Summary of Product Characteristics

1. Name of the medicinal product

Oxalither 50 (Oxaliplatin Injection USP 50mg/10mL)

2. Qualitative and quantitative composition

Each mL of Oxaliplatin Injection USP 50 mg contains
Oxaliplatin USP 5 mg

Lactose Monohydrate USP 45 mg

Water for injection USP q.s to 1 mL

For Full list of excipients see section 6.1

3. Pharmaceutical Form

Clear colorless Liquid Injection

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 tumor.
- Treatment of metastatic colorectal cancer.

4.2. Posology and method of administration

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 (see section 4.4). **Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5fluorouracil.**
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 in 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 (see sections 4.3 and 5.2). In patients with mild to moderate renal impairment, the recommended dose of Oxaliplatin is 85 mg/m^2 (see sections 4.4 and 5.2).

- Hepatic insufficiency:

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 patients:

There is no relevant indication for use of Oxaliplatin in children. The effectiveness of Oxaliplatin single agent in the paediatric populations with solid tumors has not been established (see section 5.1).

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 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 5fluorouracil.
In the event of extravasation, administration must be discontinued immediately.

Instructions for use:

Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. (See section 6.6).

4.3. Contraindications

Oxaliplatin is contraindicated in patients who

- Have a known history of hypersensitivity to Oxaliplatin.
- 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 sensitive neuropathy with functional impairment prior to first course.
- Have a severely impaired renal function (creatinine clearance less than 30 mL/min)

  (see section 5.2)

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 the dose adjusted according to toxicity (see section 5.2). *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 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 coadministered 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 laryngopharyngealdysaesthesia (see section 4.8), 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 (see section 4.8). 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 (see section 4.8).

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 < 1.5x10^9/l or platelets < 50x10^9/l), administration of the next course of therapy should be postponed until hematological 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 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), 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 (see section 4.8).
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.
Pregnancy

For use in pregnant women, see section 4.6.

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 (see section 4.6).

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, no change in the level of exposure to 5fluorouracil 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.

4.6. Fertility, pregnancy and lactation

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 apprising 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.

Excretion in breast milk has not been studied. Breast-feeding is contra-indicated during Oxaliplatin therapy.

Oxaliplatin may have an anti-fertility effect (see section 4.4).

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 increased 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 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

The most frequent adverse events of oxaliplatin in combination with 5-

fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, 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 Organ system 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 neutopenia		-Immunoallergic thrombocytopenia Haemolyticanaemia

MedDRA Organ system classes	**Very common**	**Common**	**Uncommon**	**Rare**
Nervous system disorders*	- Peripheral sensory neuropathy - ***Sensory disturbance*** - Dysgeusia - Headache	- ***Dizziness*** - Motor neuritis - Meningism		- Dysarthria - Reversible Posterior Leukoencep thy syndro (RPLS, or P (see section

Eye disorders		- ***Conjunctivitis*** -Visual disturbance		- Visual acu reduced transiently Visual field disturbance Optic neuri Transient v loss, revers following th discontinua
Ear and labyrinth disorders			Ototoxicity	- Deafn
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Cough - Epistaxis	- Hiccups - Pulmonary embolism		- Inters lung disease, sometimes - Pulm fibrosis**
Gastrointestinal disorders*	- ***Nausea*** - Diarrhoea - ***Vomiting*** - ***Stomatitis/Mucositis*** - ***Abdominal pain*** - Constipation	- ***Dyspepsia*** - ***Gastroesophageal reflux*** - Gastrointestinal hemorrhage - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Coliti including clostridium difficile diar - Pancr
Renal and urinary disorders		-Haematuria - Dysuria - Micturition frequency abnormal		
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosi		

MedDRA Organ system classes	Very common	Common	Uncommon	Rare
		s - Nail disorder		
Musculoskeletal and connective tissue disorders	- Back pain	- ***Arthralgia*** - Bone pain		
Metabolism and nutrition disorders	- Anorexia - Hyperglycaemia - Hypokalaemia - Hypernatraemia	- ***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	

* See detailed section below ** See section 4.4.

+ 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 anaphylactoidreactions, include bronchospasm, angioeodema, 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. 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).

Blood and lymphatic system disorders Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	**Metastatic Setting**			**Adjuvant Setting**		
Every 2 weeks	**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 of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorisation holder or, where applicable, via the national reporting system.

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

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03

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

Oxaliplatin is a single enantiomer, (*SP*-4-2)-[(1*R*,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*.

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.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85mg/m^2 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 randomised 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 randomised 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 5FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57)

The two randomised 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 **Response assessment every 8 weeks**	22(16-27)	49(42-56)	NA*
	P value = 0.0001		
Pretreated patients **EFC4584**	0.7(0.0-2.7)	11.1(7.6-15.5)	1.1
(refractory to CPT-11 + 5-FU/FA) **Response assessment every 6 weeks**	P value <0.0001		(0.2-3.2)
Pretreated patients **EFC 2964** (refractory to 5-FU/FA) Response assessment every 12weeks	NA*	23(13-36)	NA*

* 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 treatment EFC2962 (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 patientsEFC2964 (refractory to 5-FU/FA)	NA*	5.1(3.1-5.7)	NA*

*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)	2.1 (1.6-2.7)
	Log-rank P value = 0.09		
Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

*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 5FU/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/Duke's B2 and 1347 stage III/Duke's C) further to complete resection of the primary tumor 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	**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	

* Median follows up 44.2 months (all patients followed for at least 3 years)

The study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5-FU/FA combination (FOLFOX4) over 5-FU/FA alone (LV5FU2).

