Summary of Product Characteristics for

VSI OXALIPLATIN
OXALIPLATIN FOR INJECTION USP 50mg/100mg/vial

1. Name of the medicinal product
Oxaliplatin for Injection USP 50mg/100mg/vial

2. Qualitative and quantitative composition

Oxaliplatin For Injection USP 50mg
(Lyophilized)
Each vial contains:
Oxaliplatin USP…… 50 mg
Excipients……..QS

Oxaliplatin For Injection USP 100mg
(Lyophilized)
Each vial contains:
Oxaliplatin USP…… 100 mg
Excipients……..QS

3. Pharmaceutical form
A white lyophilized mass

4. Clinical particulars

4.1 Therapeutic indications
Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:

• Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.

• Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal products used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicinal products, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Posology

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m^2 intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m^2 intravenously repeated every 2 weeks until disease progression or unacceptable toxicity.

Dosage given should be adjusted according to tolerability.

Oxaliplatin should always be administered before fluoropyrimidines, i.e. 5-fluorouracil (5-FU).

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of glucose 5% (50 mg/ml) solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m^2.

Oxaliplatin has mainly been used in combination with continuous infusion 5-fluorouracil (5 FU) based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens (5 FU) combining bolus and continuous infusion were used.

Special Populations

Renal impairment:

Oxaliplatin must not be administered in patients with severe renal impairment. In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m^2.

Hepatic insufficiency:

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepatobiliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

Elderly patients:

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil (5 FU) in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Paediatric patients:

There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of glucose 5% (50 mg/ml) solution to give a concentration not less than 0.2 mg/ml must be infused either via a central venous line or a peripheral vein over 2 to 6 hours. Oxaliplatin infusion must always precede the administration of 5-fluorouracil (5 FU).

In the event of extravasation, administration must be discontinued immediately.

Preparation of Infusion Solution:

Reconstitution or final dilution should never be performed with a sodium chloride solution or other chloride-containing solutions.

The lyophilised injection is reconstituted by adding 10 ml (for the 50 ml vial) or 20 ml (for the 100 ml vial) of Water for Injection or 5% Dextrose Injection. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion solution of 250- 500 ml of 5% Dextrose Injection.

After reconstitution in the original vial, the solution may be stored upto 24 hours under refrigeration (2°C- 8°C, (36°F – 46°F)). After final dilution with 250- 500ml of 5% Dextrose Injection. The shelf life is 6 hours at room temperature (20°C- 25°C, (68°F – 77°F)) or upto 24 hours under refrigeration (2°C- 8°C, (36°F – 46°F)).

Oxaliplatin for injection is not light sensitive.

Oxalilatin for injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-FU) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with D5W prior to administration or any concomitant medication.

Parenteral drug should be inspected visually for particulate matter and discoloration prior to administration and discarded of present.

Needles or intravenous administration sets containing aluminium parts that may come in contact with Oxaliplatin for injection should not be used for preparation or mixing of drugs. Aluminium has been reported to cause degradation of platinum compounds.

4.3 Contraindications

Oxaliplatin is contraindicated in patients who

- have a known history of hypersensitivity to oxaliplatin or to any of the excipients listed.

- are breast feeding.

- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2x10^9$/l and/or platelet count of $<100x10^9$/l.

- have a peripheral sensory neuropathy with functional impairment prior to first course.

- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

Oxaliplatin should only be used in specialised departments of oncology and should be administered under the supervision of an experienced oncologist.

Renal impairment
Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and dose adjusted according to toxicity.

Hypersensitivity reactions
Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of oxaliplatin to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

Extravasation
In case of oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.

Neurological symptoms
Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.
For patients who develop acute laryngopharyngeal dysaesthesia, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

Peripheral neuropathy
If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:
- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.
Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paraesthesias or paraesthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration, and haematologic changes
Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy.
Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-FU.
Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischaemia, oxaliplatin treatment should be discontinued and appropriate measures initiated.
If haematological toxicity occurs (neutrophils $<$ 1.5 x 10^9/l or platelets $<$ 50 x 10^9/l), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin including fatal outcomes. If any of these events occurs, oxaliplatin should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin /5-fluorouracil (5-FU) administration so that they can urgently contact their treating physician for appropriate management.
If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1.5 x 10^9/l.
For oxaliplatin combined with 5-fluorouracil (5-FU) (with or without folinic acid (FA)), the usual dose adjustments for 5-fluorouracil (5-FU) associated toxicities should apply.
If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils < 1.0 x 10^9/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 10^9/l, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets ≤ 50 x 10^9/l) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-FU dose reductions required.

