1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

INDAXOL 30 Concentrate for solution for infusion

INDAXOL 100 Concentrate for solution for infusion

INDAXOL 300 Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

INDAXOL 30: One vial of 5 ml contains 30 mg paclitaxel.

INDAXOL 100: One vial of 16.7 ml contains 100 mg paclitaxel.

INDAXOL 300: One vial of 50 ml contains 300 mg paclitaxel.

Excipient with known effect: Ethanol 99.9% (0,385 g/ml)

Sugar Free.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

INDAXOL is a clear, colourless to pale yellow viscous solution free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

INDAXOL is indicated for:

1. The palliative treatment of stage 3 or 4 advanced local carcinoma of the ovary after surgical resection, in combination with cisplatin.

2. The palliative management of metastatic carcinoma of the ovary after failure of first line or subsequent chemotherapy.

3. The treatment of metastatic carcinoma of the breast after failure of combination chemotherapy or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contra-indicated.

4. 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

Indication 1:

Primary treatment of ovarian carcinoma: A combination regimen consisting of **INDAXOL** 175 mg/m^2 administered intravenously over 3 hours, followed by cisplatin, given every 3 weeks.

Alternatively, a combination regimen consisting of **INDAXOL** 135 mg/m^2 administered over 24 hours, followed by cisplatin, every 3 weeks. **INDAXOL** should be administered before cisplatin.

Indication 2 and 3:

Secondary treatment of ovarian carcinoma: **INDAXOL** 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 **INDAXOL** is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3 week interval between courses. **INDAXOL** 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 **INDAXOL** is 175 mg/m^2 administered over a period of 3 hours; followed by a platinum compound, with a 3 week interval between courses.

INDAXOL should not be re-administered until the neutrophil count is at least 1 500/mm3 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 4.8). The incidence and severity of neurotoxicity and haematologic toxicity increases with dose.

All patients must be premedicated prior to **INDAXOL** administration to reduce the risk of severe hypersensitivity reactions.

Such premedications may be corticosteroids, antihistamines, and H2 antagonists prior to **INDAXOL** administration, e.g., dexamethasone 20 mg orally approximately 12 and 6 hours

before **INDAXOL** or 20 mg IV approximately 30 to 60 minutes before **INDAXOL**, promethazine 25 mg IV 30 to 60 minutes prior to **INDAXOL**, and cimetidine 300 mg or ranitidine 50 mg, IV 30 to 60 minutes before **INDAXOL**.

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

Hepatic Impairment: See Section 4.4
Dosage adjustment is recommended as shown below:

Degree of Hepatic Impairment		
Transaminase levels	Bilirubin Levels [(a)]	Recommended **INDAXOL** dose[(b)]
24 HOUR INFUSION		
< 2 x ULN and	≤ 0,026 mmol/ℓ	135 mg/m^2
2 - < 10 x ULN and	≤ 0,026 mmol/ℓ	100 mg/m^2
< 10 x ULN and	0,027 – 0,128 mmol/ℓ	50 mg/m^2
≥ 10 x ULN or	> 0,128 mmol/ℓ	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 x ULN	90 mg/m^2
≥ 10 x ULN or	> 5,0 x 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.

Directions for Use/Handling

Handling: Caution should be exercised when handling **INDAXOL**. 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 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 the 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 extravasation, it is advisable to closely monitor the injection site for possible infiltration during medicine administration.

Preparation for IV Administration: **INDAXOL** must be diluted prior to infusion. **INDAXOL** 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 25^0 C) and room lighting conditions; infusions should be completed within this timeframe. There have been reports of precipitation with longer than the recommended 3 hour infusion schedules. Excessive agitation, vibration or shaking may induce precipitation and should be avoided. Infusion sets should be flushed thoroughly with a compatible diluent before use.

Devices with spikes should not be used with vials of **INDAXOL** since they can cause the stopper to collapse resulting in loss of sterile integrity of the **INDAXOL** solution.

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

Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. **INDAXOL** should be administered through an in-line filter with a microporous membrane not greater

than 0,22 µm. No significant losses in potency have been noted following delivery of the solution through IV tubing containing an in-line filter.

