Table of Contents

1.3.1.1.1 PI - Approved - PACLITAXEL AURO 1

1. NAME OF THE MEDICINE 2

2. QUALITATIVE AND QUANTITATIVE COMPOSITION 3

3. PHARMACEUTICAL FORM 3

4. CLINICAL PARTICULARS 3

5 PHARMACOLOGICAL PROPERTIES 16

6 PHARMACEUTICAL PARTICULARS 18

7 HOLDER OF THE CERTIFICATE OF REGISTRATION 20

8 REGISTRATION NUMBER(S) 20

9 DATE OF FIRST AUTHORISATION 20

10 DATE OF REVISION OF TEXT 20

1.3.1 South African Professional Information

1.3.1.1 Professional Information

1.3.1.1.1 PI - Approved

The proposed South Africa PI for **PACLITAXEL 30 mg 5 mL AURO, PACLITAXEL 100 mg 16.7 mL AURO, PACLITAXEL 150 mg25 mL AURO & PACLITAXEL 300 mg 50 mL AURO** is enclosed on pages **1.3.1.1.1 Page 2 – 20.**

The PI complies with Regulation 9 of the Act.

Applicant/PHCR: AUROGEN SA (PTY) LTD
Product proprietary name: PACLITAXEL 30 mg/5 ml AURO, PACLITAXEL 100 mg/16,7 ml AURO, PACLITAXEL 150 mg/25 ml AURO & PACLITAXEL 300 mg/50 ml AURO
Dosage form and strength: Concentrate for solution for injection containing 6 mg paclitaxel from per 1 ml solution.

Approved Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

PACLITAXEL 30 mg/5 ml AURO concentrate for solution for infusion;

PACLITAXEL 100 mg/16,7 ml AURO concentrate for solution for infusion;

PACLITAXEL 150 mg/25 ml AURO concentrate for solution for infusion;

PACLITAXEL 300 mg/50 ml AURO concentrate for solution for infusion

Warning: PACLITAXEL AURO (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 who received PACLITAXEL AURO. Patients receiving PACLITAXEL AURO 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 PACLITAXEL AURO should not be rechallenged with the medicine. PACLITAXEL AURO 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 PACLITAXEL AURO.

The polyoxyethylated castor oil in PACLITAXEL AURO 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 AURO should be carried out by using non-plasticised PVC-containing equipment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

PACLITAXEL AURO for injection contains 6 mg paclitaxel from per 1 ml solution. The medicine contains 49.7 % v/v dehydrated alcohol.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for Solution for infusion.

Clear colourless to slightly yellow viscous solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

PACLITAXEL AURO 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.

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

Indication 1: Primary treatment of ovarian carcinoma: A combination regimen consisting of PACLITAXEL AURO 175 mg/m2 administered intravenously over 3 hours, followed by cisplatin 75 mg/m2 given every 3 weeks. Alternatively a combination regimen consisting of PACLITAXEL AURO 135 mg/m2 administered over 24 hours, followed by cisplatin 75 mg/m2, every 3 weeks. PACLITAXEL AURO should be administered before cisplatin.

Indication 2 and 3: Secondary treatment of ovarian carcinoma: PACLITAXEL AURO at a dose of 175 mg/m2 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 AURO is 175 mg/m2 administered intravenously over a period of 3 hours, with a 3 week interval between courses.

PACLITAXEL AURO 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.

Indication 5: Palliative treatment of advanced non-small cell lung carcinoma: the recommended dose of PACLITAXEL AURO is 175 mg/m2 administered over a period of 3 hours; followed by a platinum compound, with a 3 week interval between courses. PACLITAXEL AURO should not be re-administered

until the neutrophil count is at least 1 500/mm3 and the platelet count is at least 100 000/mm3. Patients who experience severe neutropenia (neutrophil count <500/mm3) 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 haematological toxicity increases with dose. All patients must be premedicated prior to PACLITAXEL AURO administration to reduce the risk of severe hypersensitivity reactions. Such premedications may be corticosteroids, antihistamines, and H2 antagonists prior to PACLITAXEL AURO administration, e.g. dexamethasone 20 mg orally approximately 12 and 6 hours before PACLITAXEL AURO or 20 mg IV approximately 30-60 minutes prior to PACLITAXEL AURO, and cimetidine 300 mg or ranitidine 50 mg, IV 30 to 60 minutes before PACLITAXEL AURO. PACLITAXEL AURO should be administered through an in-line filter with a microporous membrane not greater than 0,22 µm.

