PACKAGE INSERT

Scheduling status: S4

Proprietary names and dosage forms:

Loxat 30 Concentrate solution for infusion

Loxat 100 Concentrate solution for infusion

Loxat 300 Concentrate solution for infusion

Warning:

LOXAT (paclitaxel) should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in patients receiving LOXAT. Patients receiving LOXAT should be pre-treated with corticosteroids, promethazine, and H2 antagonists to prevent these reactions (see "Dosage and directions for use"). Patients who experience severe hypersensitivity reactions to LOXAT should not be re-challenged with the medicine.

LOXAT - therapy should not be given to patients with baseline neutrophil counts of less than 1 500 cells/mm3. In order to monitor the occurrence of bone marrow suppression, primarily neutropenia, which may be severe and result in infection, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving LOXAT.

The polyoxyethylated castor oil in LOXAT can result in phthalate leaching from polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage and administration of diluted LOXAT should be carried out by using non-plasticised PVC-containing equipment.

Composition:

Loxat 30: Each vial contains: 30 mg Paclitaxel and 42,6 % v/v alcohol.

Loxat 100: Each vial contains: 100 mg Paclitaxel and 42,6 % v/v alcohol.

Loxat 300: Each vial contains: 300 mg Paclitaxel and 42,6 % v/v alcohol.

Pharmacological Classification:

A 26 Cytostatic agents

Pharmacological action:

Pharmacodynamics:

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. This stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or bundles of microtubules throughout the cell cycle and multiple asters of microtubules during mitosis.

Pharmacokinetics:

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentration. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later phase is due, in part, to a relatively low efflux of paclitaxel from the peripheral compartment. In patients treated with doses of 135 and 175 mg/m^2 given as 3 and 24 hour infusions, mean terminal half-life has ranged from 3,0 to 52,7 hours. Mean values for total body clearance ranged from 11,6 to 24 l/h/m^2. Mean steady state volume of distribution has ranged from 198 to 688 l/m^2, indicating extensive extravascular distribution and/or tissue binding.

The pharmacokinetics of paclitaxel are non-linear. There is a disproportionately large increase in C_{max} and AUC with increasing dose, accompanied by an apparent dose-related decrease in total body clearance. These findings are most readily observed in patients in whom high plasma concentrations of paclitaxel are achieved. Saturable processes in distribution and elimination/metabolism may account for these findings. There was no evidence of accumulation of paclitaxel with multiple

treatment course. *In vitro* studies of binding to human serum proteins, using paclitaxel concentrations ranging from 0,1 to 50 µg/ml, indicate that, on average, 89 % of drug is bound. The presence of cimetidine, ranitidine, dexamethasone or diphenhydramine did not affect protein binding of paclitaxel.

The disposition of paclitaxel has not been fully elucidated in humans. After intravenous administration of paclitaxel, mean values of cumulative urinary recovery of unchanged drug ranged from 1,3 to 12,6 % of the dose, indicating extensive non-renal clearance. Hepatic metabolism and biliary clearance may be the principal mechanism for disposition of paclitaxel. Paclitaxel is metabolized primarily by cytochrome P450 enzymes.

Hydroxylated metabolites have been demonstrated to be the principal metabolites. The formation of 6α -hydroxypaclitaxel, 3'-p-hydroxypaclitaxel and 6α,3'-p-dihydroxypaclitaxel is catalyzed by CYP2C8, 3A4 and both 2C8 and 3A4 respectively. The effect of the renal or hepatic dysfunction on the disposition of paclitaxel has not been investigated. The clearance of paclitaxel was not affected by cimetidine pre-treatment. Ketoconazole may inhibit the metabolism of paclitaxel. Plasma levels of doxorucibin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

Indications:

LOXAT is indicated for:

1. The palliative treatment of stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin.
2. The palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.
3. The treatment of metastatic carcinoma of the breast after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contra-indicated.
4. Palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

Contra-indications:

LOXAT is contra-indicated in patients who have a history of severe hypersensitivity reactions to LOXAT, Paclitaxel or other medicines formulated with poly-oxy-ethylated castor oil.

LOXAT should not be used in patients with baseline neutrophils of < 1 500/mm^3.

Pregnancy and lactation (see “Pregnancy and Lactation”).

The safety and effectiveness of LOXAT in children have not been established.

