SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

OXALILIVE 100

2. Qualitative and Quantitative Composition

Each ml contains:
Oxaliplatin BP……2 mg

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

Liquid Injection.
A clear colourless to almost colourless solution free from suspended particles.

4. Clinical Particulars

4.1 Therapeutic indications

Oxaliplatin is indicated in the treatment of metastatic colorectal cancer after failure of treatment with fluropyrimidines, alone by monochemotherapy or along with fluropyrimidines.

4.2 Posology and method of administration

As single agent

When used alone, the recommended dose of Oxaliplatin is 130 mg/m^2 as a continuous intravenous infusion over 2 to 6 hours. The dose may be repeated at an interval of 3 weeks

In combination therapy

IV: On day 1, administer oxaliplatin 85mg/m^2 concurrently with leucovorin 200 mg/m^2 (in separate containers using a Y line) by IV infusion over 2 hours. Then administer fluorouracil 400

mg/m^2 by IV injection over 2 to 4 minutes, followed by fluorouracil 600 mg/m^2 by IV infusion over 22 hours.

On day 2, administer leucovorin 200mg/m^2 by IV infusion over 2 hours. Then administer fluorouracil 400 mg/m^2 by IV injection over 2 to 4 minutes, followed by fluorouracil 600 mg/m^2 by IV infusion over 22 hours. Repeat regimen at intervals of 2 weeks.

Dosages adjustment in toxicity

Symptom	**Oxaliplatin Dose**	**Fluorouracil & Leucovorin**
Peripheral neuropathy	Administered over 6 hours	No adjustments required.
Persistent grade 2 Neurosensory effects	Reduce dose by 25% (i.e. 65 mg/m^2)	No adjustments required
In patients who recover from grade 3 or 4 GI toxicity , Grade 4 neutropenia or grade 3 or 4 thrombocytopenia	Reduce dose by 25% (i.e.65 mg/m^2)	Reduce Fluorouracil dose by 20% (i.e. 300 mg/m^2 by IV Injection over 2 to 4 minutes and 500 mg/m^2 by IV infusion over 22 hours.*

Do not administered next dose until neutrophil count is > 1500 / mm^3 and platelet count > 75.000
/mm^3

Renal Impairment:
In patients with impaired renal function, observe caution.
Monitoring Parameters:
Asses the patient for differential WBC count, hemoglobin, platelet count and ALT, AST billirubin and creatinine levels before each Xalipat Cycle.
Method of administration
Intravenous Route of Administration

4.3 Contraindications

Oxaliplatin is contraindicated in patients with
- History of severe allergy to the drug.
- Severe pre-existing peripheral neuropathy
- Severe renal dysfunction (Crd<30ml/min)
- Pregnancy and breast feeding

4.4 Special warning & precautions for use

Oxaliplatin should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.
Aluminium has been reported to cause degradation of platinum compounds and hence needles or intravenous administration sets containing aluminium parts that may come in contact with oxaliplatin should not be used for the preparation

or mixing of the drug.
Oxaliplatin should not be administered undiluted. Dilute with 5% Dextrose infusion.
Oxaliplatin should not be mixed with any other medication, and it should not be administered simultaneously by the infusion line.

Caution is recommended while administering oxaliplatin to patients with known hypersensitivity to other platinum agents.

Oxaliplatin is incompatible in solution with alkaline medications or media and hence it is advised that oxaliplatin should never be diluted with Sodium Chloride / Chloride containing infusion solutions.

Oxaliplatin has been found to be mutagenic in mammalian in vitro mutation chromosome test. Although carcinogenic studies have not been done. Oxaliplatin is considered probable carcinogen.

Oxaliplatin is embryotoxic in rats. Oxaliplatin may cause fetal harm when administered to pregnant women. The patient should be apprised of potential hazard to the fetus and potential risk for loss of the pregnancy if there is exposure to oxaliplatin during pregnancy.

It is not known whether oxaliplatin is excreted in human milk or not. Caution should be exercised when oxaliplatin is administered to a nursing woman as many drugs are excreted in human milk.

Inspect the solution visually for particulate matter and discolouration prior to administration.

