SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

1. NAME OF THE FINISHED PHARMACEUTICAL PRODUCT

XPLATIN (Oxaliplatin 100 mg/50 ml injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2 mg oxaliplatin.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Liquid Injection

Clear colorless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxaliplatin Injection, used in combination with infusional 5-fluorouracil and folinic acid or leucovorin, is indicated for the following:

- Adjuvant treatment of stage III (Duke's C) colon cancer in patients who have undergone complete resection of the primary tumour.
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

Oxaliplatin Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

Oxaliplatin Injection should always be administered before the fluoropyrimidines, i.e., 5-fluorouracil.

Administer Oxaliplatin Injection in combination with 5-fluorouracil/leucovorin every 2 weeks. For advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles).

Oxaliplatin Injection is administered as a 2- to 6-hour intravenous infusion in 250–500 ml of 5% glucose 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 Injection dose of 85 mg/m².

On Day1, oxaliplatin 85 mg/m^2 intravenous infusion in 250-500ml 5% Dextrose Injection and leucovorin 200mg/m^2 intravenous infusion in 5% Dextrose injection, both given over 2-6 hours at

same time in separate bags, followed by 5-fluorouracil 400 mg/m^2 intravenous bolus given over 2–4 minutes, followed by 5-fluorouracil 600 mg/m^2 intravenous infusion in 500 mL 5% Dextrose Injection, (recommended) as a 22-hour continuous infusion.

On Day 2, Leucovorin 200 mg/m^2 intravenous infusion over 120 minutes, followed by 5-fluorouracil 400 mg/m^2 intravenous bolus given over 2–4 minutes, followed by 5-fluorouracil 600 mg/m^2 intravenous infusion in 500 mL 5% Dextrose Injection, (recommended) as a 22-hour continuous infusion.

Dose Modification Recommendations

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests. Prolongation of infusion time for Oxaliplatin Injection from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-fluorouracil and leucovorin do not need to be changed.

Adjuvant Therapy in Patients with Stage III Colon Cancer

Neuropathy and other toxicities were graded using the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale, Version 1.

For patients who experience persistent grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin Injection to 75 mg/m^2 should be considered. For patients with persistent grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin Injection to 75 mg/m^2 and infusional 5-fluorouracil to 300 mg/m^2 bolus and 500 mg/m^2 infusion for 22 hours is recommended for patients after recovery from grade 3/4 gastrointestinal events (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until neutrophils are $\geq 1.5 \times 10^9$/L and platelets are $\geq 75 \times 10^9$/L.

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

Neuropathy was graded using a study-specific neurotoxicity scale. Other toxicities were graded by the NCI CTC, Version 2.0.

For patients who experience persistent grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin Injection to 65 mg/m^2 should be considered. For patients with persistent grade 3 neurosensory events, discontinuing of therapy should be considered. The 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin Injection to 65 mg/m^2 and 5-fluorouracil by 20% (300 mg/m^2 bolus and 500 mg/m^2 (22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal events (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4

thrombocytopenia. The next dose should be delayed until neutrophils are ≥1.5 × 10^9/L and platelets are ≥75 × 10^9/L.

Preparation of Infusion Solution

Concentrate Solution for Infusion

- Do not freeze the concentrated solution and protect it from light.
- Dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.
- The solution must be diluted in an infusion solution of 250–500 mL of 5% Dextrose Injection.
- After dilution with 250–500 mL of 5% Dextrose Injection, the shelf-life is 6 hours at room temperature (20–25°C) or up to 24 hours under refrigeration (2–8°C). After dilution, protection from light is not required.
- Oxaliplatin Injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through the same infusion line. The infusion line should be flushed with 5% Dextrose Injection prior to administration of any concomitant medication.
- Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration and discarded if present.
- Needles or intravenous administration sets containing aluminium parts that may come in contact with Oxaliplatin Injection should not be used for the preparation or mixing of the drug. Aluminium has been reported to cause degradation of platinum compounds.
- The medicinal product is for single use only. Any unused infusion solution should be discarded.

4.3 Contraindications

Oxaliplatin Injection should not be administered to patients with a history of known allergy to Oxaliplatin Injection or other platinum compounds.

Oxaliplatin is contraindicated in patients who

- Have a known history of hypersensitivity to Oxaliplatin Injection or other platinum compounds;
- Are breastfeeding;
- Have myelosuppression prior to starting the first course, as evidenced by baseline neutrophils <2 × 10^9/l and/or platelet count of <100 ×10^9/l;
- Have a peripheral sensitive neuropathy with functional impairment prior to the first course; and,
- Have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

Renal impairment

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the 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 is contra-indicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

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 medications 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 paresthesias or paresthesias 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 haematological 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-fluorouracil.