Pulmonary
In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis.

Blood disorders
Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (frequency not known).
Oxaliplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.
Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin treatment. If DIC is present, oxaliplatin treatment should be discontinued and appropriate treatment should be administered.

QT prolongation
QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal. The QT interval should be closely monitored on a regular basis before and after administration of oxaliplatin. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicinal products known to prolong QT interval, and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued.

Rhabdomyolysis
Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin.

Gastrointestinal ulcer/ Gastrointestinal haemorrhage and perforation

Oxaliplatin treatment can cause gastrointestinal ulcer and potential complications, such as duodenal ulcer haemorrhage and perforation, which can be fatal. In case of duodenal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken.

Hepatic
In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

Immunosuppressant Effects/Increased Susceptibility to Infections
Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving oxaliplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Pregnancy
For use in pregnant women, see section “Fertility, pregnancy and lactation”.

Fertility
Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect, which could be irreversible.
Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception.
Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).

Excipient information
This medicinal product contains less than 1 mmol sodium (23 mg) per vial. Patients on low sodium diets can be informed that this medicinal product is essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of 5-fluorouracil (5-FU), no change in the level of exposure to 5-fluorouracil (5-FU) has been observed.

In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored. Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis.

Vaccination with live or live-attenuated vaccine should be avoided in patients receiving oxaliplatin.

4.6 Fertility, pregnancy and lactation

Pregnancy
To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.

The use of oxaliplatin should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Breast-feeding
Excretion in breast milk has not been studied. Breast-feeding is contraindicated during oxaliplatin therapy.

Fertility
Oxaliplatin may have an anti-fertility effect.

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 oxaliplatin treatment resulting in an increase risk of dizziness, nausea and vomiting, and other neurological symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Adverse Effects
Frequencies in this table are defined using the following convention: very common (≥1/10) common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), rare (≥ 1/10000, < 1/1000), very rare (< 1/10000) not known (cannot be estimated from the available data).
Further details are given after the table.

System Organ Class	Frequency	Adverse Reaction
Infections and infestations*	Very Common	Infection
	Common	Rhinitis, Upper respiratory tract infection, Neutropenic sepsis
	Uncommon	Sepsis[2]
	Not Known[1]	Septic shock (including fatal outcomes)
Blood and lymphatic system disorders*	Very Common	Anaemia, Neutropenia, Thrombocytopenia, Leukopenia, Lymphopenia
	Common	Febrile neutropenia
	Rare	Immunoallergic thrombocytopenia, Haemolytic anaemia, Disseminated

		intravascular coagulation (DIC), including fatal outcomes[3]
	Not Known[1]	Secondary leukaemia, Haemolytic-uraemic syndrome, Autoimmune pancytopenia, Pancytopenia
Immune system disorders*	Very Common	Allergy/allergic reaction[2]
Metabolism and nutrition disorders	Very Common	Anorexia, Hyperglycaemia , Hypokalaemia, Hypernatraemia
	Common	Dehydration, Hypocalcaemia
	Uncommon	Metabolic acidosis
Psychiatric disorders	Common	Depression, Insomnia
	Uncommon	Nervousness
Nervous system disorders*	Very Common	Peripheral sensory neuropathy, Sensory disturbance, Dysgeusia, Headache
	Common	Dizziness, Motor neuritis, Meningism
	Rare	Dysarthria, Reversible Posterior Leukoencephalopathy Syndrome (RPLS or PRES)[3]
	Not Known[1]	Ischemic or haemorrhagic cerebrovascular disorder, Convulsion
Eye disorders	Common	Conjunctivitis, Visual disturbance
	Rare	Visual acuity reduced transiently, Visual field disturbances, Optic neuritis, Transient vision loss reversible, following therapy discontinuation
Ear and labyrinth disorders	Uncommon	Ototoxicity
	Rare	Deafness
Cardiac disorders	Not Known[1]	Acute coronary syndrome[4], QT Prolongation[5]
Vascular disorders	Common	Haemorrhage, Flushing, Deep vein thrombosis, Hypertension
Respiratory, thoracic and mediastinal disorders	Very Common	Dyspnoea, Cough, Epistaxis
	Common	Hiccups, Pulmonary embolism
	Rare	Interstitial lung disease (sometimes fatal), Pulmonary fibrosis[3]
	Not Known[1]	Laryngospasm, Pneumonia and bronchopneumonia (including fatal outcomes)