In order to minimise patient exposure to the plasticiser DEHP [di-(2-ethylexyl)phthalate], which may be leached from plasticised PVC infusion bags or sets, diluted **INDAXOL** 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 plasticised PVC tubing has not resulted in significant leaching of DEHP.

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

4.3 Contraindications

INDAXOL is contra-indicated in patients who have a history of severe hypersensitivity reactions to **INDAXOL,** or other medicines formulated with polyoxyethylated castor oil.

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

INDAXOL is contraindicated during lactation (see section 4.6).

4.4 Special warnings and precautions for use

INDAXOL 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.

INDAXOL should be administered as a diluted infusion.

INDAXOL should be given before cisplatin when used in combination.

Patients should be pre-treated with corticosteroids, antihistamines and H2 antagonists before receiving **INDAXOL**. 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 **INDAXOL**. These reactions are probably histamine mediated. Fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, **INDAXOL** infusion should be immediately discontinued, symptomatic therapy should be initiated, and the patient should not be rechallenged with paclitaxel.

Minor hypersensitivity reactions such as flushing, skin reactions, 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 **INDAXOL** treatment. Patients should not be retreated until neutrophils recover to a level > 1 500/mm^3 and platelets recover to a level > 100 000/mm3. In cases of severe neutropenia (< 500 cells/mm^3) during a course of **INDAXOL**, 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 **INDAXOL** administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with **INDAXOL**. 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 **INDAXOL**, but generally do not require treatment. In severe cases **INDAXOL** 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 **INDAXOL** infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

When **INDAXOL** is used in combination with trastuzumab for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

Neurologic:

Cross-study comparison of neurotoxicity suggests that when **INDAXOL** is given in

combination with cisplatin, the incidence of severe neurotoxicity is more common at a **INDAXOL** dose of 175 mg/m2 given by 3-hour infusion (21 %), than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

INDAXOL contains ethanol 99.9%, 385 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.

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 **INDAXOL**.

Hepatic:

Patients with hepatic impairment may be at increased risk of toxicity particularly grade III-IV myelosuppression. Dose adjustment is recommended. Patients should be monitored closely for the development of profound myelosuppression.

Hepatic necrosis and hepatic encephalopathy leading to death have been reported. Elevations in alkaline phosphatase and AST (SGOT) have been reported.

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 medicine administration.

Fertility

Paclitaxel has been shown to decrease fertility in rats.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility (see section 4.6)

Paediatric Use

The safety and effectiveness of **INDAXOL** in children have not been established. There have been reports of central nervous system toxicity (including death) in a clinical trial in paediatric patients in which **INDAXOL** 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 **INDAXOL** vehicle given over a short infusion time. The use of concomitant antihistamines may intensify this effect. 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 **INDAXOL** for use in this population.

4.5 Interaction with other medicines and other forms of interaction

The recommended regimen of **INDAXOL** administration for the primary treatment of ovarian carcinoma is for **INDAXOL** to be given before cisplatin. When **INDAXOL** is given before cisplatin, the safety profile of **INDAXOL** is consistent with that reported for single medicine use. When **INDAXOL** was given after cisplatin, patients showed a more profound myelosuppression and an approximately 33 % decrease in paclitaxel clearance.

Medications concomitantly administered with **INDAXOL** (e.g., corticosteroids, antihistamines, and H2 antagonists) did not appear to interact adversely; however, possible interactions of **INDAXOL** with concomitantly administered medicines have not been formally investigated.

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

Plasma levels of doxorubicin and doxorubicinol 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 **INDAXOL** and doxorubicin when **INDAXOL** was administered BEFORE doxorubicin and using longer than recommended infusion times.

The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of a PK 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.

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

INDAXOL 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 INDAXOL, and to inform the treating medical practitioner immediately should this occur.

Pregnancy

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

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

Breastfeeding

Paclitaxel is contraindicated during lactation (see section 4.3). It is not known whether paclitaxel is excreted in human milk. Breastfeeding should be discontinued for the duration of paclitaxel therapy.

Fertility

Paclitaxel has been shown to decrease fertility in rats.

