OXOL Oxaliplatin Concentrate for Solution for Infusion 5mg/ml

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

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

Product Description
A clear colorless solution free from visible extraneous particulate matter.

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.

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/m² 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/m² 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/m^2 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.

<u>Special Populations</u>
- *Renal impairment*
  Oxaliplatin must not be administered in patients with severe renal impairment (see sections

Contraindications and *Pharmacokinetic Properties*).
In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/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 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 (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.

Instructions 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*).

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 breast-feeding.
- 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*).

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/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued,
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paraesthesias or paraesthesias 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 *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 x 10^9/L or platelets < 50 x 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 therapy and before each subsequent course.

Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin including fatal outcomes (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 ≥ 1.5 x 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 x 10^9 /L), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0 x 10^9/L, 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 x 10^9 /L) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m² (metastatic setting) or to 75 mg/m² (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 interactio*n 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).

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 precautions for use*).

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.

Effects on Ability to Drive and Use Machines
No studies on the effects on the ability to drive and use machines have been performed. However oxaliplatin treatment resulting in an increase risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines. Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect 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.

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

Tabulated list of adverse reactions

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 Leukoencephalopath y 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**
Gastrointestin al Disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis / mucositis	- Dyspepsia -Gastroesophagea l reflux - Gastrointestinal haemorrhage	- Ileus - Intestinal obstruction	- Colitis, including Clostridium difficile diarrhoea - Pancreatitis

	- Abdominal pain - Constipation	- Rectal haemorrhage		
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, angioeodema, 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 Lympatic System Disorders

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

Frequency not known:
Haemolytic uremic syndrome
Autoimmune pancytopenia
Pancytopenia
Secondary leukemia

Frequency not known
Septic shock, including fatal outcomes.

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. 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.

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.

Frequency not known
Convulsion
Ischemic or haemorrhagic cerebrovascular disorder

Cardiac disorders

Frequency not known
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

frequency not known
Laryngospasm
Pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal Disorder

Prophylaxis and/or treatment with potent antiemetic agents is 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).

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

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 interstitial nephritis and acute renal failure.

Skin and Subcutaneous tissue disorders

Frequency not known
Hypersensitivity vasculitis

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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic 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)-[(1*R*, 2*R*)-cyclohexane-1, 2-diamine-k*N*, K*N*'] [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 discruption of DNA synthesis, leading to cytotoxic and antitumour effects.

Pharmacokinetic Properties

Absorption and distribution

The pharmacokinetics of individual active compounds have not been determined.

Biotransformation

Biotransformation 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 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 and very less in the faeces.

Special populations

Renal impairment

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 with severe renal impairment.
Elimination of oxaliplatin is significantly correlated with the creatinine clearance.
Renal clearance of PUF platinum was reduced with impaired renal function.

After intravenous doses, oxaliplatin is widely distributed throughout the body. It binds irreversibly to red blood cells, which can prolong the half-life of the drug. The mean terminal half-life has been variously stated to be 273 hours and 391 hours.

PHARMACEUTICAL PARTICULARS

List of Excipients

Water for injections.

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.

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 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 of the 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 aluminum.
- 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.

Instructions for Use with Folinic Acid (FA) (as Disodium Folinate or Calcium Folinate)
Oxaliplatin 85 mg/m² 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 0.7 mg/ml; concentration range for which the physico-chemical stability of oxaliplatin have been demonstrated.

Administer by intravenous infusion.

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*).

NEVER use sodium chloride or chloride containing solutions for dilution.

The compatibility of oxaliplatin solution for infusion has been tested with standard non-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.

Storage Condition
Unopened vial: Store below 30°C. Protect from light. Do not freeze.

After dilution in glucose 5%, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and 24 hours at 2-8°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 6 hours at 25°C and 24 hours at 2°C to 8°C.

Shelf Life
Unopened vial: 2 years from manufacturing date.

After dilution in glucose 5%, chemical and physical in-use stability has been demonstrated for 6 hours at 25°C and 24 hours at 2-8°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 6 hours at 25°C and 24 hours at 2°C to 8°C.

Presentation:
OXOL Oxaliplatin Concentrate for Solution for Infusion 5mg/ml is packed as 50mg/10ml filled in 10ml moulded amber coloured type I glass with reinforced non-PVC base, stoppered with 20mm bromobutyl rubber plug and 20mm flip off seal. Each vial is packed into secondary carton along with a package insert.

OXOL Oxaliplatin Concentrate for Solution for Infusion 5mg/ml is packed as 50mg/10ml filled in 10ml moulded amber coloured type I glass vial with reinforced non-PVC base, stoppered with 20mm grey bromobutyl fluoro coated rubber plug and 20mm aluminium flip off black seal. Each vial is packed into secondary carton along with a package insert.

Product Registration Holder:
Unimed Sdn Bhd
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Bandar Sri Damansara,
52200 Kuala Lumpur, Malaysia.

Manufactured by:
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