EFC 3313 3-year Disease Free Survival (ITT analysis)* according to Stage of disease

Patient stage	**Stage II (Duke's B2)**		**Stage III (Duke's C)**	
Treatment arm	**LV5FU2**	**FOLFOX4**	**LV5FU2**	**FOLFOX4**
Percent 3 year disease free survival (95% CI)	84.3 (80.9-87.7)	87.4 (84.3-90.5)	65.8 (62.2-69.5)	72.8 (69.4-76.2)
Hazard ratio (95% CI)	0.79 (0.57-1.09)		0.75 (0.62-0.90)	
Log-rank test	P=0.151		P=0.002	

* Medianfollows up 44.2 months (all patients followed for at least 3 years) **Overall Survival (ITT analysis):**

At time of the analysis of the 3-year disease free survival, which was the primary endpoint of the MOSAIC trial, 85.1% of the patients were still alive in the FOLFOX4 arm versus 83.8% in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10% in favour of FOLFOX4 not reaching statistical significance (hazard ratio = 0.90). The figures were 92.2% versus 92.4% in the stage II (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4% versus 78.1% in the stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months-22 years of age) with solid tumors have been treated. The effectiveness of oxaliplatin single agent in the paediatric populations treated has not been established.

Accrual in both Phase II studies was stopped for lack of tumor response.

5.2. Pharmacokinetic 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 Ultrafiltrate

Following Multiple Doses of Oxaliplatin at 85 mg/m² Every Two Weeks or at 130 mg/m² Every Three Weeks

Dose	Cmax µg/mL	AUC_{0-48} µg.h/mL	AUC µg.h/mL	t1/2α h	t1/2β h	t1/2γ h	V_{ss} L	CL L/h
85 mg/m²	0.814	4.19	4.68	0.43	16.8	391	440	17.4
Mean	0.193	0.647	1.40	0.35	5.74	406	199	6.35
SD								

130 mg/m^2	1.21	8.20	11.9	0.28	16.3	273	582	10.1
Mean	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07
SD								

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, V_{ss} and CL values were determined on Cycle 1.

C_{max}, AUC, AUC_{0-48}, V_{ss} 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).

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/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 *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/m^2 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 65mg/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 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 (see sections 4.2, 4.3 and 4.4).

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 platinumcontaining 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/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

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. Under instructions for use described in section 6.6, Oxaliplatin can be coadministered with folinic acid via a Y-line.

- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin (see section 6.6).
- DO NOTdilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).

-DO NOT mix with other drugs in the same infusion bag or infusion line (see section

6.6 for instructions concerning simultaneous administration with folinic acid).

-DO NOT use injection equipment containing aluminium.

6.3. Shelf life

2 years

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C.
From a microbiological point of view, the infusion preparation should be used immediately.
If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to

8°C unless dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store at 20^0C-25^0C (68°C - 77^0F); Excursions Permitted to 15-30^0C (59^0F -86^0F),Do not Freeze. Retain in the carton until time of use. Protect from Light.

6.5. Nature and contents of container

1 vial with 10 mLType I clear glass with 20 mm bromobutyl stopper with 20 mm dark blue colored Aluminium flip off seals

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 nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundingssolution, should come into contact with skin, wash immediately and thoroughly with water.
If oxaliplatin concentrate or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection equipment 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 medication 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 excipient and trometamol salts of others 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 85mg/m^2 IV infusion in 250 to 500 mL of 5% glucose solution is given at the same time as folinic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. These two drugs 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 5% glucose solution, never in alkaline solutions or sodium chloride or chloride containing solutions. ***Instruction for use with 5-fluorouracil***

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5fluorouracil.

After Oxaliplatin administration, flush the line and then administer 5-fluorouracil. For additional information on drugs combined with Oxaliplatin, see the corresponding manufacturer's summary of product characteristics. ***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.

Dilution before infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 mL to 500 mL of a 5% glucose solution to give an Oxaliplatin concentration between 0.2 mg/mL and 2 mg/mL; concentration range for which the physicochemical stability of Oxaliplatin has been demonstrated.

Administer by IV infusion.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2°C to +8°C and for 24 hours at +25°C. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

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, PVCbased, administration sets.

Infusion

The administration of Oxaliplatin does not require rehydration.

Oxaliplatin diluted in 250 to 500 mL of a 5% glucose solution to give a concentration not less than 0.2 mg/mL must be infused either by peripheral vein or central venous line over 2 to 6 hours. When Oxaliplatin is administered with 5-fluorouracil, the

Oxaliplatin infusion must precede the administration of 5-fluorouracil.

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 with due regard to current laws related to the disposal of hazardous waste.

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 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 labeled rigid containers. See below section “Disposal”. If Oxaliplatin concentrate or infusion

7. Marketing authorization holder

TherDose Pharma Pvt Ltd.
Plot No. 118, 119 & 120, Sy. No. 342, Road No. 6,

ALEAP Industrial Estate, Opp: JNTU Lane,

Pragathi Nagar, Gajularamaram(V), Quthbullapur(M)

Medchal-Malkajgiri (Dist)-500090, Hyderabad, Telangana State, India.

8. Marketing authorization number (s)

H2025/CTD11481/24306

9. Date of first authorization/renewal of the authorization

20/01/2025

10. Date of revision of the text

20/01/2025