Male patients should seek advice regarding cryoconservation of sperm prior to treatment with paclitaxel because of the possibility of infertility.

4.7 Effects on ability to drive and use machines

INDAXOL has not been demonstrated to interfere with this ability. However, it should be noted that the medicinal product contains alcohol (see sections 4.4 and 6.1).

The ability to drive or to use machines may be decreased due to alcohol content of this medicinal product.

4.8 Undesirable effects

The frequency and severity of adverse events are generally similar between patients receiving **INDAXOL** for the treatment of ovarian, breast or lung carcinoma.

Unless otherwise noted, the following discussion refers to the overall safety database of patients with solid tumours treated with single medicine paclitaxel 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.

Haematologic toxicities: Bone marrow suppression was the major dose-limiting toxicity of **INDAXOL**. Neutropenia, the most important haematologic 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/mm3 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 **INDAXOL** dose and schedule.

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

Rare 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 **INDAXOL** therapy. The frequency and severity of HSR were not affected by the dose or schedule of **INDAXOL** 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 **INDAXOL** therapy.

Injection site reactions: During intravenous administration, injection site reactions were usually mild and consisted of localised oedema, pain, erythema, tenderness, and induration; on occasion, extravasation can result in cellulitis. Skin sloughing and/or peeling has been reported, sometimes related to extravasation. 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 paclitaxel therapy. If patients develop significant conduction abnormalities during **INDAXOL** administration, appropriate therapy should be administered, and continuous electrocardiographic monitoring should be performed during subsequent therapy with **INDAXOL**.

Gastrointestinal (GI) Toxicity: Mild to moderate nausea/vomiting, diarrhoea and mucositis (also reported as pharyngitis or chelitis) were reported very commonly by all patients. Mucositis was schedule dependent and occurred more frequently with the 24-hour than with the 3-hour infusion.

Rare reports of neutropenic enterocolitis (typhlitis), despite the co-administration of G-CSF, were observed in patients treated with paclitaxel alone and in combination with other chemotherapeutic medicines.

Unless otherwise noted, Table 1 below lists undesirable effects regardless of severity associated with the administration of single medicine paclitaxel and Table 2 lists additional undesirable effects reported in the post marketing surveillance of paclitaxel.

Table 1: Undesirable effects associated with the administration of **INDAXOL** in clinical studies

Infections and infestations:	Frequent: infection

	Less Frequent: septic shock
Blood and the lymphatic system disorders:	Frequent: myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, fever, bleeding Frequency unknown: febrile neutropenia
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, oedema, back pain, chills)
Nervous system disorders:	Frequent: neurotoxicity (mainly peripheral neuropathy)
Cardiac disorders:	Frequent: abnormal ECG, bradycardia Less Frequent: cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction
Vascular disorders:	Frequent: hypotension Less Frequent: hypertension, thrombosis, thrombophlebitis
Gastrointestinal disorders:	Frequent: nausea, vomiting, diarrhoea, mucosal inflammation
Skin and subcutaneous tissue disorders:	Frequent: alopecia, transient and mild nail and skin changes
Musculoskeletal, connective tissue and bone disorders:	Frequent: arthralgia, myalgia
General disorders and administration site conditions:	Frequent: injection site reactions (including localised oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis)
Investigations:	Frequent: severe elevation in AST (SGOT), severe elevation in alkaline phosphatase Less Frequent: severe elevation in bilirubin

Table 2: Additional undesirable effects reported during post marketing surveillance

Infections and infestations:	Pneumonia, sepsis, peritonitis
Blood and the lymphatic system disorders:	Acute myeloid leukaemia, myelodysplastic syndrome, disseminated intravascular coagulation
Immune system disorders: Metabolism and nutrition disorders:	Anaphylactic reactions (with fatal outcome), anaphylactic shock Anorexia, tumour lysis syndrome
Psychiatric disorders: Nervous system disorders:	Confusional state Motor neuropathy (with resultant distal weakness), autonomic neuropathy (resulting in paralytic ileus and orthostatic hypotension), grand mal seizures, convulsions, encephalopathy, dizziness, headache, ataxia
Eye disorders:	Reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received