4.5 Interaction with other medicinal products and other forms of interactions

Oxaliplatin induces Irinotecan-related cholinergic syndrome by potentiating irinotecan inhibition of acetylcholinesterase. Oxaliplatin has no influence on fluorouracil and topotecan pharmacokinetics. Preclinical studies have shown oxaliplatin to be synergistic with fluorouracil and SN-38, the active metabolite of irinotecan.
There are no other studies documenting any major interactions of oxaliplatin with other drug.

4.6 Pregnancy and lactation

Oxaliplatin is embryotoxic in rats. Oxaliplatin may cause fetal harm when administered to pregnant women. The patient should be apprised of potential hazard to the fetus and potential risk for loss of the pregnancy if there is exposure to oxaliplatin during pregnancy.
It is not known whether oxaliplatin is excreted in human milk or not. Caution should be exercised when oxaliplatin is administered to a nursing woman as many drugs are excreted in human milk.

4.7 Effects on ability to drive and use machine

Not known.

4.8 Undesirable effects

Commonly occurring adverse effects of Oxaliplatin

are: Sensory neuropathy (dose limiting toxicity)
Anaemi
a Fever
Nausea & vomiting
Liver function abnormalities
Infections
Alopecia
Pharynoglolaryngeal dysesthesia

Other side effects that become more pronounced when used in combination with fluorouracil and leucovorin are
- Neutropenia
- Thrombocytopenia
- Diarrhoea
- Mucositis

Summary of the safety profile
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 neurophathy). 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 arm) 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**
Infections and infestations *	- Infection	- Rhinitis -Upper respiratory tract infection - Neutropenic sepsis	Sepsis +	
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocyto-penia - Leukopenia	- Febrile neutropenia		- Immunoallergic thrombocytopenia - Haemolytic anaemia***[rare]

	- Lymphopenia			
Immune system disorders *	-Allergy/ allergic reaction ++			
Metabolism and nutrition disorders	- Anorexia - Hyperglycaemia - Hypokalaemia - Hypernatraemia	- 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) (see section 4.4)
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

Vascular disorders		- Haemorrhage - Flushing - Deep vein thrombosis - Hypertension		
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 - Gastro-esophageal reflux - Gastrointestinal hemorrhage - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhoea - Pancreatitis
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculoskeletal 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 - Fever +++ - Asthenia - Pain - Injection site reaction ++++			
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)		
Injury, poisoning, and procedural complications		- Fall		

* See detailed section below.
** See section 4.4.
*** Microangiopathic haemolytic anaemia associated with haemolytic uraemic syndrome (HUS) or Coombs positive haemolytic anaemia, see section 4.4)
+ Including fatal outcomes.
++ Very common allergies/allergic reactions, occurring mainly during infusion, sometimes fatal. Common allergic reactions include skin rash, particularly urticaria, conjunctivitis, and rhinitis. Common anaphylactic or anaphylactoid reactions, include bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.
+++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).
Description of selected adverse reactions

Blood and lymphatic system disorders

Incidence 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
Anaemia	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

Rare (≥1/10000, <1/1000)
Disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4).
Postmarketing experience with frequency not known
Hemolytic uremic syndrome
Autoimmune pancytopenia
Pancytopenia
Secondary leukemia

Infections and infestations

Incidence by patients (%)

Oxaliplatin and 5-FU/FA 85 mg/m² Every 2 weeks	**Metastatic Setting**	**Adjuvant Setting**
	All grades	All grades
Sepsis *(including sepsis and neutropenic sepsis)*	1.5	1.7

Postmarketing experience with frequency not known
Septic shock, including fatal outcomes.

Immune system disorders

Incidence of allergic reactions 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
Allergic reactions /Allergy	9.1	1.0	<1	10.3	2.3	0.6

Nervous system disorders
The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the

extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95% of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.
The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).
This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m² (12 cycles). In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localized paresthesias of moderate intensity (2.3%) or with paresthesias that may interfere with functional activities (0.5%).
Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paresthesia, dysesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1% - 2% of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing); Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4). Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/ pain. In addition, cranial nerve dysfunctions may be associated with above mentioned events, or also occur as an isolated event such as ptosis, diplopia, aphonia/ dysphonia/ hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/ facial pain/ eye pain, decrease in visual acuity, visual field disorders.
Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.
Postmarketing experience with frequency not known
Convulsion
Ischemic or haemorrhagic cerebrovascular disorder

Cardiac disorders

Post-marketing experience with frequency not known
QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section 4.4).
Acute coronary syndrome, including myocardial infarction and coronary arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5- FU and bevacizumab.