Warnings:

LOXAT should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic agents. Since severe hypersensitivity reactions may occur, appropriate supportive equipment should be available.

LOXAT should be administered as a diluted infusion.

LOXAT should be given before cisplatin when used in combination. Patients should be pre-treated with corticosteroids, antihistaminics and H_2-antagonists before receiving LOXAT. **Severe hypersensitivity reactions**, probably histamine-mediated, characterized by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema and generalized urticaria have occurred in patients receiving LOXAT**.** In cases of severe hypersensitivity reactions, LOXAT infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be re-challenged with the agent.

Minor hypersensitivity reactions such as flushing and rash do not require interruption of therapy.

Bone marrow suppression (primary neutropenia) is the principal dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during LOXAT treatment. Patients should not be re-treated until neutrophils recover to a level >1 500/mm^3 and platelets recover to a level >100 000/mm^3.

Severe cardiac conduction abnormalities have been reported. If patients develop significant conduction abnormalities during LOXAT administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with LOXAT.

Severe cardiovascular events were observed more frequently in patients with non-small cell lung carcinoma than breast or ovarian carcinoma.

Interactions:

The recommended regimen of LOXAT administration for the primary treatment of ovarian carcinoma is for LOXAT to be given before cisplatin. When LOXAT is given before cisplatin, the safety profile of LOXAT is consistent with that reported for single agent use. When LOXAT is given after cisplatin, patients showed a more profound myelosuppression and an approximately 20 % decrease in paclitaxel clearance.

Medications concomitantly administered with LOXAT (e.g., corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible interactions of LOXAT with concomitantly administered medications have not been formally investigated.

Based on *in vitro* data, there is the possibility of an inhibition of LOXAT metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with LOXAT when they are receiving ketoconazole as concomitant therapy.

Plasma levels of doxorubicin and doxorubucinol may be increased when paclitaxel and doxorubicin are used in combination.

The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4, caution should be exercised when administering LOXAT concomitantly with known substrates or inhibitors of these isoenzymes.

Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted LOXAT **solution should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.**

LOXAT should be administered through an in-line filter with a microporous membrane not greater than 0,22 microns. Use of filter devices such as IVEX-2 filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

Pregnancy and lactation:

LOXAT has been shown to be embryotoxic, fetotoxic and to decrease fertility in animal studies.

LOXAT should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with LOXAT, and to inform the treating doctor immediately should this occur.

It is not known whether LOXAT is excreted in human milk. Breast feeding should be discontinued for the duration of LOXAT therapy.

Dosage and directions for use:

Primary treatment of ovarian carcinoma:

A combination regimen consisting of LOXAT 135 mg/m^2 administered over 24 hours, followed by cisplatin 75 mg/m^2, every 3 weeks. LOXAT should be administered before cisplatin.

Secondary treatment of ovarian and breast carcinoma:

LOXAT at a dose of 175 mg/m^2, administered intravenously over 3 hours every 3 weeks has been shown to be effective in patients with metastatic carcinoma of the ovary or breast after the failure of first line or subsequent chemotherapy.

Palliative treatment of advanced non-small cell lung carcinoma:

The recommended dose of LOXAT is 175 mg/m^2 administered over a period of 3 hours; followed by a platinum compound, with a 3 week interval between courses.

LOXAT should not be re-administered until the neutrophil count is at least 1 500/mm^3 and the platelet count is at least 100 000/mm^3. Patients who experience severe neutropenia (neutrophil count < 500/mm^3) or moderate to severe peripheral neuropathy, should receive a dose reduction of 20 % for subsequent courses (see "Side-effects and special precautions"). The incidence and severity of neurotoxicity and haematologic toxicity increases with an increase in dose.

All patients should be pre-medicated with corticosteroids, antihistamines, and H_2 antagonists prior to LOXAT administration, e.g. dexamethasone 20 mg orally approximately 12 and 6 hours before LOXAT, promethazine 25 mg IV 30 to 60 minutes prior to LOXAT, and cimetidine 300 mg or ranitidine 50 mg IV 30 to 60 minutes before LOXAT.

LOXAT should be administered through an in-line filter with a microporous membrane not greater that 0,22 µm.

Directions for Use/Handling:

Handling:

Caution should be exercised when handling LOXAT. Dilution should be carried out by trained personnel in a designated area. Adequate protective gloves should be worn. Precautions should be taken to avoid contact with the skin, and mucous membranes. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the skin, the area should be washed with soap and water. In the event of contact with mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning eyes, sore throat and nausea have been reported.