Gastrointestinal disorders*	Very Common	Nausea, Diarrhoea, Vomiting, Stomatitis/Mucositis, Abdominal pain, Constipation
	Common	Dyspepsia, Gastroesophageal reflux, Gastrointestinal haemorrhage, Rectal haemorrhage
	Uncommon	Ileus, Intestinal obstruction
	Rare	Colitis including *Clostridium difficile* diarrhoea, Pancreatitis
	Not Known[1]	Intestinal ischaemia (including fatal outcomes)[3], Gastrointestinal ulcer and perforation (which can be fatal)[3], Oesophagitis
Hepato-biliary disorders*	Very Rare	Liver sinusoidal obstruction syndrome (also known as veno-occlusive disease of liver)[6]
	Not Known[1]	Focal nodular hyperplasia
Skin and subcutaneous tissue disorders	Very Common	Skin disorder, Alopecia
	Common	Skin exfoliation (i.e. Hand and Foot syndrome), Rash erythematous, Rash, Hyperhidrosis, Nail disorder
	Not Known[1]	Hypersensitivity vasculitis
Musculoskeletal and connective tissue disorders	Very Common	Back pain
	Common	Arthralgia, Bone pain
	Not Known[1]	Rhabdomyolysis (including fatal outcomes)[3]
Renal and urinary disorders	Common	Haematuria, Dysuria, Micturition frequency abnormal
	Very Rare	Acute tubular necrosis, Acute interstitial nephritis, Acute renal failure
General disorders and administration site conditions	Very Common	Fatigue, Fever[7], Asthenia, Pain, Injection site reaction[8], Rigors
Investigations	Very Common	Hepatic enzyme increase, Blood alkaline phosphatase increase, Blood bilirubin increase, Blood lactate dehydrogenase increase, Weight increase (adjuvant setting)
	Common	Blood creatinine increase, Weight decrease (metastatic setting)

Injury, poisoning and procedural complications	Common	Fall

***** See detailed section below

[1] Post-marketing experience with frequency unknown

[2] Very common allergies/allergic reactions, occurring mainly during infusion, sometimes fatal. Common allergic reactions include skin rash particularly urticaria, conjunctivitis, and rhinitis. Common anaphylactic or anaphylactoid reactions, include bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.

[3] See section 4.4

[4] Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab.

[5] QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section 4.4 – "QT prolongation").

[6] Or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases

[7] Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

[8] Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation may also result in local pain and inflammation which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein (see section 4.4).

4.9 Overdose

There is no known antidote to oxaliplatin.

In cases of overdose, exacerbation of adverse events can be expected.

Monitoring of haematological parameters should be initiated and symptomatic treatment given.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Oxaliplatin is an antineoplastic active substance belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group.

Oxaliplatin is a single enantiomer, (*SP*-4-2)-[(1R,2*R*)-Cyclohexane-1,2-diamine-k*N*, k*N*'] [ethanedioato(2-)-kO^1, kO^2] platinum.

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models.

A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*.

Mechanism of action

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

5.2 Pharmacokinetic properties

Absorption

Peak plasma concentrations (obtained within 5 minutes of the end of the infusion) were 3.2 to 45.5 µg/ml. Plasma concentrations of the parent compound following a dose of 1,000 mg/m^2/30-minutes are greater than

5 µg/ml for approximately 30-minutes after the end of the infusion, and greater than 0.4 µg/ml for an additional hour.

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg /m^2 every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m^2 every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m^2 Every Two Weeks or at 130 mg/m^2 Every Three Weeks

Dose	Cmax	AUC0-48	AUC	$t_{1/2\alpha}$	$t_{1/2\beta}$	$t_{1/2\gamma}$	Vss	CL
	µ g/ml	µg.h/ml	µg.h/ml	h	h	h	L	L/h
85 mg/m^2								
Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m^2								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m^2) or cycle 5 (130 mg/m^2).
Mean AUC, Vss and CL values were determined on Cycle 1.
C_{max}, AUC, AUC_{0-48}, Vss and CL values were determined by non-compartmental analysis.
$t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$, were determined by compartmental analysis (Cycles 1-3 combined).

Distribution

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks or 130mg/m^2 every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation

Biotransformation in vitro is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact active substance was detectable in plasma ultrafiltrate at the end of a 2h-infusion. Several cytotoxic biotransformation products including the monochloro-, dichloro- and diaquo-DACH platinum species have been identified in the systemic circulation together with a number of inactive conjugates at later time points.

Elimination

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration.

By day 5, approximately 54% of the total dose was recovered in the urine and < 3% in the faeces.

Renal impairment

The effect of renal impairment on the disposition of oxaliplatin was studied in patients with varying degrees of renal function.