Respiratory, thoracic and mediastinal disorders

Postmarketing experience with frequency not known
Laryngospasm

Pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Nausea	69.9	8	< 1	73.7	4.8	0.3
Diarrhoea	60.8	9	2	56.3	8.3	2.5
Vomiting	49.0	6	1	47.2	5.3	0.5
Mucositis/Stomatitis	39.9	4	< 1	42.1	2.8	0.1

Prophylaxis and/or treatment with potent antiemetic agents is indicated. 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 (5-FU) (see section 4.4).

Post-marketing experience with frequency not known

Intestinal ischaemia, including fatal outcomes (see section 4.4).

Gastrointestinal ulcer and perforation, which can be fatal (see section 4.4).

Oesophagitis

Hepato-biliary disorders

Very common (>1/ 10)

Hepatic enzyme increase, blood bilirubin increase

Very rare (<1/ 10,000)

Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Frequency not known

Focal nodular hyperplasia

Musculoskeletal and connective tissue disorders

Post-marketing experience with frequency not known

Rhabdomyolysis, including fatal outcomes (see section 4.4).

Renal and urinary disorders

Very rare (<1/ 10,000)

Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Skin and Subcutaneous tissue disorders

Post-marketing experience with frequency not known

Hypersensitivity vasculitis

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 for oxaliplatin over dosage. In general, supportive care and frequent monitoring of vital signs should be administered.

5. Pharmacological Properties

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group:
Antineoplastic agent
ATC code: L01XA03

Clinical Pharmacology:
Mechanism of Action: The exact mechanism of action of oxaliplatin is not known. The mechanism of action of oxaliplatin is probably similar to that of cisplatin. Oxaliplatin forms reactive platinum complexes that are believed to inhibit DNA synthesis by forming interstrand and intrastrand cross-linking of DNA molecules. Oxaliplatin is not cross resistant to Cisplatin or Carboplatin, probably due to the DACH group and resistance to DNA mismatch repair. Oxaliplatin is a radiation sensitizing agent.

5.2 Pharmacokinetic Properties

After intravenous distribution, Oxaliplatin is mainly accumulated in erythrocytes and does not diffuse into the plasma. 85.88% of platinum is protein found in the first 5 hours after administration. Oxaliplatin undergoes rapid nonenzymatic biotransformation to reactive platinum complexes. The active metabolites of oxaliplatin are DACH platinum species. Oxaliplatin is excreted by renal excretion. Approximately 50% of the administered dose is excreted in the urine within the first 3 days. Fecal excretion is approximately 0.5% per day and reaches 5% of the total dose by day 11. The terminal half-life of ultra-filterable platinum (Oxaliplatin and free Oxaliplatin metabolites) is 273 ±19 hrs. The platinum elimination from the erythrocytes takes about 48 days.

5.3 Preclinical safety data

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

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

6.0 Pharmaceutical Particulars

6.1 List of Excipients
Water for Injection BP

6.2 Incompatibilities
None

6.3 Shelf life
The shelf life of the medicinal product as package for sale
24 Months

The shelf life after dilution or reconstitution according to directions
Not Applicable.

The shelf life after first opening the container
Not Applicable

6.4 Special precaution for storage
Store below 30°C. Protect from light. Do not freeze.

6.5 Nature and contents of container
UNIT PACK: 50 ml amber coloured moulded Glass Type I vial sealed with 20 mm slotted GBBR stopper and sealed with yellow aluminium flip off seal packed in a printed carton along with pack insert.

7. Marketing Authorization Holder and Manufacturing site address
Name of Marketing Authorization Holder:
Khandelwal Laboratories Pvt. Ltd.

Address of manufacturing site:
B-1, Wagle Industrial
Estate, Thane - 400 604,
India
Telephone: 00 91 22 25821793 / 0794
Fax: 00 91 22 25823837

8. Marketing Authorization Numbers
H2024/CTD10929/24329

9. Date of first authorization / renewal of the authorization
2024 March 25

10. Date of revision of the text
2024 March 25