Table 1: Degree of hepatic impairment		
Transaminase levels	**Bilirubin levels (a)**	**Recommended PACLITAXEL dose (b)**
24 hour infusion		
< 2 x ULN and 2-< 10 x ULN and < 10 x ULN and ≥ 10 x ULN or	≤ 1,5 mg/dl ≤ 1,5 mg/dl 1,6-7,5 mg/dl > 7,5 mg/dl	175 mg/m2 135 mg/m2 90 mg/m2 Not recommended
	3 hour infusion	
< 10 x ULN and < 10 x ULN and < 10 x ULN and ≥ 10 x ULN or	≤ 1,25 x ULN 1,26 – 2,0 x ULN 2,01 – 5,0 x ULN > 5,0 ULN	175 mg/m2 135 mg/m2 90 mg/m2 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.

Special populations

Hepatic impairment: See section 4.4

Dosage adjustment is recommended as shown above: (see table 1)

Paediatric population

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

Method of administration:

PACLITAXEL AURO is for intravenous infusion.

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

Reconstitution and preparation of dosage form

4.3. Contraindications

• Should not be administered to patients that have had severe hypersensitivity reactions to paclitaxel or other medicines formulated in Cremophor EL (polyoxyethylated castor oil), or to any of the excipients of PACLITAXEL AURO (see section 6.1).

• Should not be used in patients with severe baseline neutropenia (< 1500 cells/mm3).

• Safety in pregnancy and lactation has not been established. (see section 4.6)

• Safety in children has not been established.

•Liver impairment. Since PACLITAXEL AURO is partially metabolised in the liver, treatment of patients with severe hepatic conditions should be approached with added precaution. (see section 4.4).

4.4. Special warnings and precautions for use

Paclitaxel therapy must be overseen by a qualified medical practitioner with experience in the utilisation of cancer chemotherapy medicines. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available.

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

Patients must be pretreated with corticosteroids, antihistamines and H2 antagonists (section 4.2).

Paclitaxel should be given before cisplatin when used in combination (section 4.5).

Hypersensitivity:

Severe hypersensitivity characterised by dyspnoea and hypotension requiring treatment, angioedema, and generalised urticaria have occurred in patients receiving paclitaxel after adequate premedication. Fatal hypersensitivity reactions have occurred in patients despite premedication. These reactions are probably histamine mediated. In the case of severe hypersensitivity reactions, paclitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated, and the patient should not be challenged with paclitaxel. Macrogolglycerol ricinoleate (polyoxyl castor oil), an excipient in this medicinal product, can cause these reactions.

Haematology:

Bone marrow suppression, primarily neutropenia, is the dose-limiting toxicity. Neutrophil nadirs occurred at a median of 11 days. Frequent monitoring of blood counts should be instituted. Patients should not be retreated until the neutrophil count is ≥1.5 x 109/l and the platelets recover to ≥100 x 109^{9}/l).

Cardiovascular:

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

Hypotension, hypertension, and bradycardia have been observed during paclitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital signs monitoring, particularly during the first hour of paclitaxel infusion, is recommended. Severe cardiovascular events were observed more frequently in patients with non-small cell lung cancer than in those with breast or ovarian carcinoma.

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 paclitaxel administration and ECG alterations is not clear.

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When paclitaxel is used in combination with doxorubicin or trastuzumab for initial treatment of metastatic breast cancer, attention should be placed on the monitoring of cardiac function. When patients are candidates for treatment with paclitaxel in these combinations, they should undergo baseline cardiac assessment including history, physical examination, electrocardiogram (ECG), echocardiogram, and/or multigated acquisition (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 treating physicians should carefully assess the cumulative dose (mg/m2) of anthracycline administered when making decisions regarding frequency of ventricular function assessment. When testing indicates deterioration in cardiac function, even asymptomatic, treating physicians 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 1-2cycles). For more details see Professional Information of trastuzumab or doxorubicin.

Neurological:

Peripheral neuropathy: The occurrence of peripheral neuropathy is frequent; the development of severe symptoms is rare. In severe cases, a dose reduction of 20% is recommended for all subsequent courses of paclitaxel. In non-small cell lung cancer patients, the administration of paclitaxel in combination with cisplatin resulted in a

greater incidence of severe neurotoxicity than administration of single agent paclitaxel. In first-line ovarian cancer patients, administration of paclitaxel as a 3-hour infusion combined with cisplatin resulted in a greater incidence of severe neurotoxicity than administration of a combination of cyclophosphamide and cisplatin.

