Applicant : Eurolab (Pty) Ltd
Proprietary name : Paclitaxel 30 Eurolab & Paclitaxel 100 Eurolab & Paclitaxel 300 Eurolab
Dosage form and strength : Concentrate for solution for infusion 30 mg & 100 mg & 300 mg
Date of submission : 15 September 2022
Approval date : 27 September 2022

APPROVED PROFESSIONAL INFORMATION PACLITAXEL EUROLAB

SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

Paclitaxel 30 Eurolab, 30,0 mg per 5 ml, concentrate for solution for infusion

Paclitaxel 100 Eurolab, 100,0 mg per 16,7 ml, concentrate for solution for infusion

Paclitaxel 300 Eurolab, 300,0 mg per 50 ml, concentrate for solution for infusion

Warning: Paclitaxel Eurolab (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 who received **Paclitaxel Eurolab.** Patients receiving **Paclitaxel Eurolab** should be pretreated with corticosteroids, promethazine, and H_2 antagonists to prevent these reactions (see section 4.2). Patients who experience severe hypersensitivity reactions to **Paclitaxel Eurolab** should not be rechallenged with the medicine.
Paclitaxel Eurolab 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 **Paclitaxel Eurolab**.
The polyoxyethylated castor oil in **Paclitaxel Eurolab** 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 **Paclitaxel Eurolab** should be carried out by using non-plasticised PVC-containing equipment.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Paclitaxel 30 Eurolab: Each vial contains 30 mg paclitaxel per 5 ml

Paclitaxel 100 Eurolab: Each vial contains 100 mg paclitaxel per 16,7 ml

Paclitaxel 300 Eurolab: Each vial contains 300 mg paclitaxel per 50 ml

Sugar free.

Excipient(s) with known effect:

Polyoxyl 35 castor oil 527,0 mg/ml and anhydrous ethanol 391 mg/ml.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

A clear, colourless to slightly yellow solution, free from visible evidence of contamination.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Paclitaxel Eurolab 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 combination chemotherapy or relapse within 6 months of adjuvant chemotherapy.
   Prior therapy should have included an anthracycline unless clinically contra-indicated.
4. First line therapy of advanced or metastatic breast cancer in combination with trastuzumab in patients who over-express HER-2 at a 2+ or 3+ level as determined by immunohistochemistry.
5. 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

Paclitaxel should only be administered under the supervision of a qualified oncologist in units specialised in the administration of cytotoxic agents (see section 6.6).

All patients must be premedicated prior to Paclitaxel Eurolab administration to reduce the risk of severe hypersensitivity reactions. Such premedications may be corticosteroids, antihistamines, and H_2 antagonists prior to Paclitaxel Eurolab infusion, e.g.

Medicine	**Dose**	**Administration prior to**

		Paclitaxel Eurolab
dexamethasone	20 mg oral or IV	For oral administration: approximately 12 and 6 hours or for IV administration: 30 to 60 min
diphenhydramine*	50 mg IV	30 to 60 min
cimetidine or ranitidine	300 mg IV 50 mg IV	30 to 60 min

* or an equivalent antihistamine e.g. chlorpheniramine

Indication 1 - Primary treatment of ovarian carcinoma: A combination regimen consisting of Paclitaxel Eurolab 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin 75 mg/m^2 given every 3 weeks. Alternatively a combination regimen consisting of Paclitaxel Eurolab 135 mg/m^2 administered over 24 hours, followed by cisplatin 75 mg/m^2, every 3 weeks. Paclitaxel Eurolab should be administered before cisplatin.

Indication 2 and 3 - Secondary treatment of ovarian carcinoma: Paclitaxel Eurolab 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.

Indication 4 - Combination, first-line therapy of advanced or metastatic breast cancer: In combination with trastuzumab, the recommended dose of Paclitaxel Eurolab is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3 week interval between courses.

Paclitaxel Eurolab infusion may be started the day following the first dose of trastuzumab or immediately after the subsequent dose of trastuzumab if the preceding dose of trastuzumab was well tolerated.

4.3 Contraindications

Paclitaxel Eurolab is contraindicated in patients who have a history of severe hypersensitivity to paclitaxel or other medicines formulated with polyoxyethylated castor oil or to any excipients listed in section 6.1.

Paclitaxel Eurolab should not be used in patients with baseline neutrophils < 1 500/mm^3 at the start of therapy.

Paclitaxel Eurolab is contraindicated during pregnancy and lactation (see section 4.6).

The safety and effectiveness of Paclitaxel Eurolab in children has not been established.

