Summary of Product Characteristics

1. Name of the Medical Product

Drug Product	**:**	Oxaliplatin Injection USP (50 mg / 25 mL)
Generic Name	**:**	Oxaliplatin Injection USP
Strength	**:**	Each mL of sterile preservative and pyrogen free aqueous clear and colourless solutioncontaining 2.0 mg of Oxaliplatin USP in 1.0 mLof Water for Injection USP

2. Composition, Quality and Quantitative formula

Composition

Each mL contains:

Oxaliplatin USP	2.0 mg
Water for Injection USP	qs.

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Sterile preservative and pyrogen free aqueous clear and colourless solution for Intravenous Infusion

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 (Dukes' 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 medical product used, in conditions that guarantee the integrity of the medical 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/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² 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.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 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 on clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens 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/m².

Hepatic impairment

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary 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 in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Paediatric population

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

Method of administration

Oxaliplatin is administered by intravenous infusion.The administration of oxaliplatin does not require hyper hydration.Oxaliplatin diluted in 250 to 500 mL of 5% glucose solution to give a concentration not less than 0.2 mg/mL must be infused via a central venous line or peripheral vein over 2 to 6 hours.Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

Instruction for use

Oxaliplatin must be diluted before use. Only 5% glucose diluents is to be used to dilute the concentrate for solution for infusion product. (For instructions on dilution of the medicinal product before administration,

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

4.3 Contraindications

Oxaliplatin is contraindicated in patients who:

- Have a known history of hypersensitivity to the active substance or to any of the excipients of Oxaliplatin Injection.

- Are breast feeding.

- Have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2x109/l and/or platelet count of <100x109l.

- Have a peripheral sensitive neuropathy with functional impairment prior to first course.

S- 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 specialized departments of oncology and should be administered under the supervision of an experienced oncologist.

Renal impairment

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient.
In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

Hypersensitivity reactions

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contra-indicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.
In case of oxaliplatin extravasations, 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 dysesthesia, 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, dysesthesia) 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/m2 (metastatic setting) or 75 mg/m2 (adjuvant setting).

- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m2 (metastatic setting) or 75 mg/m2 (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.

If haematological toxicity occurs (neutrophils < 1.5x109/l or platelets < 50x109/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.

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 occur with or without Neutropenia, the next treatment should be delayed until recovery from mucositis/ stomatitis to grade 1 or less and/or until the neutrophils count is ≥ 1.5 x 109/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 <1.0x109/l), grade 3-4 thrombocytopenia (platelets < 50x109/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, dyspnea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease.

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.

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.

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 medicinal products and other form of interactions

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed. In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylate, granisetron, paclitaxel, and sodium valproate.

4.6 Pregnancy and lactation

Pregnancy

There is no data from the use of oxaliplatin in pregnant women. Animal studies, have shown reproductive toxicity.

Oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraception.

The use of oxaliplatin should only be considered after suitably apprising the patient of the risk to the fetus 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.

Breastfeeding

It is unknown whether oxaliplatin is excreted in human milk.

Oxaliplatin is contra-indicated during breast-feeding.

Fertility

Oxaliplatin may have an anti-fertility effect

4.7 Effects on ability to drive and use machine

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 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 Undesirable effects

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. 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**
Investigations	Hepatic enzyme increase Blood alkaline phosphatase increase Blood bilirubin increase Blood lactate dehydrogenase increase Weight increase (adjuvant setting)	Blood creatinine Increase Weight decrease (metastatic setting)		
Blood and lymphatic system disorders*	Anaemia Neutropenia Thrombocytopenia Leukopenia Lymphopenia	Febrile neutropenia		Immunoallergic thrombocytopenia Haemolytic anaemia
Nervous system disorders*	Peripheral sensory	Dizziness		Dysarthria

	neuropathy Sensory disturbance Dysgeusia Headache	Motor neuritis Meningism		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
Respiratory, thoracic and mediastinal disorders	Dyspnoea Cough Epistaxis	Hiccups Pulmonary embolism		Interstitial lung disease, sometimes fatal Pulmonary fibrosis**
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
Renal and urinary disorders		Haematuria Dysuria Micturition frequency abnormal		
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		
Metabolism and nutrition disorders	Anorexia Hyperglycaemia Hypokalaemia Hyponatraemia	Dehydration	Metabolic acidosis	
Infections and infestations *	Infection	Rhinitis Upper respiratory tract infection Neutropenic sepsis		
Vascular disorders		Haemorrhage Flushing Deep vein thrombosis Hypertension		
General disorders and administration site conditions	Fatigue Fever++ Asthenia Pain Injection site reaction+++			
Immune system disorders*	Allergy/ allergic reaction +			
Psychiatric disorders		Depression Insomnia	Nervousness	

+ 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, angiooedema, hypotension, sensation of chest pain and anaphylactic shock.
++ Very common fever, rigors (tremors), either from infection (with or without febrile Neutropenia) or possibly from immunological mechanism.
+++ Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasations 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 .