Oxaliplatin was administered at a dose of 85 mg/m2 in the control group with a normal renal function (CLcr > 80 ml/min, n=12) and in patients with mild (CLcr = 50 to 80 ml/min, n=13) and moderate (CLcr = 30 to 49 ml/min, n=11) renal impairment, and at a dose of 65 mg/m^2 in patients with severe renal impairment (CLcr < 30 ml/min, n=5). Median exposure was 9, 4, 6, and 3 cycles, respectively, and PK data at cycle 1 were obtained in 11, 13, 10, and 4 patients respectively.

There was an increase in plasma ultrafiltrate (PUF) platinum AUC, AUC/dose and a decrease in total and renal CL and Vss with increasing renal impairment especially in the (small) group of patients with severe renal impairment: point estimate (90% CI) of estimated mean ratios by renal status versus normal renal function for AUC/dose were 1.36 (1.08, 1.71), 2.34 (1.82, 3.01) and 4.81 (3.49, 6.64) for patients with mild and moderate and in severe renal failure respectively.

Elimination of oxaliplatin is significantly correlated with the creatinine clearance.

Total PUF platinum CL was respectively 0.74 (0.59, 0.92), 0.43 (0.33, 0.55) and 0.21 (0.15, 0.29) and for Vss respectively 0.52 (0.41, 0.65), 0.73 (0.59, 0.91) and 0.27 (0.20, 0.36) for patients with mild, moderate and severe renal failure respectively. Total body clearance of PUF platinum was therefore reduced by respectively 26% in mild, 57% in moderate, and 79% in severe renal impairment compared to patients with normal function.

Renal clearance of PUF platinum was reduced in patients with impaired renal function by 30% in mild, 65% in moderate, and 84% in severe renal impairment compared to patients with normal function.

There was an increase in beta half life of PUF platinum with increasing degree of renal impairment mainly in the severe group.

Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment.

5.3 Preclinical safety data

The target organs identified in preclinical species (mice, rats, dogs, and/or monkeys) in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing medicinal products and DNA-damaging, cytotoxic medicinal products used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m^2) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na+ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. Pharmaceutical particulars

6.1 List of excipients

Lactose Monohydrate USP
Oxalic Acid IH
Sodium Hydroxide USP
Water for Injection USP

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products except for those mentioned. Oxaliplatin can be co-administered with folinic acid via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipients and trometamol salts of other medicinal products. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

- DO NOT dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).

- DO NOT use injection equipment containing aluminium.

- DO NOT mix with other medicinal products in the same infusion bag or line.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Oxaliplatin for Injection USP is available in a vial containing 50mg and 100mg of Oxaliplatin USP.

6.6 Special precautions for disposal and other handling

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

Instructions for Handling

The handling of this cytotoxic agent by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.
The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicines, in

accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.
Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.
Excreta and vomit must be handled with care.
Pregnant women must be warned to avoid handling cytotoxic agents.
Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers.
If oxaliplatin concentrate or solution for infusion, should come into contact with skin, wash immediately and thoroughly with water.
If oxaliplatin concentrate or solution for infusion, should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration
- DO NOT use injection material containing aluminium.
- DO NOT administer undiluted.
- Only glucose 5% infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipients and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Instruction for use with folinic acid (as calcium folinate or disodium folinate)
Oxaliplatin 85 mg/m^2 intravenous infusion in 250 to 500 ml of glucose 5 % solution is given at the same time as folinic acid intravenous infusion in glucose 5 % solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.
These two medicinal products should **not** be combined in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic glucose 5 % solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil (5FU)
Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil (5-FU). After oxaliplatin administration, flush the line and then administer 5-fluorouracil (5-FU).
For additional information on drugs combined with oxaliplatin.

Concentrate for solution for infusion
Inspect visually prior to use. Only clear solutions without particles should be used. The medicinal product is for single use only. Any unused concentrate should be discarded.

Inspect visually prior to use. Only clear solutions without particles should be used. The medicinal product is for single use only. Any unused infusion solution should be discarded.
NEVER use sodium chloride or chloride containing solutions for dilution.
The compatibility of Oxaliplatin solution for infusion has been tested with representative, PVC-based administration sets.

Disposal

Remnants of the medicinal product as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents and in accordance with local requirements related to the disposal of hazardous waste.

7. Marketing authorisation holder

<< maketing authorisation holder details >>

8. Marketing authorisation number(s)

<< marketing authorisation number details >>

9. Date of first authorisation/renewal of the authorisation

<< date of authorisation/renewal >>

10. Date of revision of the text

17-Nov-2023

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