4.4 Special warnings and precautions for use

Paclitaxel Eurolab 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.

Paclitaxel Eurolab should be administered as a diluted infusion. Paclitaxel Eurolab should be given before cisplatin when used in combination (see section 4.5).

Patients should be pre-treated with corticosteroids, antihistamines and H_2 antagonists before receiving Paclitaxel Eurolab (see section 4.2).

Anaphylaxis and severe hypersensitivity reactions characterised by dyspnoea, flushing, chest pain and tachycardia and hypotension requiring treatment, angioedema and generalised urticaria have occurred in patients receiving Paclitaxel Eurolab. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, Paclitaxel Eurolab infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with the medicine. Minor hypersensitivity reactions such as flushing, skin reactions, and not requiring treatment 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 Paclitaxel Eurolab treatment. Patients should not be retreated until neutrophils recover to a level > 1 500/mm^3 and platelets recover to a level > 100 000/mm^3. In cases of severe neutropenia (< 500 cells/mm^3) during a course of Paclitaxel Eurolab, 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.

Severe cardiac conduction abnormalities have been reported. If patients develop significant cardiac conduction abnormalities during Paclitaxel Eurolab administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Paclitaxel Eurolab. Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of Paclitaxel Eurolab infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung carcinoma than breast or ovarian carcinoma.

In severe cases, Paclitaxel Eurolab infusions may need to be interrupted or discontinued at the discretion of the treating medical practitioner.

When Paclitaxel Eurolab is used in combination with trastuzumab for treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with Paclitaxel Eurolab in this combination, they should undergo baseline cardiac assessment including history, physical examination, ECG, echocardiogram, and/or MUGA scan. Cardiac function should be further monitored during treatment (e.g. every three months). Monitoring may help to identify patients who develop cardiac dysfunction and the treating medical practitioner should carefully assess the cumulative dose (mg/m^2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating medical practitioners should carefully assess the clinical benefits of further therapy against the potential for producing cardiac damage, including potentially irreversible damage. If further treatment is administered, monitoring of cardiac function should be more frequent (e.g. every 1-2 cycles).

Neurologic

Cross-study comparison of neurotoxicity suggests that when Paclitaxel Eurolab is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a Paclitaxel Eurolab 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 %). Although the occurrence of peripheral neuropathy is frequent, the development of severe symptoms is rare and requires a dose reduction of 20 % for all subsequent courses of Paclitaxel Eurolab.

Hepatic

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. When paclitaxel is given as a longer infusion, increased myelosuppression may be seen in patients with moderate to severe hepatic impairment. Patients should be monitored closely for the development of profound myelosuppression. Dose adjustment is recommended (see section 4.2). Hepatic necrosis and hepatic encephalopathy leading to death have been reported. Elevations in alkaline phosphatase and AST (SGOT) have been reported.

No data are available for patients with severe baseline cholestasis. Patients with severe hepatic impairment must not be treated with Paclitaxel Eurolab.

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 efficacy of Paclitaxel Eurolab in children has not been established. There have been reports of central nervous system toxicity (less frequently associated with death) in a clinical trial in paediatric patients in which Paclitaxel Eurolab 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 Paclitaxel Eurolab vehicle given over a short infusion time. The use of concomitant anti-histamines 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 Paclitaxel Eurolab for use in this population.

Special care should be taken to avoid intra-arterial application of paclitaxel, since in animal studies testing for local tolerance severe tissue reactions were observed after intra-arterial application.
Paclitaxel Eurolab in combination with radiation of the lung, irrespective of their chronological order, may contribute to the development of *interstitial pneumonitis*.
Paclitaxel Eurolab contains anhydrous ethanol (391 mg/ml). 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.
Paclitaxel Eurolab contains Polyoxyl 35 Castor oil, which may cause severe allergic reactions.

Pseudomembranous colitis has been rarely reported including cases in patients who have not been concomitantly treated with antibiotics. This reaction should be considered in the differential diagnosis of cases of severe or persistent diarrhoea occurring during or shortly after treatment with Paclitaxel Eurolab.
Paclitaxel has shown to be teratogenic, embryotoxic and mutagenic in many experimental systems.
Therefore sexually active fertile female and male patients should use effective methods of contraception during treatment and up to six months after treatment for men and women (see section 4.6). Hormonal contraception is contraindicated in hormone receptor positive tumors.