Hepatic:

Impaired hepatic function: 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. No data are available for patients with severe baseline cholestasis. 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 (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.

Inadequate data are available to recommend dosage alterations in patients with mild to moderate hepatic impairments (see section 5.2). Patients with severe hepatic impairment must not be treated with paclitaxel.

Excipients

Ethanol: This product contains 49.7% vol ethanol (alcohol). 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 AURO contains polyoxyl castor oil which may cause severe allergic reactions.

Pseudomembranous colitis

Pseudomembranous colitis has also 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 paclitaxel.

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

Fertility

Paclitaxel 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 paclitaxel.

Macular oedema

There have been reports of reduced visual acuity due to cystoid macular oedema (CME) during treatment with paclitaxel as well as with other taxanes. Patients with visual impairment during paclitaxel treatment should seek a prompt and complete ophthalmologic examination. Discontinue paclitaxel treatment if a CME diagnosis is confirmed. Clinicians should consider whether the benefits of restarting paclitaxel treatment after CME resolution are expected to exceed the risks of further therapy

Paediatric use

The safety and efficacy of PACLITAXEL AURO 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 AURO was infused intravenously over 3 hours at doses ranging from 350 mg/m2 to 420 mg/m2. The toxicity is most likely attributable to the high dose of the ethanol component of the PACLITAXEL AURO 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 AURO for use in this population.

4.5 Interaction with other medicines and other forms of interaction

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: Paclitaxel is recommended to be administered before cisplatin. When given before cisplatin, the safety profile of paclitaxel is consistent with that reported for single agent use. Administration of paclitaxel after cisplatin treatment leads to greater myelosuppression and about a 20% decrease in paclitaxel clearance. Patients treated with paclitaxel and cisplatin may have an increased risk of renal failure as compared to cisplatin alone in gynaecological cancers.

Doxorubicin: Since the elimination of doxorubicin and its active metabolites can be reduced when paclitaxel and doxorubicin are given closer in time, paclitaxel for initial treatment of metastatic breast cancer should be administered 24hours after doxorubicin (see section 5.2).

Sequence effects characterised by more profound neutropenic and stomatitis episodes have been observed with combination use of paclitaxel and doxorubicin when paclitaxel was administered before doxorubicin and using longer than recommended infusion times (paclitaxel administered over 24 hours; doxorubicin over 48 hours).

Active substances metabolised in the liver: The metabolism of paclitaxel is catalysed, in part, by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Therefore, in the absence of a Pharmacokinetics drug-drug interaction study, caution should be exercised when administering paclitaxel 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.

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 AURO 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 paclitaxel.

Pregnancy

PACLITAXEL AURO should not be used during pregnancy. There is no information on the use of PACLITAXEL AURO in pregnant women. PACLITAXEL AURO may cause foetal harm when administered to pregnant women.

Breastfeeding

It is not known whether PACLITAXEL AURO is excreted in human milk.

Breast feeding should be discontinued for the duration of PACLITAXEL AURO therapy.

Fertility

PACLITAXEL AURO 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 paclitaxel because of the possibility of infertility.

4.7 Effects on ability to drive and use machines

This medicinal product contains alcohol. It may also lead to eye disorders ,which may impair the ability to drive or operate machines.

In addition, some side effects such as hypotension and eye disorders may impair ability to drive

4.8 Undesirable effects

a) Summary of adverse effects

The frequency and severity of adverse events are generally similar between patients receiving PACLITAXEL AURO for the treatment of ovarian, breast or lung carcinoma. None of the observed toxicities were clearly influenced by age.

b.) Tabulated list of adverse reactions

The table below lists undesirable effects regardless of severity associated with the administration of single agent paclitaxel administered as a three -hour infusion in the metastatic setting (812 patients treated in clinical studies) and as reported in the post-marketing surveillance of paclitaxel.