Cases of intestinal ischemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischemia, oxaliplatin treatment should be discontinued and appropriate measures initiated.

If haematological toxicity occurs (neutrophils < $1.5x10^9$/l or platelets < $50x10^9$/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 and 5-fluorouracil 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 (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils <$1.0x10^9$/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 10^9/L, temperature > 38.3°C or a sustained temperature > 38°C for more than one hour), or grade 3-4 thrombocytopenia (platelets < $50x10^9$/l) occur, the dose of oxaliplatin

should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting), in addition to any 5-fluorouracil 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.

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 (see section 4.8). 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 ulcer haemorrhage and perforation

Oxaliplatin treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal 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 including oxaliplatin, 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.

4.5 Interaction with other FPP's and other forms of Interaction

No specific CYP450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m2 oxaliplatin and 5 fluorouracil/leucovorin has been observed in patients treated every 2 weeks. Increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m^2 oxaliplatin dosed every 3 weeks. Because platinum-containing species are eliminated primarily through the kidneys, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds; although, this has not been specifically studied.

4.6 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 for up to 4 months for women and 6 months for men.

Oxaliplatin may have an anti-fertility effect.

Lactation: Excretion in breast milk has not been studied. Breastfeeding is contraindicated during oxaliplatin therapy.

Pediatric Use: The effectiveness of oxaliplatin in children has not been established.

Geriatric Use: No significant effect of age on the clearance of ultrafilterable platinum has been observed.

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

Patients ≥ 65 years of age receiving the oxaliplatin combination therapy experienced more grade 3-4 granulocytopenia than patients < 65 years of age (45% versus 39%). The incidence of diarrhea, dehydration, hypokalemia, leucopenia, fatigue and syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in patients ≥65 years old.

Patients with Renal Impairment

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m2. In patients with severe renal impairment, the initial recommended oxaliplatin dose should be reduced to 65 mg/m^2.

The combination of oxaliplatin injection and 5-fluorouracil/leucovorin should be used with caution in patients with pre-existing renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafilterable platinum is decreased in patients with mild, moderate and severe renal impairment. A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

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 neurologic 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 a patient's 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 Undesirable effects

Summary of the safety profile

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

Tabulated list of adverse reactions

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5-FU/FA treatment arms) and from post marketing experience.

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.

MedDRA system organ classes	**Very common**	**Common**	**Uncommon**	**Rare**	**Not Know**
Infections and infestations	Infection	Rhinitis Upper respiratory tract infection Neutropenic sepsis+	Sepsis +	-	-
Blood and lymphatic system disorders	Anaemia Neutropenia Thrombocytopenia Leukopenia Lymphopenia	Febrile neutropenia	-	Immunoallergic thrombocytopenia Haemolytic anaemia	-
Immune system disorders	Allergy/allergic reaction	-	-	-	-
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypokalaemia Hyponatraemia	Dehydration Hypocalcaemia	Metabolic acidosis	-	-
Psychiatric disorders	-	Depression Insomnia	Nervousness	-	-
Nervous system disorders	Peripheral sensory neuropathy, Sensory disturbance, Dysgeusia, Headache	Dizziness Motor neuritis Meningism	-	Dysarthria Reversible Posterior Leukoencephalopathy syndrome (RPLS, or PRES)	-
Eye disorders	-	Conjunctivitis Visual disturbance	-	Visual acuity reduced transiently Visual field	-

				disturbances Optic neuritis Transient vision loss, reversible following therapy discontinuation	
Ear and labyrinth disorders	-	-	Ototoxicity	Deafness	-
Cardiac disorders	-	-	-	-	Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab
Vascular disorders	-	Haemorrhage Flushing Deep vein thrombosis Hypertension	-	-	
Respiratory, thoracic and mediastinal	Dyspnoea Cough Epistaxis	Hiccups Pulmonary embolism	-	Interstitial lung disease Pulmonary fibrosis	-

disorders					
Gastrointestinal disorders	Nausea Diarrhoea Vomiting Stomatitis /Mucositis Abdominal pain Constipation	Dyspepsia Gastroesophageal reflux Gastrointestinal haemorrhage Rectal haemorrhage	Ileus Intestinal obstruction	Colitis including clostridium difficile diarrhoea Pancreatitis	Oesophagitis
Skin and subcutaneous tissue disorders	Skin disorders Alopecia	Skin exfoliation (i.e. Hand & Foot syndrome) Rash erythematous Rash Hyperhidrosis Nail disorder	-	-	-
Musculo-skeletal and connective tissue disorders	Back pain	Arthralgia Bone pain	-	-	-
Renal and urinary disorders	-	Haematuria Dysuria Micturition frequency abnormal	-	-	-
General disorders and administration site conditions	Fatigue Feve Asthenia Pain Injection site reaction	-	-	-	-
Investigations	Hepatic enzyme increase Blood alkaline phosphatase increase	B lood creatinine increase Weight decrease (metastatic setting)	-	-	-