4.5 Interaction with other medicines and other forms of interaction

The recommended regimen of Paclitaxel Eurolab administration for the primary treatment of ovarian carcinoma is for Paclitaxel Eurolab to be given before cisplatin. When Paclitaxel Eurolab is given before cisplatin, the safety profile of Paclitaxel Eurolab is consistent with that reported for single agent use. When Paclitaxel Eurolab was given after cisplatin, patients showed a more profound myelosuppression and an approximately 33 % decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynecological cancers.

Medications concomitantly administered with Paclitaxel Eurolab (e.g. corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible interactions of Paclitaxel Eurolab with concomitantly administered medications have not been formally investigated.
Plasma levels of doxorubicin and doxorubicinol may be increased when Paclitaxel Eurolab and doxorubicin are used in combination. Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been observed with combination use of Paclitaxel Eurolab and doxorubicin, when Paclitaxel Eurolab was administered before doxorubicin and using longer than recommended infusion times. Paclitaxel Eurolab for initial treatment of metastatic breast cancer, should be administered 24 hours after doxorubicin (see section 5.2).

The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of formal clinical interaction studies, caution should be exercised when administering Paclitaxel Eurolab concomitantly with medicines known to inhibit either CYP2C8 or CYP3A4 (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and nelfinavir) because toxicity of paclitaxel may be increased due to higher paclitaxel exposure. Administering paclitaxel 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.

Contact of the undiluted concentrate with plasticised polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion is not recommended. In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted Paclitaxel

Eurolab solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Paclitaxel Eurolab 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 potential

Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Paclitaxel Eurolab and to inform the treating medical practitioner immediately should this occur.

Women of childbearing potential should use effective contraception during and up to 6 months after receiving treatment with Paclitaxel.

Male patients treated with paclitaxel are advised not to father a child during and up to six months after treatment.

Pregnancy

Paclitaxel Eurolab should not be used during pregnancy. Paclitaxel Eurolab has been shown to be embryotoxic, foetotoxic and to decrease fertility in animal studies.

Breastfeeding

Paclitaxel Eurolab is contraindicated during lactation (see section 4.3). Breastfeeding should be discontinued for the duration of Paclitaxel Eurolab therapy.

Fertility

Paclitaxel induced infertility in animal studies. Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of irreversible infertility.

4.7 Effects on ability to drive and use machines

Paclitaxel has not been demonstrated to interfere with this ability. However, it should be noted that the formulation of Paclitaxel Eurolab contains alcohol (see section 4.4 and 6.1). The ability to drive or to use machines may be decreased due to the alcohol content of this medicine.

4.8 Undesirable effects

a) Summary of the safety profile

The frequency and severity of adverse events are generally similar between patients receiving Paclitaxel Eurolab for the treatment of ovarian carcinoma, breast carcinoma, or lung carcinoma. None of the observed toxicities were clearly influenced by age. Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent Paclitaxel Eurolab in clinical studies administered as one of two doses (135 or 175 mg/m^2) 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 Paclitaxel Eurolab. Neutropenia, the most important haematological toxicity, was dose and schedule dependent and was generally rapidly reversible. Even 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 Paclitaxel Eurolab dose and schedule.

Neurologic: In general, the frequency and severity of neurologic manifestations were dose dependent in patients receiving single-agent Paclitaxel Eurolab.

The frequency of peripheral neuropathy increased with cumulative dose. Paraesthesia commonly occurs in the form of hyperaesthesia. Peripheral neuropathy was the cause of Paclitaxel Eurolab discontinuation in 1 % of all patients. Sensory symptoms have usually improved or resolved within several months of Paclitaxel Eurolab discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contra-indication for Paclitaxel

Eurolab therapy. In frequent reports in the literature of abnormal visual evoked potentials in patients have suggested persistent optic nerve damage.

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

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

b) Tabulated summary of adverse reactions

System Organ Class	**Frequency / Adverse Reactions**
Infections and infestations	Frequent: Infection (mainly urinary tract and upper respiratory tract infections, with reported cases of fatal outcome Less Frequent: Septic shock, pneumonia, sepsis, pseudomembranous colitis
Blood and lymphatic system disorders	Frequent: Myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, fever, bleeding Less Frequent: Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome Frequency unknown: disseminated intravascular coagulation
Immune system disorders	Frequent: Minor hypersensitivity reactions (mainly flushing and rash)