Blood and lymphatic system disordersIncidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Anemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2
Febrile Neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

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 EFDA yellow Card Scheme, online at https://primaryreporting.who-umc.org/ET or toll free call 8482 to Ethiopian food and drug authority (EFDA).

4.9 Over dosage

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse even can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment should be given.

5. Pharmacological properties

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03
Oxaliplatin is an antineoplastic drug 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,2R)-Cyclohexane-1,2-diamine-kN, kN'] [ethanedioato(2-)-kO1, kO2] platinum.

Mechanism of action

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.

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

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 anti-tumour effects.

Clinical and efficacy and safety

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m2 repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in three clinical studies:

- in front-line treatment, the 2-arm comparative phase III EFC2962 study randomized 420 patients either to 5-FU/FA alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210).

- in pretreated patients, the comparative three arms phase III study EFC4584 randomized 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).

- finally, the uncontrolled phase II EFC2964 study included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57).

The two randomized clinical trials, EFC2962 in front-line therapy and EFC4584 in pretreated patients, demonstrated a significantly higher response rate and a prolonged progression free survival (PFS)/time to progression (TTP) as compared to treatment with 5-FU/FA alone. In EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Response rate under FOLFOX4 versus LV5FU2

Response rate, % (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	22 (16-27)	49 (42-46)	NA*
Response assessment every 8weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value < 0.0001		
Pretreated patients			
EFC2964	NA*	23	NA*
(refractory to 5-FU/FA)		(13-36)	
Response assessment every 12weeks			

* NA : Not Applicable

Median Progression Free Survival (PFS) / Median Time to Progression (TTP) FOLFOX4 versus LV5FU2

Median PFS/TTP Months (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatmentEFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5-FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pretreated patients			
EFC2964	NA*	5.1	NA*
(refractory to 5-FU/FA)		(3.1-5.7)	

*NA : Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pretreated patients			
EFC2964	NA*	10.8	NA*
(refractory to 5-FU/FA)		(9.3-12.8)	

*NA : Not Applicable

In pretreated patients (EFC4584), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 5-FU/FA experienced a significant improvement of their disease related symptoms compared to those treated with 5-FU/FA alone (27.7% vs 14.6% p = 0.0033).

In non-pretreated patients (EFC2962), no statistically significant difference between the two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting. In the adjuvant setting, the MOSAÏC comparative phase III study (EFC3313) randomized 2246 patients (899 stage II/Dukes' B2 and 1347 stage III/Dukes' C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2/C) = 451/672).

EFC 3313 3-year disease free survival (ITT analysis)* for the overall population.

Treatment arm FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% CI)	73.3 (70.6-75.9)	78.7 (76.2-81.1)
Hazard ratio (95% CI)	0.76 (0.64-0.89)	
Stratified log rank test	P=0.0008	

5.2 Pharmacokinetics Properties

The pharmacokinetics of individual active compounds has 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 /m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultra filtrate Following Multiple Doses of Oxaliplatin at 85 mg/m2 Every Two Weeks or at 130 mg/m2 Every Three Weeks

Dose 85 mg/m²	Cmax µg/mL	AUC 0-48 µg.h /mL	AUC µg.h /mL	t 1/2α h	t 1/2β h	t 1/2γ h	Vss L	CL L/h
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/m²								
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 AUC0-48, and Cmax values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).
Mean AUC, Vss, CL, and CLR0-48 values were determined on Cycle 1.
Cend, Cmax, AUC, AUC0-48, Vss and CL values were determined by non-compartmental analysis.
t1/2α, t1/2β, and t1/2γ, were determined by compartmental analysis (Cycles 1-3 combined).

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 ultra filtrate following 85 mg/m² every two weeks or 130 mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

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 drug was detectable in plasma ultra filtrate 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. 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.

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/m2 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 ultra filtrate (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 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. Cardio toxicity 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 cardio toxicity 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

Following excipients used during the manufacturing of Oxaliplatin Injection USP

Water for Injection USP

6.2 Incompatibilities

This medicinal product should not be mixed with other medicinal products.

-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 medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipients and trometamol salts of others active substances.

Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin.

6.3 Shelf life

24 months from the date of manufacturing, when retained in the original carton.

6.4 Special precautions for storage

Store protected from light at a temperature not more than 25º (77°F), excursions permitted between 15º and 30º (59º F and 86º F). Do not refrigerate.

6.5 Special precautions for disposal and other handlings

Keep container in the outer carton in order to protect from light. Do not refrigerate or freeze.

6.6. Nature and contents of container

30 mL Amber Glass Vial USP Type I

20 mm Bromo butyl rubber plug

20 mm Aluminium flip off seal

7. Marketing authorisation holder

Beta Drugs Limited
Kharuni-Lodhimajra Road,
Vill: Nandpur, Baddi, Distt. Solan,
Himachal Pradesh, 173205 INDIA

8. Marketing authorisation number(s)

08060/08180/NMR/2020

9. Date of first authorization

01 Nov 2022

10. Date of revision of the text

July 2024