System Organ Class	Frequency	Event
Infections and infestations	Frequent	Infection (mainly urinary tract and upper respiratory tract infections), with reported cases of fatal outcome
	Less frequent	Septic shock Pneumonia, peritonitis, Pseudomembranous colitis, Sepsis
Blood and lymphatic system disorders	Frequent	Myelosuppression, neutropenia, anaemia, thrombocytopenia, leucopenia, bleeding
	Less frequent	Febrile neutropenia, Acute myeloid leukaemia, myelodysplastic syndrome, agranulocytosis, haemolytic anaemia
	Frequency unknown	Disseminated intravascular coagulation (DIC
Immune system disorders	Frequent	Minor hypersensitivity reactions (mainly flushing and rash)
	Less frequent	Significant hypersensitivity reactions requiring therapy (e.g., hypotension, angioneurotic oedema, respiratory distress, generalised urticaria, chills, back pain, chest pain, tachycardia, abdominal pain, pain in extremity, diaphoresis, and hypertension) Anaphylactic reactions 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**) can persist beyond 6 months of paclitaxel discontinuation)
	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
Eye disorders	Frequency not known	Macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders	Less frequent	Ototoxicity, hearing loss, tinnitus, vertigo
Cardiac disorders	Frequent	Abnormal ECG, Bradycardia
	Less frequent	Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, atrio-ventricular block and syncope, myocardial infarction, Cardiac failure 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, interstitial pneumonia, lung fibrosis, Cough pulmonary embolism, respiratory failure
Gastro-intestinal disorders	Frequent	Nausea, vomiting, diarrhoea, mucosal inflammation.
	Less Frequent	Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, neutropenic colitis oesophagitis, constipation, ascites
Hepato-biliary disorders	Less frequent	Hepatic necrosis, hepatic encephalopathy (both with reported cases of fatal outcome)
Skin and subcutaneous tissue disorders		
	Frequent	Alopecia, Transient and mild nail and skin changes
	Less frequent	Pruritus, rash, erythema, cellulitis, skin exfoliation necrosis and fibrosis, radiation recall. Stevens-Johnson syndrome, epidermal necrolysis, erythema multiforme, exfoliative dermatitis, urticaria, onycholysis (patients on therapy should wear sun protection on hands and feet)
	Frequency unknown	Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal and connective tissue 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 extravasation can result in cellulitis, skin fibrosis and skin necrosis)
	Less frequent	Asthenia, pyrexia, oedema, malaise

Investigations	Frequent	Severe elevation in aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase (SGOT)), severe elevation in alkaline phosphatase
	Less frequent	Increase in blood creatinine. Severe elevation in bilirubin,

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the: Med Safety APP (Medsafety X SAHPRA)and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

See side effects. Complications resulting from PACLITAXEL AURO overdosage may result in bone marrow suppression, peripheral neurotoxicity, and mucositis.

Treatment:

There is no known curative measure for excessive doses (antidote). Treatment is symptomatic and supportive. Overdoses in paediatric patients may be associated with acute ethanol toxicity

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological Classification: A 26. Cytostatic agents. Pharmacotherapeutic group: Antineoplastic agent/taxanes ATC code: L01C D01

Paclitaxel is an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilises microtubules by preventing depolymerisation. This stability inhibits the normal dynamic reorganisation of the microtubule network, which 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

Absorption

Following intravenous administration, paclitaxel exhibits a biphasic decline in plasma concentrations. The pharmacokinetics of paclitaxel were determined following 3 and 24-hour infusions at doses of 135 and 175 mg/m2.The mean half-life was between 3.0 and 52.7 hours, and the mean non-compartmentally derived value for total body clearance was between 11.6 and 24.0 L/hr/m2. The total body clearance appeared to decrease with higher plasma concentrations. The mean steady-state volume of distribution was between 198 and 688 l/m2, indicating extensive
extravascular distribution and/or tissue binding. Dose increases associated with the 3-hour infusion resulted in non-linear pharmacokinetics. When the dose increased by 30% from 135 mg/m2 to 175 mg/m2, the maximum plasma concentration (Cmax) increased by 75% and the area under the plasma concentration time curve (AUC0-∞) by 81%. The variation of systemic paclitaxel exposure in the same patient was found to be minimal. No signs of cumulative effects were found for paclitaxel in association with multiple treatment courses.

Distribution

In vitro studies of serum protein binding indicate that 89-98% of paclitaxel is bound to proteins. Cimetidine, ranitidine,dexamethasone or diphenhydramine were not found to affect the protein binding of paclitaxel.

Biotransformation and elimination

The distribution and metabolism of paclitaxel in humans has not been fully investigated. The cumulative excretion of unchanged paclitaxel in the urine has been between 1.3% and 12.6% of the dose on

average, which is an indication of extensive non-renal clearance. Hepatic metabolism and biliary clearance are possibly the principal mechanisms for elimination of paclitaxel. Paclitaxel is primarily metabolised by the action of CYP450 enzyme. An average of 26% of the radioactively marked dose of paclitaxel was eliminated in the faeces as a 6α-hydroxypaclitaxel, 2% as 3'pdihydroxypaclitaxel and 6% as 6α-3'p-dihydroxypaclitaxel.