	Less Frequent: Significant hypersensitivity reactions requiring therapy (e.g. hypotension, angioedema, respiratory distress, generalised urticaria, oedema, back pain, chills, chest pain, tachycardia, abdominal pain, pain in extremities, diaphoresis and hypertension), anaphylactic reactions (with fatal outcome), anaphylactic shock Frequency unknown: Bronchospasm
Metabolism and nutrition disorders	Less Frequent: Dehydration, anorexia Frequency unknown: tumour lysis syndrome
Psychiatric disorders	Less Frequent: Confusional state
Nervous system disorders	Frequent: Neurotoxicity (mainly peripheral neuropathy) Less 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
Eye disorders	Less Frequent: Reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended, photopsia, visual floaters Frequency unknown: macular oedema
Ear and labyrinth disorders	Less Frequent: Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders	Frequent: Abnormal ECG, bradycardia Less Frequent: Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction, atrial fibrillation, supraventricular tachycardia
Vascular disorders	Frequent: Hypotension, hypertension, thrombosis, thrombophlebitis Less Frequent: Shock Frequency unknown: phlebitis
Respiratory, thoracic and mediastinal disorders	Less Frequent: Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough
Gastro-intestinal disorders	Frequent: Nausea, vomiting, diarrhoea, mucosal inflammation Less Frequent: Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, oesophagitis, constipation, ascites
Hepato-biliary disorders	Less Frequent: Hepatic necrosis (with fatal outcome), hepatic encephalopathy

	(with fatal outcome)
Skin and subcutaneous tissue disorders	Frequent: Alopecia, transient and mild nail and skin changes Less Frequent: Pruritus, rash, erythema, phlebitis, cellulitis, skin exfoliation, necrosis and fibrosis, radiation recall, Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet) Frequency unknown: scleroderma, Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent: Arthralgia, myalgia Frequency unknown: systemic lupus erythematosus, scleroderma
General disorders and administration site conditions	Frequent: Mucosal inflammation, injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasations can result in cellulitis). Less Frequent: Asthenia, malaise, pyrexia, dehydration, oedema
Investigations	Frequent: Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase Less Frequent: Severe elevation in bilirubin, increase in blood creatinine.

c) Description of selected adverse reactions

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 Paclitaxel Eurolab therapy. If patients develop significant conduction abnormalities during Paclitaxel Eurolab administration, appropriate therapy should be administered and continuous electrocardiographic monitoring should be performed during subsequent therapy with Paclitaxel Eurolab.

Gastro-intestinal (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 Paclitaxel Eurolab alone and in combination with other chemotherapeutic agents.

Paclitaxel Eurolab and cisplatin: Cross-study comparison of neurotoxicity suggests that when Paclitaxel Eurolab is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at a Paclitaxel Eurolab 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 %).

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

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

4.9 Overdose

There is no antidote for Paclitaxel Eurolab overdosage. In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated complications of overdosage which consist of bone marrow suppression, peripheral neurotoxicity and mucositis.

Paediatric population

Overdoses in paediatric patients may be associated with acute ethanol toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.26 Cytostatic agents

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability results in the inhibition of the normal dynamic reorganisation 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 concentrations, with a mean terminal half-life of 5 to 17 hours. The steady-state volume of distribution is reported to range from 42 to 162 litres per m^2, indicating extensive extravascular distribution, tissue binding, or both.

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.

Paclitaxel is about 89 % bound to plasma protein in vitro. The elimination of paclitaxel has not been fully elucidated: only about 12 % or less of a dose is reported to be excreted in urine, as unchanged drug, indicating extensive non renal clearance. Paclitaxel is thought to be metabolised in the liver by cytochrome P450 enzymes, and high paclitaxel concentrations have been reported in bile.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Anhydrous ethanol

Polyoxyl 35 castor oil

6.2 Incompatibilities

Polyoxyethylated 35 castor oil can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticised polyvinyl chloride (PVC) containers, at levels, which increase with time and concentration. Consequently, the preparation, storage and administration of diluted paclitaxel should be carried out using non-PVC-containing equipment.

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

6.3 Shelf life

Unopened vial:

24 months.

After opening before dilution:

Chemical and physical in-use stability has been demonstrated for 28 days at 25 °C following multiple needle entries and product withdrawal. From a microbiological point of view, once opened the product may be stored for a maximum of 28 days at 25 °C.

After dilution:

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 5 °C and at 25 °C for 7 days when diluted in 5 % Dextrose solution, and for 14 days when diluted in 0,9 % Sodium Chloride Injection. From a microbiological point of view, the product 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 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 ˚C. To be kept in outer container until required. Protect from light.

Discard any unused portion.

Do not refrigerate.

KEEP OUT OF REACH OF CHILDEN.

