FRONT

hovid

hovid Oxaliplatin Powder
for Concentrate for Solution for Infusion

VIOXA01-var2 (MY)

DESCRIPTION
White or off-white loose massive or powder for solution for infusion. Upon reconstitution, Oxaliplatin powder yields a colorless solution.

COMPOSITION
hovid Oxaliplatin Powder 50 mg for Concentrate for Solution for Infusion:
One vial contains oxaliplatin 50 mg.

hovid Oxaliplatin Powder 100 mg for Concentrate for Solution for Infusion:
One vial contains oxaliplatin 100 mg.

One ml of reconstituted solution contains oxaliplatin 5 mg.

ACTIONS AND PHARMACOLOGY
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'] [ethanedioato(2-)-kO^1, kO^2] platinum.

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* anti-tumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models.

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

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and anti-tumour effects.

PHARMACOKINETICS
Distribution
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.

Metabolism
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. 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 urine, with clearance mainly in the 48 hours following administration. By day 5, approximately 54% of the total dose was recovered in the urine and < 3% in the faeces. Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Renal clearance of platinum is decreased in patients with renal impairment.

INDICATION
Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:
- adjuvant treatment of stage III (Dukes' C) colon cancer after complete resection of primary tumour
- treatment of metastatic colorectal cancer.

CONTRAINDICATIONS
Oxaliplatin is contraindicated in patients who:
- have a known history of hypersensitivity to the active substance or to any of the excipients.
- are breast feeding
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <$2x10^9$/l and/or platelet count of <$100x10^9$/l
- have a peripheral sensitive neuropathy with functional impairment prior to first course
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

WARNINGS AND PRECAUTIONS
The use of oxaliplatin should be confined to units specialized in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a physician qualified in the use of anticancer chemotherapy.

Renal impairment
Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity.

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 medications with specific neurological toxicity.

A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia, during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

Peripheral neuropathy
If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:
- if symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting)
- if paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting)
- if paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued
- if these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localized moderate paresthesias or paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)
Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances. Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Nausea, vomiting, diarrhoea, dehydration and haematological changes
Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy.

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

If haematological toxicity occurs (neutrophils < $1.5x10^9$/l or platelets < $50x10^9$/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.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/ stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

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

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

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils <$1.0x10^9$/l), grade 3-4 thrombocytopenia (platelets < $50x10^9$/l) occur, the dose of oxaliplatin should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

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

Hepatic
In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

Fertility
Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect which could be irreversible.

Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception.

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.

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 and 6 months for men.

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

DRUG INTERACTIONS
In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil 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.

MAIN SIDE/ ADVERSE EFFECTS
Infections and infestations
Very Common: Infection
Common: Rhinitis, Upper respiratory tract infection, Neutropenic sepsis

Blood and lymphatic system disorders
Very Common: Anaemia, Neutropenia, Thrombocytopenia, Leukopenia, Lymphopenia
Common: Febrile neutropenia
Rare: Immunoallergic thrombocytopenia, Haemolytic anaemia, Disseminated intravascular coagulation (DIC), including fatal outcomes
Not Known: Haemolytic uraemic syndrome Autoimmune pancytopenia

BACK

Immune system disorders
Very Common: Allergy/allergic reaction

Metabolism and nutrition disorders
Very Common: Anorexia, Hyperglycaemia, Hypokalaemia, Hypernatraemia
Common: Dehydration, Hypocalcaemia
Uncommon: Metabolic acidosis

Psychiatric disorders
Common: Depression, Insomnia
Uncommon: Nervousness

Nervous system disorders
Very Common: Peripheral sensory neuropathy, Sensory disturbance, Dysgeusia, Headache
Common: Dizziness, Motor neuritis, Meningism
Rare: Dysarthria, Reversible Posterior Leukoencephalopathy syndrome (RPLS or PRES)
Not Known: Convulsion

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or parasthesia 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.

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. In the majority of cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued.

Acute neurosensory manifestations 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 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.

Eye disorders
Common: Conjunctivitis, Visual disturbances
Rare: Visual acuity reduced transiently, Visual field disturbance, Optic neuritus, Transient vision loss (reversible, following therapy discontinuation)

Ear and labyrinth disorders
Uncommon: Ototoxicity
Rare: Deafness

Cardiac disorders
Not Known: QT Prolongation

Vascular disorders
Common: Haemorrhage, Flushing, Deep vein thrombosis, Hypertension

Respiratory, thoracic and medistinal disorders
Very Common: Dyspnoea, Coughing, Epistaxis
Common: Hiccups, Pulmonary embolism
Rare: Interstitial lung disease, sometimes fatal, Pulmonary fibrosis
Not Known: Laryngospasm

Gastointestinal disorders
Very Common: Nausea, Diarrhoea, Vomiting, Stomatitis/mucositis, Abdominal pain, Constipation
Common: Dyspepsia, Gastroesophageal reflux, Rectal haemorrhage, Gastrointestinal haemorrhage
Uncommon: Ileus, Intestinal obstruction
Rare: Colitis including *Clostridium difficile* diarrhoea, Pancreatitis
Not Known: Intestinal ischaemia, including fatal outcomes[2], Gastrointestinal ulcer and perforation, which can be fatal