Preparation for IV administration:

LOXAT must be diluted prior to infusion. The concentrate for infusion is stable for 48 hours when diluted with 0,9 % sodium chloride or 5 % glucose solution to concentrations of 0,3 mg/ ml or 1,2 g/ ml when stored below 25 °C.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit.

LOXAT should be administered through an in-line filter with a microporous membrane not greater than 0, 22 µm. No significant losses in potency have been noted following delivery of the solution through IV tubing containing an in-line filter.

In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl) phthalate], which may be leached from plasticized PVC infusion bags or sets, **diluted LOXAT solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.** Use of filter devices which incorporate short inlet and/or outlet plasticized PVC tubing has not resulted in significant leaching of DEHP.

Disposal:

All items used for reconstitution, administration or otherwise coming into contact with LOXAT should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

Side effects and special precautions:

Side effects:

The frequency and severity of adverse events are generally similar between patients receiving LOXAT for the treatment of ovarian, breast or lung carcinoma. None of the observed toxicities were clearly influenced by age. Safety of the LOXAT /platinum combination has been evaluated in a randomized trial in ovarian carcinoma and 2 phase III trials in non-small cell lung carcinoma. Unless otherwise mentioned the combination of LOXAT with platinum agents did not result in clinically relevant changes to the safety profile of single agent LOXAT.

Bone marrow suppressions and peripheral neuropathy are the principal dose-related adverse effects associated with LOXAT. Myelosuppression is less frequent and less severe with a 3-hour infusion than with a 24-hour infusion schedule.

The recommended LOXAT / cisplatin regimen for the primary treatment of ovarian cancer caused more severe myelosuppression than single dose LOXAT using the recommended schedule of 175 mg/m^2 over 3-hour infusion. There was no increase in clinical sequelae, however.

Haematological:

Frequent:

Neutropenia (compared to 24-hour infusion schedules, neutropenia is less common when LOXAT is given as a 3-hour infusion), thrombocytopenia (observed only during the first two courses), anaemia (red cell transfusions are required in some patients) and leukopenia.

LOXAT therapy should not be administered to patients with baseline neutrophil counts of less than 1 500 cells/mm^3. In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving LOXAT. Patients should not be re-treated with subsequent cycles of LOXAT until neutrophils recover to a level $>$ 1 500 cells/mm^3 and platelets recover to a level $>$ 100,000 cells/mm^3. In the case of severe neutropenia ($<$ 500 cells/mm^3 for seven days or more) during a course of LOXAT therapy, a 20 % reduction in dose for subsequent courses of therapy is recommended.

Hypersensitivity reactions:

Hypersensitivity reactions may occur requiring therapeutic intervention and/or early discontinuation of LOXAT infusion despite pre-medication. Severe symptoms occur within the first hour of LOXAT infusion.

Frequent:

Dyspnoea, flushing, chest pains, tachycardia, rash and hypotension have been reported.

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g. cyclosporine for injection concentrate and teniposide for injection concentrate) should not be treated with LOXAT. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with LOXAT should be pre-medicated with corticosteroids (such as dexamethasone), promethazine and H_2 antagonists (such as cimetidine or ranitidine). Symptoms such as flushing, skin reaction, dyspnoea, hypotension or tachycardia do not require interruption of therapy. However, reactions, such as hypotension requiring treatment, dyspnoea requiring bronchodilators, angioedema or generalised urticaria require immediate discontinuation of LOXAT and aggressive symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with LOXAT.

Cardiovascular:

Less frequent:

Hypotension, bradycardia, congestive heart failure and abnormal electrocardiogram (ECG).

Hypotension and bradycardia have been observed during administration of LOXAT, but generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of LOXAT infusion is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities (see “Warnings”). Cases of myocardial infarction have been reported. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines.

Patients may experience severe cardiovascular events possibly related to LOXAT administration. Included are hypertension, venous thrombosis, ventricular tachycardia, and atrioventricular conduction block.

ECG alterations are experienced by some patients.

The most frequently reported ECG modification is non-specific repolarization abnormalities, sinus tachycardia and premature beats. The relationship between LOXAT administration and ECG alterations is not clear.