6.5 Nature and contents of container

- **Paclitaxel 30 Eurolab:** 5 ml filled in a 5 ml or 6 ml clear glass vial with an omniflex rubber stopper sealed with an aluminium seal and red coloured flip off top.
- **Paclitaxel 100 Eurolab:** 16,7 ml filled in a 20 ml clear glass vial with an omniflex rubber stopper sealed with an aluminium seal and red coloured flip off top.
- **Paclitaxel 300 Eurolab:** 50 ml filled in a 50 ml clear glass vial with an omniflex rubber stopper sealed with an aluminium seal and red coloured flip off top.

6.6 Special precautions for disposal and other handling

Handling:

As with all antineoplastic agents, caution should be exercised when handling Paclitaxel Eurolab. This includes all handling activity in clinical settings, pharmacies, storerooms and home healthcare settings, including during unpacking and inspection, transport within a facility, and dose preparation and administration. Dilution should

be carried out under aseptic conditions 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. In the event of contact with the skin, the area should be washed with soap and water. Following topical exposure, tingling, burning and redness have been observed. In the event of contact with the mucous membranes, these should be flushed thoroughly with water. Upon inhalation, dyspnoea, chest pain, burning throat and nausea have been reported. Following multiple needle entries and product withdrawals, the vials maintain microbial, chemical and physical stability for up to 28 days at 25 °C. Devices with spikes should not be used with vials of Paclitaxel Eurolab since they can cause the stopper to collapse resulting in loss of sterile integrity of the Paclitaxel Eurolab solution.

Preparation for IV administration:

Paclitaxel Eurolab must be diluted prior to infusion using aseptic techniques. Paclitaxel Eurolab should be diluted in 0,9 % Sodium Chloride Injection, or 5 % Dextrose Injection, or 5 % Dextrose and 0,9 % Sodium Chloride Injection or 5 % Dextrose in Ringer's Injection to a final concentration of 0,3 to 1,2 mg/ml. The prepared solutions are physically and chemically stable for up to 27 hours at ambient temperature (approximately 25 °C) and room lighting conditions. Infusions should be completed within this timeframe. From a microbiological point of view, **the product 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. After dilution the solution is for single use only.

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle, and is not removed by filtration. Paclitaxel Eurolab should be administered through an in-line filter with a microporous membrane ≤ 0,22 µm. No significant losses in potency have been noted following delivery of the solution through IV tubing containing an in-line filter.

There have been rare reports of precipitation during paclitaxel 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, paclitaxel should be used as soon as possible after dilution, and excessive agitation, vibration or shaking should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

Parenteral medicines should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. During infusion, the appearance of the solution should be regularly inspected and the infusion should be stopped if precipitation is present.

To minimise patient exposure to the plasticiser DEHP [di-(2-ethylhexyl)phthalate], which may be leached from plasticised PVC infusion bags or sets, diluted Paclitaxel Eurolab solutions should preferably be stored in non-PVC 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 plasticised PVC tubing has not resulted in significant leaching of DEHP.

Protection instructions for preparation of Paclitaxel solution for infusion:

1. Protective chamber should be used and protective gloves as well as protective gown should be worn. If there is no protective chamber available mouth cover and goggles should be used.
2. Pregnant women or women who may become pregnant, should not handle this product.
3. Opened containers, like injection vials and infusion bottles and used canules, syringes, catheters, tubes, and residuals of cytostatics should be considered as hazardous waste and undergo disposal according to local guidelines for the handling of HAZARDOUS WASTE.
4. Follow the instructions below in case of spillage:
    - protective clothing should be worn
    - broken glass should be collected and placed in the container for HAZARDOUS WASTE
    - contaminated surfaces should be flushed properly with copious amounts of cold water
    - the flushed surfaces should then be wiped thoroughly and the materials used for wiping should be disposed as HAZARDOUS WASTE
5. In the event of contact of Paclitaxel Eurolab with the skin, the area should be rinsed with plenty of running water and then washed with soap and water. In case of contact with mucous membranes, wash the contacted area thoroughly with water. If you have any discomfort, contact a doctor.
6. In case of contact of Paclitaxel Eurolab with eyes, wash them thoroughly with plenty of cold water. Contact an ophthalmologist immediately.

Disposal:

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Eurolab (Pty) Ltd.

Woodmead Office Park,

3 Stirrup Lane, Van Reenens Avenue,

Woodmead,

2144

8 REGISTRATION NUMBER

Paclitaxel 30 Eurolab: 44/26/0374

Paclitaxel 100 Eurolab: 44/26/0375

Paclitaxel 300 Eurolab: 44/26/0376

9 DATE OF FIRST REGISTRATION

02 March 2012

10 DATE OF REVISION OF THE TEXT

27 September 2022