APPROVED PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

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 medicines. 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 H_2 antagonists to prevent these reactions (see section 4.2). 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/mm^3. 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.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Loxat 30: Each vial contains: 30 mg Paclitaxel per 5 ml (6 mg/ml) and 49,7 % v/v alcohol. Sugar free.

Loxat 100: Each vial contains: 100 mg Paclitaxel per 16.67 ml (6 mg/ml) and 49,7 % v/v alcohol. Sugar free.

Loxat 300: Each vial contains: 300 mg Paclitaxel per 50 ml (6 mg/ml) and 49,7 % v/v alcohol. Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate solution for infusion.

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.

4. CLINICAL PARTICULARS:

4.1 Therapeutic 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 contraindicated.
4. Palliative treatment of advanced non-small cell lung cancer in patients who are not candidates for potentially curative surgery and/or radiation therapy.

4.2 Posology and method of administration

Posology

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 section 4.4). 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 than 0,22 µm.

Special Populations

Hepatic impairment:

See section 4.4. Dosage adjustment is recommended as shown below:

Transaminase levels	Bilirubun levels (a)	Recommended LOXAT dose
24 hour infusion		
< 2 x ULN and	≤ 1,5 mg/dl	135 mg/m^2
2-< 10 x ULN and	≤ 1,5 mg/dl	100 mg/m^2
< 10 x ULN and	1,6 - 7,5 mg/dl	50 mg/m^2
≥ 10 x ULN or	> 7,5 mg/dl	Not recommended
3 hour infusion		
< 10 x ULN and	≤ 1,25 x ULN	175 mg/m^2
< 10 x ULN and	≤ 1,26 – 2,0 x ULN	135 mg/m^2
< 10 x ULN and	2,01 – 5,0 ULN	90 mg/m^2
≥ 10 x ULN or	> 5,0 ULN	Not recommended
(a) Differences in criteria for bilirubin levels between the 3- and 24-hour infusion are due to differences in clinical trial design. {b) Dosage recommendations are for the first course of therapy: further dose reduction in subsequent courses should be based on individual tolerance.		

ULN = upper limit of normal

Paediatric population:

The safety and efficacy of LOXAT in children has not been established (see section 4.4).

Method of administration

Intravenous use only.

Information on instructions for preparation, dilution, disposal and other handling, see section 6.6.

4.3 Contraindications

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 or to any of the excipients listed in section 6.1.

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

Pregnancy and lactation (see section 4.6).

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

4.4 Special warnings and precautions for use

LOXAT should be administered under the supervision of a medical practitioner experienced in the use of cancer chemotherapeutic medicines. 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:

Anaphylaxis and 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.

Patients with a history of severe hypersensitivity reactions to products containing Cremophor EL (e.g. ciclosporin 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 premedicated with corticosteroids (such as dexamethasone), promethazine and H_2 antagonists (such as cimetidine or ranitidine).

Rare fatal reactions have occurred in patients despite pre-treatment. 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 medicine.
Minor hypersensitivity reactions such as flushing and rash do not require interruption of therapy.

Bone marrow suppression:

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. 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.
The incidence of neurotoxicity and the severity of neutropenia increase with dose within a regimen.

Cardiovascular

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.

Hypotension, hypertension and bradycardia have been observed during administration of LOXAT but generally do not require treatment. In severe cases, LOXAT infusions may need to be interrupted or discontinued at the discretion of the treating medical practitioner.

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.

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 and include: hypertension, venous thrombosis, ventricular tachycardia, and atrioventricular conduction block.

ECG alterations are experienced by some patients. The most frequently reported are non-specific repolarisation abnormalities, sinus tachycardia and premature beats. The relationship between LOXAT administration and ECG alterations is not clear.

Neurologic:

Neurologic 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 contraindication 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 greater incidence of neurotoxicity than usually seen in patients receiving single-agent LOXAT.

Hepatic:

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. Dose adjustment is recommended (see section 4.2).

There is no evidence that the toxicity of LOXAT is increased when given as a 3-hour infusion in patients with mildly abnormal liver function. No data are available for patients with severe 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. Patients should be monitored closely for the development of profound myelosuppression. Hepatic necrosis and hepatic encephalopathy leading to death have been reported.

