For the Use of a Registered Medical Practitioner or a Hospital or Laboratory only.

OXAPLIN 50 & 100

(Oxaliplatin Injection 5 mg/ml, 10 ml & 20 ml)

PRODUCT NAME

Oxaliplatin Injection 5 mg/ml, 10 ml & 20ml

PRODUCT DESCRIPTION

A clear, colourless solution in a clear glass vial. When examined under suitable conditions of visibility it should be practically free from particles.

PHARMACODYNAMICS / PHARMACOKINETICS

PHARMACODYNAMICS

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03

Oxaliplatin is an antineoplastic drug 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'*] [ethanedioato(2-)-k*O*^{1}, k*O*^{2}] platinum.

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro*and *in vivo*.

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

PHARMACOKINETICS

The pharmacokinetics of individual active compounds has not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg /m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m² Every Two Weeks or at 130 mg/m² Every Three Weeks

Dose	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	Vss L	CL L/h
85 mg/m²								
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/m²								
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/m²) or cycle 5 (130 mg/m²).

Mean AUC, Vss, CL, and CLR_{0-48} values were determined on Cycle 1.

Cend, Cmax, AUC, AUC_{0-48}, Vss and CL values were determinedby non-compartmental analysis.

$t_{1/2}\alpha$, $t_{1/2}\beta$, and $t_{1/2}\gamma$, were determined by compartmental analysis (Cycles 1-3 combined).

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring. Oxaliplatin undergoes extensive biotransformation in patients, and no intact drug was detectable in plasma 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. 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.

A significant decrease in clearance from 17.6 ± 2.18 l/h to 9.95 ± 1.91 l/h in renal impairment was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 l. The effect of severe renal impairment on platinum clearance has not been evaluated.

INDICATION

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

• Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor.

• Treatment of metastatic colorectal cancer.

RECOMMENDED DOSE & MODE OF ADMINISTRATION

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks.

Dosage given should be adjusted according to tolerability.

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

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

<u>Special Populations</u>

- Renal impairment:

Oxaliplatin has not been studied in patients with severe renal impairment.

In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose. There is no need for dose adjustment in patients with mild renal dysfunction.

- Hepatic insufficiency:

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

- Elderly patients:

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

- Paediatric patients:

There is no relevant indication for use of oxaliplatin in children. The effectiveness of oxaliplatin single agent in the paediatric populations with solid tumors has not been established.

<u>Method of administration</u>

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of 5% glucose solution to give a concentration not less than 0.2 mg/ml must be infused via a central venous line or peripheral vein over 2 to 6 hours. Oxaliplatin infusion must always precede the administration of 5-fluorouracil.

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

Instructions for use:
Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product.

CONTRAINDICATION
Oxaliplatin is contraindicated in patients who
- have a known history of hypersensitivity to oxaliplatin.
- 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
Oxaliplatin should only be used in specialized departments of oncology and should be administered under the supervision of an experienced oncologist.
Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient.
In this situation, renal function should be closely monitored and dose adjusted according to toxicity.
Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contra-indicated.
In case of oxaliplatin extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.
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.

INTERACTIONS WITH OTHER MEDICAMENTS
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.

PREGNANCY AND LACTATION
To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.
The use of oxaliplatin should only be considered after suitably 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.
Excretion in breast milk has not been studied. Breast-feeding is contra-indicated during oxaliplatin therapy.
Oxaliplatin may have an anti-fertility effect.

UNDESIRABLE EFFECTS
The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neurophathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

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.

STORAGE CONDITION
Keep the vial in the outer carton in order to protect from light. Store below 30°C. Do not freeze.

After dilution of the solution in 5% glucose solution, chemical and physical in-use stability has been demonstrated for up to 48 hours at 2°C to 8°C and for 24 hours at 25°C.

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

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.

DOSAGE FORMS AND PACKAGING AVAILABLE
Oxaliplatin Injection 5 mg/ml, 10 ml & 20ml is packed as 1 vial per carton.

Manufactured by:

INTAS PHARMACEUTICALS LTD.
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Bavla Road, Dist.- Ahmedabad,
Gujarat, India.