Neurological:

Frequent:

Peripheral neuropathy, including mild paraesthesia, occurs and is dose dependent.

Neurological symptoms may occur following the first course and the frequency of symptoms may increase with increasing exposure to LOXAT. Sensory symptoms have usually improved or resolved within several months of LOXAT discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contra-indication for LOXAT therapy. Although the occurrence of peripheral neuropathy is frequent, the development of moderate to severe symptomatology is unusual and requires a dose reduction of 20 % for all subsequent courses of LOXAT. In non-small cell lung carcinoma patients, the administration of LOXAT in combination with cisplatin resulted in a greater incidence of neurotoxicity than usually seen in patients receiving single agent LOXAT.

Less frequent:

Grand mal seizure, optic nerve and/or visual disturbances (scintillating scotomata), syncope, ataxia and neuroencephalopathy.

The following side effects have been reported and the frequencies are unknown:

Ototoxicity, motor neuropathy with resultant minor distal weakness and autonomic neuropathy resulting in paralytic ileus and orthostatic hypotension, particularly in patients who have received higher doses than recommended.

These effects generally have been reversible.

LOXAT contains dehydrated alcohol, and consideration should be given to possible CNS and other effects of alcohol.

Arthralgia/Myalgia:

Frequent: Arthralgia/myalgia usually consisting of pain in the large joints of the arms and legs occurs but is usually mild. The symptoms are usually transient occurring two or three days after LOXAT administration and resolving within a few days.

Hepatic:

Less frequent:

Elevated serum hepatic enzymes, hepatic necrosis and hepatic encephalopathy.

There is no evidence that the toxicity of LOXAT is enhanced when given as a 3-hour infusion in patients with elevated liver enzymes, but no data are available for patients with baseline cholestasis. When LOXAT is given as a 24-hour infusion to patients with moderate to severe hepatic impairment, increased myelosuppression may be seen as compared to patients with mildly elevated liver function tests given 24-hour infusions.

Analysis restricted to patients with normal baseline liver function, shows instances of elevated bilirubin elevated alkaline phosphate, and elevated AST (SGOT). Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Other Clinical Events:

Frequent:

Nausea, vomiting, diarrhoea and mucositis

Alopecia has been observed in almost all patients.

Gastrointestinal side effects are usually mild to moderate at the recommended dose.

Less frequent:

Bowel obstructions/perforations, ischaemic colitis, transient and mild nail and skin changes and abnormalities related to radiation recall, fibrotic phlebitis, extravasation with phlebitis or cellulitis.

Extravasation during intravenous administration may lead to oedema, pain, erythema and induration and ulceration. Extravasation can result in cellulitis. Skin discolouration may also occur.

Recurrence of skin reactions at a site of previous extravasation following administration of LOXAT at a different site i.e. “recall reaction” has been reported. A specific treatment for extravasation reactions is unknown at this time.

The following side effects have been reported and the frequencies are unknown:

Neutropenic enterocolitis, radiation pneumonitis in patients receiving concurrent radiotherapy.

Paediatric Use:

The safety and effectiveness of LOXAT in children have not been established.

Known symptoms of overdosage and particulars of its treatment:

There is no antidote for LOXAT overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Treatment is symptomatic and supportive.

Identification:

Loxat 30: Clear colourless to pale yellow solution, practically free from visible particles.

Loxat 100: Clear colourless to pale yellow solution, practically free from visible particles.

Loxat 300: Clear colourless to pale yellow solution, practically free from visible particles.

Presentations:

Loxat 30: Single 5 ml clear glass vial in a cardboard carton.

Loxat 100: Single 20 ml clear glass vial in a cardboard carton.

Loxat 300: Single 50 ml clear glass vial in a cardboard carton.

Storage instructions:

Store below 25 °C. After first use, any unused concentrate may be stored at room temperature not exceeding 25 °C for up to 28 days.

The concentrate for infusion is stable for 48 hours when diluted with 0,9 % sodium chloride or 5 % glucose solution to concentrations of 0,3 mg/ ml or 1,2 g/ ml when stored below 25 °C. Keep in outer carton until required for use.

KEEP OUT OF REACH OF CHILDREN.

Registration Numbers:

LOXAT 30: 41/26/1095

LOXAT 100: 41/26/1096

LOXAT 300: 41/26/1097

Name and business address of the holder of the certificates of registration:

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