OLIPTIN 5MG/ML CONCENTRATE FOR SOLUTION FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

Oliptin 5mg/ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml concentrate for solution for infusion contains 5mg oxaliplatin.

10 ml of concentrate for solution for infusion contains 50mg of oxaliplatin
20ml of concentrate for solution for infusion contains 100mg of oxaliplatin

3. PHARMACEUTICAL FORM

Oxaliplatin Injection, 50 mg/10 mL and 100 mg/20 mL (5 mg/mL) are terminally sterilized injections, which are supplied as a sterile, colorless, clear, aqueous solution for intravenous administration. Product would be a clear colourless liquid after dilution.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

- Adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of the primary tumor
- Treatment of metastatic colorectal cancer

4.2 Posology and Method of Administration

The preparation of injectable solutions of cytotoxic agents must always be carried out by trained specialist personnel with knowledge of the medicines used, in conditions ensuring drug integrity, the protection of the environment and in particular protection of the personnel handling the medicines, according to hospital practice. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area (see section Special Precautions for Disposal and Other Handling).

Posology

FOR USE IN ADULTS ONLY

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

The recommended dose of oxaliplatin in the treatment of metastatic colorectal cancer is 85 mg/m^2 intravenously, repeated every two weeks.

The dose should be adjusted according to tolerability (see section Special Warnings and Precautions for Use).

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

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution (50 mg/ml) in order to obtain a concentration of between 0.2 mg/ml and 0.7 mg/ml; 0.7 mg/ml is equivalent to the highest concentration observed in clinical practice for an 85 mg/m2 dose of oxaliplatin.

Oxaliplatin has mostly been administered in combination with continuous infusion of 5-fluorouracil (5FU). For the two-weekly treatment schedule, a 5-fluorouracil (5FU) regimen with bolus and continuous infusion were used.

Special Populations

Renal Impairment
Oxaliplatin must not be administered in patients with severe renal impairment (see sections Contraindication and Pharmacokinetic Properties).
In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin in 85mg/m^2 (see section Special Warnings and Precautions for Use and Pharmacokinetic Properties)

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

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

Paediatric Patients
There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumours has not been established (see section Pharmacodynamic Properties).

Method of Administration
Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of glucose 5% solution (50 mg/ml) 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 (5-FU).

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

Instruction for Use
Oxaliplatin must be diluted before use. Only glucose 5% solution (50 mg/ml) is to be used to dilute the concentrate for solution for infusion (see section Special Precautions for Disposal and Other Handling).

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 listed in section *List of Excipients.*
- Are breastfeeding.
- Have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2 x 10^9/L and/or platelet count <100 x 10^9/L.
- Have a peripheral sensitive neuropathy with functional impairment prior to first course.
- Have a severely impaired renal function (creatinine clearance < 30 ml/min) (see section Pharmacokinetic Properties).

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
Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and dose adjusted according to toxicity (see section Pharmacokinetic Properties).

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

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

Neurological Symptoms
Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see section Undesirable Effects) 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 dose adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued,
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paraesthesias or paraesthesias thatmay interfere with functional activities can persist after up to 3 years following treatment cessationin 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 Undesirable Effects).
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 Undesirable Effects).

Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5- fluorouracil (5-FU).

Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischaemia, oxaliplatin treatment should be discontinued and appropriate measures initiated. (see section Undesirable effects).

If haematological toxicity occurs (neutrophils $<1.5 \times 10^9$/L or platelets $<50 \times 10^9$/L), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapyand 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 fataloutcomes (see section Undesirable effects). 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 (5-FU) administration so that they can urgently contact their treating physician for appropriate management.

If mucositis/stomatitis occurs, with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1.5 \times 10^9$/L.

For oxaliplatin combined with 5-fluorouracil (5-FU) (with or without folinic acid (FA)), the usual dose adjustments for 5-fluorouracil (5-FU) -associated toxicities should apply.

If grade 4 diarrhoea, grade 3 - 4 neutropenia (neutrophils $< 1 \times 10^9$/L), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $< 1.0 \times 10^9$/L, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), or grade 3 - 4 thrombocytopenia (platelets $< 50 \times 10^9$/L) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m^2 (metastatic setting) or to 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil (5-FU) dose reductions required.

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

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. (see section Undesirable effects) Caution should be exercised in patients with conditions that are associated with DIC such as infections, sepsis, etc.

QT Prolongation
QT prolongation may lead to an increased risk for ventricular arrhythmias including Torsade de Pointes, which can be fatal (see section Undesirable effects). 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. (see sections Interaction with other medicinal products and other forms of interaction and Undesirable effects).

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. (see sections Interaction with other medicinal products and other forms of interaction and Undesirable effects)

Gastrointestinal Ulcer/ Gastrointestinal Ulcer Haemorrhage and Perforation
Oxaliplatin treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal hemorrhage and perforation, which can be fatal. In case of gastrointestinal ulcer, oxaliplatin treatment should be discontinued and appropriate measures taken. (see section Undesirable effects)

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 *Fertility, Pregnancy and Lactation*.

