is recommended if the patient wishes to have children after ending treatment.

Breast-feeding
Cisplatin is excreted in breast milk. Cisplatin is contra-indicated during breast-feeding (see section 4.3)

Fertility

Since a treatment with cisplatin may cause irreversible infertility, it is recommended that men, who wish to become fathers in the future, ask for advice regarding cryoconservation of their sperm prior to treatment.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

Nevertheless, the profile of undesirable effects (like nephrotoxicity) may influence the ability to drive vehicles and use machinery.

4.8 Undesirable effects

The most frequently reported adverse events 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).

Table of Adverse Drug Events Reported During Clinical or Postmarketing Experience.

System Organ Class	Frequency	Adverse Event

Infections and infestations	Not known	Infectiona
	Common	Sepsis
Blood and lymphatic system disorders	Very common	Bone marrow failure, thrombocytopenia, leukopenia, anaemia
	Not known	Coombs positive haemolytic anaemia
Neoplasmsbenign, malignant,andunspecified(including cysts and polyps)	Rare	Acute leukaemia
Immune system disorders	Uncommon	Anaphylactoidb reaction
Endocrine disorders	Not known	Blood amylase increased, inappropriate antidiuretic hormone secretion (SIADH)
Metabolism and nutrition disorders	Not known	Dehydration, hypokalaemia, hypophosphatemia, hyperuricemia, hypocalcaemia, tetany
	Uncommon	Hypomagnesaemia
	Very common	Hyponatraemia
Nervous system disorders	Not known	Cerebrovascular accident, haemorrhagic stroke, ischaemic stroke ageusia, cerebral arteritis, Lhermitte's sign, myelopathy, autonomic neuropathy
	Rare	Convulsion,peripheral neuropathies,leukoencephalopathy,reversibleposteriorleukoencephalopathy syndrome
Eye disorders	Not known	Vision blurred, colour blindness acquired, blindness cortical, optic neuritis, papilledema, retinal pigmentation
Ear and labyrinth disorders	Uncommon	Ototoxicity
	Not known	Tinnitus, deafness
Cardiac disorders	Not known Common	Cardiac disorder Arrhythmia, bradycardia, tachycardia
	Rare	Myocardial infarction
	Very rare	Cardiac arrest
Vascular disorders	Common	Venous thromboembolism
	Not known	Thrombotic microangiopathy (haemolytic uremic syndrome), Raynaud's phenomenon
Gastrointestinal disorders	Not known	Vomiting, nausea, anorexia, hiccups, diarrhoea
	Rare	Stomatitis
Hepatobiliary disorders	Not known	Hepatic enzymes increased, blood bilirubin increased
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary embolism
Skin and subcutaneous tissue disorders	Not known	Rash, alopecia
Musculoskeletal, connective tissue and bone disorders	Not known	Muscle spasms
Renal and urinary disorders	Not known	Renal failure acute, renal failurec , renal tubular disorder
Reproductive system and breast disorders	Uncommon	Abnormal spermatogenesis
General disorders and administration site condition	Not known	Pyrexia (very common), asthenia, malaise, injection site extravasation[d]

a: Infectious complications have led to death in some patients.b: Symptoms include facial edema, flushing wheezing, bronchospasm, tachycardia, and hypotension will be included in the parentheses for anaphylactoid reaction in the AE frequency table.

c: Elevations in BUN and creatinine, serum uric acid, and/or a decrease in creatinine clearance are subsumed under renal insufficiency/failure.
d: Local soft tissue toxicity including cellulitis, fibrosis, and necrosis (common) pain (common), oedema (common) and erythema (common) as the result of extravasation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie

4.9 Overdose

CAUTION IS ESSENTIAL IN ORDER TO PREVENT AN INADVERTANT OVERDOSE.

Acute overdosage with cisplatin may result in an enhancement of its expected toxic effects such as renal failure, liver failure, severe neurosensorial toxicities (deafness), ocular toxicity (including detachment of the retina), significant myelosuppression, untreatable nausea and vomiting and/or neuritis. Death may also occur. Renal function, cardiovascular function and blood counts should be monitored daily in order to assess the potential toxicity to these systems. Serum magnesium and calcium levels should be carefully monitored as should symptoms and signs of voluntary muscle irritability. If symptomatic tetany develops, electrolyte supplements should be administered. Serum liver enzymes and uric acid should also be monitored daily after an acute overdose.

There is no specific antidote in the event of an overdosage of cisplatin. Haemodialysis is only effective, even then partially, up to 3 hours after administration. If haemodialysis is initiated 4 hours after the overdose, it has little effect on the elimination of cisplatin from the body due to rapid and extensive binding of platinum to plasma proteins.

Treatment in the event of an overdose consists of general support measures.