Hepato-biliary Disorders
Very Common: Hepatic enzyme increase, Blood bilirubin increase
Very Rare: Liver sinusoidal obstruction syndrome (also known as veno-occlusive disease of liver)

Skin and subcutaneous tissue disorders
Very Common: Skin disorder, Alopecia
Common: Skin exfolation (i.e Hand and foot syndrome), Rash erythematous, Rash, Hyperhidrosis, Nail disorder
Not Known: Hyper-sensitivity vasculitis

Musculo-skeletal, connective tissue disorders
Very Common: Back pain
Common: Arthralgia, Bone pain
Not Known: Rhabdomyolysis (including fatal outcomes)

Renal and urinary disorders
Common: Dysuria, Micturition frequency abnormal, Haematuria
Very rare: Acute tubular necrosis, Acute interstitial nephritis, Acute renal failure

General disorders and administration site conditions
Very Common: Fatigue, Fever, Asthenia, Pain, Injection site reaction, Rigors

Investigations
Very Common: Blood alkaline phosphatase increase, Blood lactate dehydrogenase increase, Weight increase (adjuvant setting)
Common: Weight decrease (metastatic setting), Blood creatinine increase

OVERDOSE AND TREATMENT

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

DOSAGE AND ADMINISTRATION

Oxaliplatin is administered by intravenous infusion. The administration of oxaliplatin does not require hyperhydration. In the event of extravasation, administration must be discontinued immediately.

For adults only
The recommended dose of oxaliplatin as adjuvant treatment is 85mg/m^2 via the intravenous route, repeated every two weeks for 12 cycles (6 months). The recommended dose of oxaliplatin in the treatment of metastatic colorectal cancer is 85mg/m^2 via the intravenous route, repeated every two weeks.

The dose should be adjusted as a function of tolerability.

Oxaliplatin should always be administered before fluoropyrimidines.

Oxaliplatin is administered in a 2 to 6-hour intravenous infusion in 250 to 500ml 5% dextrose solution, so as to obtain a concentration higher than 0.2mg/ml.

In most cases, oxaliplatin has been administered in combination with 5-fluorouracil in a continuous infusion. For treatment repeated every two weeks, a regimen containing 5-Fluorouracil in a bolus and in a continuous infusion has been employed.

Population at risk
Patient with renal insufficiency
Oxaliplatin has not been studied in patients with severe renal impairment (See Contraindications). In patients presenting with moderately impaired renal function, treatment can be adjusted according to toxicity (see Warnings and Precautions). It is not necessary to adjust the dosage in patients with mildly impaired renal function.

Patients with hepatic insufficiency
Oxaliplatin has not been studied in patients presenting with severe hepatic insufficiency. No aggravation of the acute toxicity of oxaliplatin has been observed in the sub-group of patients presenting with abnormal liver function. During clinical development, no dosage adjustments were made in patients presenting with liver function abnormalities.

Elderly subjects
No aggravation of the acute toxicity of oxaliplatin, used alone or in combination with 5-Fluorouracil, has been observed in subjects over the age of 65 years. Consequently, no dosage adjustment is necessary in elderly subjects.

Directions for reconstitution
Oxaliplatin must be reconstituted and diluted before use. Water for Injections or 5% Dextrose Injection should be used to reconstitute the solution.

- For a vial of 50 mg: add 10 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml
- For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml

The reconstituted solution can be stored at 2°C to 8°C for 24 hours. It must be further diluted before use. Withdraw the required amount of reconstituted solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5% Dextrose Injection to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml. 0.7 mg/ml is the highest concentration on clinical practice for an oxaliplatin dose of 85 mg/m^2. The diluted oxaliplatin in 250 to 500 ml of 5% Dextrose Injection to give a concentration not less than 0.2 mg/ml must be infused via a central venous line or peripheral vein for 2 to 6 hours.

After diluted with 5% Dextrose Injection, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C and for 6 hours at room temperature. From a microbiological point of view, this infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused infusion solution should be discarded.

Caution for Usage
- DO NOT use injection equipment containing aluminium.
- DO NOT administer undiluted.
- Only 5% Dextrose Injection is to be used as diluents. DO NOT reconstitute or dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT mix with any other medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline medicinal products or solutions, in particular 5 fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others active substances. Alkaline medicinal products or solutions will adversely affect the stability of oxaliplatin.
- As with other antineoplastic agents, oxaliplatin must be prepared and handled with caution. The use of protective goggles, protection masks and sterile single-use gloves is required.
- If oxaliplatin solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water.
- If oxaliplatin solution or infusion solution should come into contact with the mucous membranes, wash immediately with water.
- **Disposal:** All materials used for dilution and administration should be disposed of according to hospital standard procedures applicable to cytotoxic agents.

Note: The information given here is limited. For further information consult your doctor or pharmacist.

Storage: Store below 30°C. Protect from light and moisture.

After reconstitution with WFI or 5% Dextrose Solution, store at 2°C - 8°C for 24 hours. After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C and for 6 hours at 25°C.

From a microbiological point of view, the infusion preparation should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C unless dilution has taken place in controlled and validated aseptic conditions.

Do not freeze.

Presentation/Packing: Vial of 50 mg, Vial of 100 mg

Product Registration Holder (Malaysia)/ Product Owner: **HOVID Bhd.**
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Information date: February 2020

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