Fertility
Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore, male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment, and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect which could be irreversible. Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception (see section Fertility, Pregnancy and Lactation).

Peritoneal hemorrhage may occur when oxaliplatin is administered by intraperitoneal route (off-label route of administration).

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

In patients who have received a single dose of 85 mg/m² of oxaliplatin immediately before administration of 5-fluorouracil (5-FU), no change in the level of exposure to 5-fluorouracil (5-FU) has been observed.
In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed

with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored (see section Special warnings and precautions for use). Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis. (see section Special warnings and precautionsfor use).

4.6 Fertility, Pregnancy and Lactation

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

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

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

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

Fertility
Oxaliplatin may have an anti-fertility effect (see section Special Warnings and Precautions for Use). Due to the potential genotoxic effects of oxaliplatin, appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

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 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

Summary of the Safety Profile
The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil (5-FU)/ 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.

Frequencies in this are defined using the following convention: very common, common, uncommon, rare, very rare, and 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 - Thrombocytopenia - Leukopenia - Lymphopenia	- Febrile neutropenia		- Immunoallergic thrombocytopenia - Haemolytic anemia
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 Special Warnings and Precautions for Use)
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 - Gastroesophageal reflux - Gastrointestinal haemorrhage - 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	- Fatigue - Fever +++ - Asthenia			
Site Conditions	- 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 Special Warnings and Precautions for Use.
+ 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 (tremor), 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 Special Warnings and Precautions for Use).

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	Grade 3	Grade 4	All Grades	Grade 3	Grade 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

Rare

Disseminated intravascular coagulation (DIC), including fatal outcomes (see section Special warnings and precautions for use)

Post Marketing Experience with Frequency Not Known:

Haemolytic Uremic Syndrome

Autoimmune Pancytopenia

Pancytopenia

Secondary Leukemia

Infections and Infestations

Incidence by Patient (%)

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

Post Marketing 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	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Allergic reactions/ allergies	9.1	1	< 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 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 Special Warnings and Precautions for Use).

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/m^2 (10 cycles) is approximately 10% and 20% for a cumulative dose of 1020 mg/m^2 (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 Preclinical Safety Data) 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 Special Warnings and Precautions for Use).
Occasionally other symptoms that have been observed include jaw spasm/ muscle spasm/ muscle contractions-involuntary/ muscle twitching/ myoclonus/ coordination abnormal/ gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/ pain. In addition, cranial nerve dysfunction 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.

<u>Post Marketing Experience with Frequency Not Known:</u>
Convulsion
Ischemic or haemorrhagic cerebrovascular disorder

Cardiac Disorders

<u>Post Marketing Experience with Frequency Not Known:</u>
QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section Special warnings and precautions for use).

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

Post Marketing Experience with Frequency Not Known:
Laryngospasm
Pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal Disorders

Incidence by Patient (%), by Grade

Oxaliplatin and 5-FU/FA 85 mg/m² Every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 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 are indicated.

Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/ emesis particularly when combining oxaliplatin with 5-fluorouracil (5-FU) (see section Special Warnings and Precautions for Use).

Post Marketing Experience with Frequency Not Known:
Intestinal ischaemia, including fatal outcomes (see section Special warnings and precautions for use).
Gastrointestinal ulcer and perforation, which can be fatal. (see section Special warnings and precautions for use).

Oesophagitis

Hepatobiliary Disorders

Very Rare
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.

Musculoskeletal and Connective Tissue Disorders

Post Marketing Experience with Frequency Not Known:
Rhabdomyolysis, including fatal outcomes (see section Special warnings and precautions for use).

Renal and Urinary Disorders

Very Rare
Acute tubular necrosis, acute intestinal nephritis and acute renal failure.

Skin and Subcutaneous Tissue Disorders

Post Marketing Experience with Frequency Not Known:
Hypersensitivity vasculitis

4.9 Overdose

Symptoms

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected.

Management

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics Properties

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds,

ATC code: L01XA03

Mechanism of Action

Oxaliplatin is an antineoplastic active substance belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, (SP-4-2)-[(1R, 2R)-cyclohexane-1, 2-diamine-kN, KN'] [ethanediato(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 (5-FU) 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 intrastrand cross-links, resulting in the disruption of DNA synthesis, leading to cytotoxic and antitumour effects.