If fever develops during prolonged myelosuppression, appropriate presumptive antibiotic coverage should be instilled after cultures have been obtained.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Cisplatin is a platinum-containing antineoplastic agent. Cisplatin has biochemical properties similar to those of bifunctional alkylating agents. The drug inhibits DNA synthesis by producing intrastrand and interstrand cross-links in DNA. Protein and RNA synthesis are also inhibited to a lesser extent.

Although the principal mechanism of action of cisplatin appears to be inhibition of DNA synthesis, other mechanisms, including enhancement of tumour immunogenicity may be involved in its antineoplastic activity. Cisplatin also has immunosuppressive, radio-sensitising, and antimicrobial properties.

Cisplatin does not appear to be cell-cycle or phase specific. Besides tumour cells, the target tissues are mainly those characterised by rapid cell proliferation such as bone marrow, gastrointestinal mucosa and gonads.

5.2 Pharmacokinetic properties

Absorption
Cisplatin is usually administered by the intravenous route, and preferably by IV infusion over 6-8 hours. During conventional IV infusions, plasma levels of total platinum increase gradually and peak at the end of the infusion.

Steep concentration gradients between intraperitoneal and plasma drug levels can be achieved by intraperitoneal administration.

Distribution

There is good uptake of cisplatin by the kidneys, liver, prostate and intestine. More than 90% of platinum containing species remaining in the blood are bound (possibly irreversibly) to plasma proteins. Penetration into the Cerebrospinal Fluid (CSF) is poor although significant amounts of cisplatin can be detected in intracerebral tumours.

The clearance of total platinum from plasma is rapid during the first four hours after intravenous administration, but then proceeds more slowly because of covalent binding to serum proteins. Levels of unbound platinum fall with a half-life of 20 minutes to 1 hour depending on the rate of drug infusion.

Following repeated treatment courses, platinum appears to accumulate in body tissues and has been detected in some tissues for up to 6 months after the last dose of the drug

Biotransformation
The metabolic fate of cisplatin has not been completely elucidated. Biotransformation occurs by rapid nonenzymatic conversion to inactive metabolites, which have not been definitely identified.

Elimination
The elimination of intact drug and various platinum-containing biotransformation products is via the urine. About 15-25% of administered platinum is rapidly excreted in the first 2-4 hours after administration of cisplatin. This early excretion is mostly of intact cisplatin. In the first 24 hours after administration, 20-80% is excreted, the remainder representing drug bound to tissues or plasma protein.

5.3 Preclinical safety data

In non-clinical repeat dose toxicity studies, renal damage, bone marrow depression, gastrointestinal disorders, ototoxicity, neurotoxicity, and immunosuppression have been observed at exposure levels similar to clinical exposure levels.

Non-clinical data indicate cisplatin is mutagenic, genotoxic and carcinogenic. Thymic lymphomas, mammary adenocarcinomas, fibro-liposarcoma, and lung adenomas were reported from repeat-dose studies of up to 19 weeks duration in mice. Leukemia and renal fibrosarcoma were reported from repeat-dose studies of up to 3 weeks in rats.

Non-clinical studies in mice showed that cisplatin caused direct damage to primordial follicle oocytes, leading to apoptosis, and ovarian depletion. Cisplatin causes testis damage and decreased sperm counts in mice, primarily through effects on differentiated spermatogonia. These findings suggest potential clinically relevant effects on male and female fertility that may be irreversible.

Developmental toxicity studies indicate cisplatin is embryotoxic in mice and rats, and teratogenic in both species at exposure levels similar to clinical exposure levels.

Studies in rodents have shown that exposure during pregnancy can cause tumors in adult offspring.

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
3 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 take 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.

A crystal or precipitate may formed as a result of exposure to low temperatures, in case a cloudy solution (i.e a precipitate or crystal) is observed inside the vial, see section 6.6.

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/20 mm flip off seal transparent.

For 25 ml
30 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal/20 mm flip off seal transparent.

For 50 ml
50 ml type I amber glass vial with a chlorobutyl grey stopper, sealed with an aluminium flip off transparent white seal/20 mm flip off seal transparent.

For 100ml
100 ml type I amber glass vial with a 20 mm S127-4432/50 grey rubber stopper sealed with 20 mm aluminium flip off transparent white seal/20 mm flip off seal transparent.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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.

7 MARKETING AUTHORISATION HOLDER

Accord Healthcare Ireland Ltd.
Euro House
Euro Business Park
Little Island
Cork T45 K857
Ireland

8 MARKETING AUTHORISATION NUMBER

PA2315/081/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 7th October 2011
Date of last renewal: 3rd June 2015

10 DATE OF REVISION OF THE TEXT

September 2023