	Blood bilirubin increase Blood lactate dehydrogenase increase Weight increase (adjuvant setting)				
Injury, poisoning and procedural complications	-	Fall	-	-	-

4.9 Overdose

There is no known antidote for oxaliplatin injection overdose. In addition to thrombocytopenia, the anticipated complications of an oxaliplatin injection overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhoea and neurotoxicity.

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

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

Oxaliplatin is an anti-neoplastic 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 exhibits a wide spectrum of both in vitro cytotoxicity and in vivo anti-tumour 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.

Oxaliplatin undergoes non-enzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaquo- and diaquo-DACH platinum, which covalently bind with macromolecules. Both inter- and intra-strand Pt-DNA cross-links are formed. Cross-links are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These cross-links inhibit DNA replication and transcription resulting in the disruption of DNA synthesis, leading to cytotoxic and anti-tumour effects. Cytotoxicity is

cell-cycle nonspecific. In vivo studies have shown the anti-tumour activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil, oxaliplatin exhibits in vitro and in vivo antiproliferative activity greater than either compound alone in several tumour models (HT29 , GR and L1210).

5.2 Pharmacokinetic properties

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases (t½α; 0.43 hours and t½β; 16.8 hours) and a long terminal elimination phase (t½γ; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of oxaliplatin at a dose of 85 mg/m^2 expressed as ultrafilterable platinum were a C_{max} of 0.814 mcg/mL and a volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0\text{-}48\ hr}$) assessed over three cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

Distribution

At the end of a 2-hour infusion of oxaliplatin, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every 2 weeks.

Metabolism

Oxaliplatin undergoes rapid and extensive non-enzymatic biotransformation. There is no evidence of cytochrome P450 (CYP450)-mediated metabolism *in vitro*.

Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species (monochloro-DACH platinum, dichloro-DACH platinum, and monoaquo- and diaquo-DACH platinum) and a number of non-cytotoxic, conjugated species.

Elimination

The major route of platinum elimination is renal excretion. At 5 days after a single 2-hour infusion of oxaliplatin, urinary elimination accounted for about 54% of the platinum eliminated, with faecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10–17 L/hour)

that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/hour). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with the GFR.

Renal Impairment

The AUC0-48 hr of platinum in the plasma ultrafiltrate increases as renal function decreases. The AUC0-48 hr of platinum in patients with mild (creatinine clearance 50 to 80 mL/min), moderate (CLcr 30 to <50 mL/min) and severe renal (CLcr <30 mL/min) impairment is increased by about 60%, 140% and 190%, respectively, compared to patients with normal renal function (CLcr >80 mL/min).

There was decrease in total and renal CL and Vss with increasing renal impairment especially in the (small) group of patients with severe renal impairment.

Total body clearance of plasma ultrafiltrate (PUF) platinum was reduced by 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 drugs and DNA-damaging, cytotoxic drugs 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/m²) 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

Water for Injection USP

6.2 Incompatibilities

The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Oxaliplatin can be co-administered with folinic acid.

DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. 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 chloride).

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

DO NOT use injection equipment containing aluminium.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at controlled room temperature (15℃ to 25℃). Protected from light. DO NOT FREEZE.

6.5 Nature and contents of container

50 ml Amber moulded glass vial closed with 20 mm rubber plug and sealed with 20mm Aluminium flip off Seal is placed in a carton along with pack insert.

7. MARKETING AUTHORIZATION HOLDER

M/S VHB MEDI SCIENCES LTD.

50 AB, Govt industrial Estate,

Charkop, Kandivali (W)

Mumbai-400067, INDIA

Manufacturing site:

VHB MEDI SCIENCES LTD.

Plot No.20-22 & 49-51, IIE, Sector-5,

SIDCUL, Pantnagar, Udham Singh Nagar,

Uttarakhand, INDIA.

Tel. No.: +912241639000

8. MARKETING AUTHORIZATIONNUMBER

06671/08166/NMR/2020

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORIZATION

19/10/2021

10. DATE OF REVISION OF THE TEXT

18/07/2023