6α-hydroxypaclitaxel is formed by the effect of CYP2C8, 'phydroxypaclitaxel by CYP3A4 and 6α-3'p-dihydroxypaclitaxel by CYP2C8 and CYP3A4. The effect of renal or hepatic impairment on the elimination of paclitaxel after 3-hour infusions has not been studied. The pharmacokinetic parameters of a patient on haemodialysis were of values similar to those of non-dialysis patients when the administration rate was 135 mg/m2 of paclitaxel as a 3-hour infusion.

In clinical trials where paclitaxel and doxorubicin were administered concomitantly, the distribution and elimination of doxorubicin and its metabolites were prolonged. Total plasma exposure to doxorubicin was 30% higher when paclitaxel immediately followed doxorubicin than when there was a 24-hour interval between drugs.

For use of paclitaxel in combination with other therapies, please consult the professional information of cisplatin, doxorubicin or trastuzumab for information on the use of these medicinal products.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

PACLITAXEL AURO contain the following inactive ingredients:

Anhydrous Citric Acid Ph.Eur

Macrogoglycerol ricinoleate

Ethanol Anhydrous

Nitrogen

6.2 Incompatibilities

PACLITAXEL AURO must not be mixed with other medicines except those mentioned in section 4.2.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store at or below 25 °C.

6.5 Nature and contents of container

Paclitaxel 6 mg/mL Concentrate for Solution for Infusion (30 mg/ 5 mL) is proposed to be marketed in glass vial clear tubular Type – I, 6 R with 13 mm neck stoppered with 13 mm grey bromobutyl rubber stopper and sealed with Aluminium seal with PP disc of 13 mm parrot green color.

Paclitaxel 6 mg/mL Concentrate for Solution for Infusion (100 mg/16.7 mL) is proposed to be marketed Glass vial tubular type –I, 26 mL clear with 20 mm neck (20R ISO Vial) stoppered with 20mm Rubber stoppers Grey bromo butyl and sealed with aluminium seal with PP disk of 20 mm SkyBlue colour safe seal.

Paclitaxel 6 mg/mL Concentrate for Solution for Infusion (150 mg/25 mL) is proposed to be marketed in Glass vial molded type –I, 30 mL clear with 20 mm neck stoppered with 20 mm Rubber stoppersGrey bromo butyl and sealed with aluminium seal with PP disk of 20 mm Sky Blue colour safe seal.

Paclitaxel 6 mg/mL Concentrate for Solution for Infusion (300 mg/50 mL) is proposed to be marketed in Glass vial moulded type –I, 50 mL clear with 20 mm neck stoppered with 20 mm Rubber stoppers Grey bromo butyl and sealed with aluminium seal with PP disk of 20 mm Sky Blue colour safe seal.

This vial shall be placed in printed carton along with package insert

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

PACLITAXEL AURO is an antineoplastic agent and, as with other potentially toxic agents, caution should be exercised during handling and preparing solutions of PACLITAXEL AURO.

Due to the extracting effect of Cremophor EL on plastics, PVC equipment or devices used to prepare solutions for infusion are not recommended. Contact of PACLITAXEL AURO with PVC causes leaching of DEHP [di-(2-ethylhexyl) phtalate]. PACLITAXEL AURO solutions should be stored in bottles (glass,

polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene lined administration sets. It is recommended to filter the solution using in-line filters of 0,22m.

PACLITAXEL AURO for Injection must be diluted prior to infusion. PACLITAXEL AURO should be diluted in 0,9 % Sodium Chloride Injection, 5 % Dextrose Injection or 5 % Dextrose in Ringer's Injection to a final concentration of 0,3 to 1,2 mg/ml. It is recommended to filter the solution using in-line filters of 0,22 microns. The solutions are physically and chemically stable for up to 30 hours at room temperature (15 – 30 °C).

PACLITAXEL AURO is cytotoxic and must be handled with care. Should accidental skin contact occur, the affected part must be washed immediately with soap and water. If PACLITAXEL AURO contacts eyes or mucous membranes, flush with water.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8 REGISTRATION NUMBER(S)

PACLITAXEL 30 mg/5 ml AURO: 57/26/0205.201

PACLITAXEL 100 mg/16,7 ml AURO: 57/26/0206.202

PACLITAXEL 150 mg/25 ml AURO: 57/26/0207.203

PACLITAXEL 300 mg/50 ml AURO: 57/26/0208.204

9 DATE OF FIRST AUTHORISATION

10 JUNE 2025

10 DATE OF REVISION OF TEXT

N/A