Analysis restricted to patients with normal baseline liver function, shows instances of elevated bilirubin, elevated alkaline phosphate and elevated AST (SGOT).

Injection site reaction:

A specific treatment for extravasation reactions is unknown. Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during administration.

Paediatric use:

The safety and effectiveness of LOXAT in children have not been established (see section 4.3). There have been reports of central nervous system toxicity (including death) in a clinical trial in paediatric patients in which LOXAT was infused intravenously over 3 hours at doses ranging from 350 mg/m^2 to 420 mg/m^2. The toxicity is most likely attributable to the high dose of the ethanol component of the LOXAT vehicle given over a short infusion time. The use of concomitant antihistamines may intensify these effects. Although a direct effect of the paclitaxel itself cannot be discounted, the high doses used in this study (over twice the recommended adult dose) must be considered in assessing the safety of LOXAT for use in this population.

Pseudomembranous colitis:

Pseudomembranous colitis has been reported, rarely, including cases in patients who have not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhoea occurring during or shortly after treatment with LOXAT.

Interstitial pneumonitis

A combination of pulmonary radiotherapy and LOXAT treatment (irrespective of the order of the treatments) may promote the development of interstitial pneumonitis.

Fertility:

LOXAT has been shown to be a teratogen, embryotoxic and a mutagen in several experimental systems. Therefore, female and male patients of reproductive age must take contraceptive measures for themselves and/or their sexual partners during and for at least 6 months after therapy (see section 4.6). Male patients are advised to seek advice on conservation of sperm prior to treatment because of the possibility of irreversible infertility due to therapy with LOXAT.

Macular oedema:

There have been reports of reduced visual acuity due to cystoid macular oedema (CME) during treatment with LOXAT. Patients with visual impairment during LOXAT treatment should seek a prompt and complete ophthalmologic examination. Discontinue LOXAT treatment if a CME diagnosis is confirmed.

Excipients:

LOXAT contains dehydrated alcohol, 49,7 % *v/v.* Consideration should be given to possible central nervous system and other effects of alcohol for all patients. Children may be more sensitive than adults to the effects of alcohol.

LOXAT contains polyoxyethylated castor oil which may cause severe allergic reactions.

4.5 Interaction with other medicines and other forms of interaction

Cisplatin:

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.

Patients treated with LOXAT and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Ketoconazole:

Medicines 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.

Doxorubicin:

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

Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been observed with combination use of LOXAT and doxorubicin, when LOXAT was administered before doxorubicin and using longer than recommended infusion times.

Active substances metabolised in the liver:

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 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of LOXAT may be increased due to higher paclitaxel exposure. Administering LOXAT concomitantly with medicines known to induce either CYP2C8 or CYP3A4 (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, nevirapine) is not recommended because efficacy may be compromised because of lower paclitaxel exposures.

PVC equipment:

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.

4.6 Fertility, pregnancy and lactation

Women of childbearing age/contraception in men and women

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with LOXAT and to inform the treating medical practitioner immediately should this occur. Female and male patients of fertile age, and/or their partners should use contraception for at least 6 months after treatment with LOXAT.

Pregnancy:

LOXAT should not be used during pregnancy. There is no information on the use of LOXAT in pregnant women.

LOXAT may cause foetal harm when administered to pregnant women.

Breastfeeding

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

Fertility

LOXAT has been shown to be embryotoxic, foetotoxic and to decrease fertility in animal studies. Male patients should seek advice regarding cryo-conservation of sperm prior to treatment with LOXAT because of the possibility of infertility.

4.7 Effects on ability to drive and use machines

LOXAT contains alcohol which may impair the ability to drive or operate machines. Consideration should be given to possible CNS and other effects of alcohol.

4.8 Undesirable effects

a. Summary of the safety profile

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.