5.2 Pharmacokinetic Properties

Absorption and Distribution

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg /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/m^2 Every Three Weeks

Dose	C_{max} µg/ml	AUC_{0-48} µg.h/ml	AUC µg.h/ml	$t_{1/2}\alpha$ h	$t_{1/2}\beta$ h	$t_{1/2}\gamma$ h	V_{ss} L	CL L/h
85 mg/m^2								
Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m^2								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m^2) or Cycle 5 (130 mg/m^2). Mean AUC, 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 observedin plasma ultrafiltrate following 85 mg/m^2 every two weeks or 130 mg/m^2 every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation

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

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

Elimination

Platinum is predominantly excreted in the urine, with clearance mainly in the 48 hours following administration.
At Day 5, approximately 54% of the dose is recovered in the urine and less than 3% in the feces.

Special Populations

Renal Impairment

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

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

Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Total PUF

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

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

There was an increase in beta half-life of PUF platinum with increasing degree of renal impairment mainly in the severe group. Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment (see sections Posology and Method of Administration, Contraindications and Special Warnings and Precautions for Use).

6 PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Water for injections

6.2 Incompatibilities
The diluted medicinal product should not be mixed with other medicinal products in the same infusion bag or infusion line. Under instructions for use described in section Special precautions for disposal and other handling, oxaliplatin can be co-administered with folinic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicinal products or solutions, in particular 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipient, and trometamol salts of others active substances. Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin (see section Special Precautions for Disposal and Other Handling).
- DO NOT reconstitute or dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- DO NOT mix with other medicinal products in the same infusion bag or infusion line (see section Special Precautions for Disposal and Other Handling for instructions concerning simultaneous administration with folinic acid (FA)).
- DO NOT use injection equipment containing aluminium

6.3 Shelf-Life
24 months

After dilution in glucose 5% (50mg/ml), chemical and physical in-use stability has been demonstrated for 24 hours at +2°C to +8°C and for 6 hours at +25°C.
From a microbiological point of view, the solution for infusion 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 below 30°C.
Keep the vial in the outer carton in order to protect from light.
Do not freeze.
For storage conditions of the diluted medicinal product, see section *Shelf-Life*.

6.5 Nature and Contents of Container

20ml Type 1 glass vial, covered with butyl coated rubber stoppers and aluminium-plastic caps.

Pack size: 1 vial per box.

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.

Instruction for Handling
The handling of this cytotoxic agent by healthcare personnel requires a set of precautions to ensure the protection of the handler and his/her surroundings.

The preparation of cytotoxic solutions for injection must be carried out by trained specialist personnel with knowledge of the medicines used, under conditions that guarantee the integrity ofthe product, the protection of the environment and in particular the protection of the personnel handling the medicines, according to 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 and 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 section on Disposal below).

If oxaliplatin concentrate or solution for infusion should come into contact with the skin, wash immediately and thoroughly with water.

If oxaliplatin concentrate or solution for infusion should come into contact with the 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% (50mg/ml) infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, particularly 5-fluorouracil (5-FU), folinic acid (FA) preparations containing trometamol as an excipients and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Instruction for Use with Folinic Acid (FA) (as Disodium Folinate or Calcium Folinate)
Oxaliplatin 85 mg/m^2 IV infusion in 250 to 500 ml of glucose 5% (50 mg/ml) solution is given at the same time as folinic acid intravenous infusion in glucose 5% (50 mg/ml) solution, over 2 to 6 hours, using a Y line placed immediately before the site of infusion.

These two medicinal products should not be combined in the same infusion bag. Folinic acid (FA) must not contain trometamol as an excipient and must only be diluted using isotonic glucose 5 % (50 mg/ml) solution, never in alkaline solutions or solutions containing chloride or sodium chloride.

Instructions for Use with 5-Fluorouracil (5-FU)
Oxaliplatin should always be administered before fluoropyrimidines, i.e. 5-fluorouracil (5-FU).
After oxaliplatin administration, rinse the infusion line and then administer 5-fluorouracil (5 FU). For further information about medicinal products combined with oxaliplatin, see the respective 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 for Intravenous Infusion
Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 to 500 ml of glucose 5% (50mg/ml) solution to give an oxaliplatin concentration of between 0.2 mg/ml and 2mg/ml; concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.

Administer by intravenous infusion.

After dilution in glucose 5 % (50 mg/ml) solution, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C and +8°C and for 6 hours at +25°C.

From a microbiological point of view, the solution for infusion 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 solution should be discarded (see section Disposal below).

NEVER use sodium chloride or chloride containing solutions for dilution.

The compatibility of oxaliplatin solution for infusion has been tested with standard PVC-based administration sets.

Infusion
The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 to 500 ml of a glucose 5 % (50 mg/ml) 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 (5-FU), the oxaliplatin infusion must precede the administration of 5-fluorouracil (5FU).

Disposal
Remnants of the medicinal product, as well as all materials that have been used for dilution and

administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents and in accordance with local requirements related to the disposal of hazardous waste.

CAUTION: CYTOTOXIC AGENT
CONTROLLED MEDICINE

KEEP MEDICINE OUT OF REACH OF CHILDREN
JAUHI UBAT DARIPADA KANAK-KANAK

Reg No.: MALXXXXXXXXXX

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