b. Tabulated list of adverse reactions

System Organ Class	Adverse reaction	Frequency
Infections and infestations	Infections (mainly urinary tract infections and infections in the upper respiratory tract), with reported cases of fatal outcome	Frequent
	Septic shock, pneumonia, peritonitis, sepsis	Less frequent
Blood and lymphatic system disorders	Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding	Frequent
	Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome	Less frequent
	Disseminated intravascular coagulation (DIC)	Frequency unknown
Immune system disorders	Mild hypersensitivity reactions (mainly flushing and rash)	Frequent
	Significant hypersensitivity reactions requiring treatment (e.g. hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremities,	Less frequent

	diaphoresis and hypertension), anaphylactic reactions, anaphylactic shock	
	Bronchspasm	Frequency unknown
Metabolism and nutrition disorders	Anorexia, dehydration	Less frequent
	Tumour lysis syndrome	Frequency unknown
Psychiatric disorders	Confusional state	Less frequent
Nervous system disorders	Neurotoxicity (mainly peripheral neuropathy; can persist beyond 6 months of LOXAT discontinuation)	Frequent
	Motor neuropathy (with resultant minor distal weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia	Less frequent
Eye disorders	Optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended	Less frequent

	Macular oedema, photopsia, vitreous floaters	Frequency unknown
Ear and labyrinth disorders	Ototoxicity, loss of hearing, tinnitus, vertigo	Less frequent
Cardiac disorders	Abnormal ECG, bradycardia	Frequent
	Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV-block and syncope, myocardial infarction, cardiac failure, atrial fibrillation, supraventricular tachycardia	Less frequent
Vascular disorders	Hypotension	Frequent
	Hypertension, thrombosis, thrombophlebitis, shock	Less frequent
	Phlebitis	Frequency unknown
Respiratory, thoracic and mediastinal disorders	Dyspnoea, pleural effusion, interstitial pneumonia, lung fibrosis, pulmonary embolism, respiratory failure, cough	Less frequent
Gastrointestinal disorders	Nausea, vomiting, diarrhoea, mucositis	Frequent

	Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites, neutropenic colitis	Less frequent
Hepatobiliary disorders	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)	Less frequent
Skin and subcutaneous tissue disorders	Alopecia, transient and mild nail and skin changes	Frequent
	Pruritus, rash, erythema, Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)	Less frequent
	Palmar-plantar erythrodysesthesia syndrome	Frequency unknown
Musculoskeletal, connective tissue and bone disorders	Arthralgia, myalgia	Frequent
	Systemic lupus erythematosus, scleroderma	Frequency unknown
Reproductive system and breast disorders	Infertility	Frequency unknown

General disorders and administration site conditions	Injection site reactions (including localised oedema, pain, erythema, induration, extravasation with phlebitis or cellulitis, skin fibrosis and skin necrosis)	Frequent
	Asthenia, pyrexia, oedema, malaise	Less frequent
Investigations	Severe elevation of AST (SGOT), severe elevation of alkaline phosphatase	Frequent
	Severe elevation in bilirubin, increase in blood creatinine	Less frequent
Injury, poisoning and procedural complications	Radiation recall, radiation pneumonitis in patients receiving concurrent radiotherapy.	Frequency unknown

c. Description of selected adverse reactions

Unless otherwise noted, the following discussion refers to published information on the overall safety database of 812 patients with solid tumours treated with single-agent paclitaxel in clinical studies administered as one of two doses (135 or 175 mg/m2) and one of the two schedules (3 or 24 hours) in the metastatic setting.

Haematological toxicities: Bone marrow suppression was the major dose-limiting toxicity of LOXAT. Neutropenia, the most important haematological toxicity, was dose and schedule dependent and was generally rapidly reversible. Severe neutropenia (< 500 cells/ mm^3) was more frequent with the 24-hour than with the 3-hour infusion; infusion duration had a greater impact on myelosuppression than dose. Neutropenia did not appear to increase with cumulative exposure

and did not appear to be more frequent nor more severe for patients previously treated with radiation therapy. Infectious episodes occurred very commonly and were fatal in 1 % of all patients, and included sepsis, pneumonia and peritonitis. Urinary tract infections and upper respiratory tract infections were the most frequently reported infectious complications. The use of supportive therapy, including G-CSF, is recommended for patients who have experienced severe neutropenia.

Twenty percent of the patients experienced a drop in their platelet count below 100 000 cells/ mm^3 at least once while on treatment; 7 % had a platelet count < 50 000 cells/mm^3 at the time of their worst nadir. Bleeding episodes were reported in 4 % of all courses and by 14 % of all patients but most of the haemorrhagic episodes were localised and the frequency of these events was unrelated to the LOXAT dose and schedule.

Neurologic: In general, the frequency and severity of neurologic manifestations were dose dependent in patients receiving single-agent LOXAT. The frequency of peripheral neuropathy increased with cumulative dose. Paraesthesia commonly occurs in the form of hyperaesthesia. Peripheral neuropathy was the cause of LOXAT discontinuation in 1 % of all patients. Sensory symptoms have usually improved or resolved within several months of LOXAT discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for LOXAT therapy.

Infrequent reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

Hypersensitivity reactions (HSR): All patients in clinical trials received premedication prior to LOXAT therapy. The frequency and severity of HSR were not affected by the dose or schedule of LOXAT administration. The most frequent symptoms observed during these severe reactions were dyspnoea, flushing, chest pain and tachycardia.

A significant hypersensitivity reaction with possible fatal outcome (defined as hypotension requiring therapy, angioedema, respiratory distress requiring bronchodilator therapy, or generalised urticaria) occurred in two (< 1 %) patients. Thirty-four percent of patients (17 % of all courses) experienced minor hypersensitivity reactions.
Abdominal pain, pain in the extremities, diaphoresis and hypertension are also noted. Minor hypersensitivity reactions, mainly flushing and rash, did not require therapeutic intervention nor did they prevent continuation of LOXAT therapy.

Injection site reactions: During intravenous administration, injection site reactions were usually mild and consisted of localised oedema, pain, erythema, tenderness and indurations; on occasion, extravasations can result in cellulitis. Skin sloughing and/or peeling has been reported sometimes related to extravasations. Skin discolouration may also occur. These reactions have been observed more frequently with the 24-hour infusion than with the 3-hour infusion. In some cases, the onset of the injection site reaction either occurred during a prolonged infusion or was delayed by a week to 10 days.

Cardiovascular: Hypotension, during the first 3 hours of infusion, occurred in 12 % of all patients and 3 % of all courses administered. Bradycardia, during the first 3 hours of infusion, occurred in 3 % of all patients and 1 % of all courses. ECG alterations in the form of re-polarisation abnormalities like sinus tachycardia, sinus bradycardia, and premature beats have been observed in clinical studies. Severe cardiac conduction abnormalities have been reported in < 1 % of patients during LOXAT therapy. If patients develop significant conduction abnormalities during LOXAT administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with LOXAT.

Gastrointestinal (GI) toxicity: Mild to moderate nausea, vomiting, diarrhoea and mucositis (also reported as pharyngitis or cheilitis) were reported frequently by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion. Less frequent reports of neutropenic enterocolitis (typhilitis), despite the co-administration of G-CSF, were observed in patients treated with LOXAT alone and in combination with other chemotherapeutic medicines.

LOXAT and cisplatin: Cross-study comparison of neurotoxicity suggests that when LOXAT is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a LOXAT dose of 175 mg/m^2 given by 3-hour infusion (21 %) than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

LOXAT and radiotherapy: radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose:

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents (taxanes),

ATC Code: L01CD01

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.

5.2 Pharmacokinetic properties

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydous

Polyoxyl 35 castor oil

Ethanol anhydrous

6.2 Incompatibilities

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.

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vials: 2 years.

After dilution: 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.

The diluted solutions should not be stored refrigerated. From a microbiological viewpoint the solution should be used immediately.

6.4 Special precautions for storage

Store below 30 °C. After first use, any unused concentrate may be stored at room temperature not exceeding 25 °C for up to 28 days. Keep in outer carton until required for use.

For the storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

Loxat 30: Single 10 ml amber glass vial in a cardboard carton.

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

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

6.6 Special precautions for disposal

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.

Given the possibility of extravasations, it is advisable to closely monitor the injection site for possible infiltration during medicines administration.

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.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration.

There have been rare reports of precipitation during LOXAT infusions, usually towards the end of a 24-hour infusion period. Although the cause of this precipitation has not been elucidated, it is probably linked to the supersaturation of the diluted solution. To reduce the precipitation risk, LOXAT should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. The infusion sets should be flushed thoroughly before use. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

Parenteral medicines 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.

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.

The product must be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Oethmaan Biosims (Pty) Ltd

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8 REGISTRATION NUMBER(S):

LOXAT 30: 41/26/1095

LOXAT 100: 41/26/1096

LOXAT 300: 41/26/1097

9 DATE OF FIRST AUTHORISATION

14 August 2009

10 DATE OF REVISION OF THE TEXT

26 November 2024