Ear and labyrinth disorders:	higher doses than recommended, photopsia, visual floaters, macular oedema Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders:	Atrial fibrillation, supraventricular tachycardia, cardiac failure
Vascular disorders: Respiratory, thoracic and mediastinal disorders:	Shock, phlebitis Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough
Gastrointestinal disorders:	Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, pseudomembranous colitis, oesophagitis, constipation, ascites
Hepato-biliary disorders:	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)
Skin and subcutaneous tissue disorders:	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), scleroderma
General disorders and administration site conditions:	Asthenia, malaise, pyrexia, dehydration, oedema
Investigations:	Increase in blood creatinine

INDAXOL and cisplatin:

Cross-study comparison of neurotoxicity suggests that when **INDAXOL** is given in combinations with cisplatin, the incidence of severe neurotoxicity is more common at a **INDAXOL** dose of 175 mg/m2 given by 3-hour infusion (21 %) than at a dose of 135 mg/m^2 given by 24-hour infusion (3 %).

INDAXOL and Radiotherapy:

Radiation pneumonitis has been reported in patients receiving concurrent radiotherapy.

INDAXOL and trastuzumab:

When administered as a 3-hour infusion in combination with trastuzumab for the first line treatment of patients with metastatic breast cancer, the following events (regardless of relationship to **INDAXOL** or trastuzumab) were reported more frequently than with single medicine paclitaxel: heart failure, infection, chills, fever, cough, rash, arthralgia, tachycardia, diarrhoea, hypertonia, epistaxis, acne, herpes simplex, accidental injury, insomnia, rhinitis, sinusitis and injection site reaction. Some of these frequency differences may be due to the increased number and duration of treatments with **INDAXOL**/trastuzumab combination vs. single medicine paclitaxel.

Administration of trastuzumab in combination with paclitaxel in patients previously treated with anthracyclines resulted in an increased frequency and severity of cardiac dysfunction in comparison with patients treated with paclitaxel single medicine and rarely has been associated with death. In most cases, patients responded to appropriate medical treatment.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug 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 **INDAXOL** overdosage. The primary anticipated complications of overdosage would consist of bone marrow suppression, peripheral neurotoxicity and mucositis. Overdoses in paediatric patients may be associated with acute ethanol toxicity.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: Plant alkaloids and other natural products,taxanes ATC code: L01C D01

Paclitaxel is an antimicrotubule medicine 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. The initial rapid decline represents distribution to the peripheral compartment and elimination; the later phase is due, in part, to a relatively slow 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 courses. 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 paclitaxel 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 paclitaxel 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 metabolised 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 catalysed 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 doxorubicin and doxorubicinol may be increased when paclitaxel and doxorubicin are used in combination.

5.3 Preclinical safety data

The carcinogenic potential of paclitaxel has not been studied. However, paclitaxel is a potential carcinogenic and genotoxic agent, based upon its pharmacodynamic mechanism of action. Paclitaxel has been shown to be mutagenic in both in vitro and in vivo mammalian test systems.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid anhydrous

Ethanol 99.9%

Polyoxyl 35 Castor oil

6.2 Incompatibilities

Polyoxyethylated castor oil (Macrogolglycerol ricinoleate) can result in DEHP (di-(2-ethylhexyl)phthalate) leaching from plasticized 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 medicinal product must not be mixed with other medicinal products except those mentioned in in section 4.2

6.3 Shelf life

Unopened vial:

3 years

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 reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep vial in carton to protect from light

KEEP OUT OF REACH OF CHILDREN.

After first use any unused concentrate may be stored at or below 25^0 C for up to 28 days.

Solutions for infusion prepared as recommended in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets, are stable at ambient temperature (approximately 25^0 C) and lighting conditions for up to 27 hours.

6.5 Nature and contents of container

INDAXOL 30 / 100 / 300: Clear, colourless to pale yellow viscous, sterile, pyrogen free solution free from visible particles in 5 ml / 20 ml / 50 ml Tubular clear 20 mm collar flat bottom vial with 20mm flurotec coated chlorobutyl rubber stopper and sealed with 20mm aluminium flip-off seal of Raymond blue colour button in unit carton.

6.6 Special precautions for disposal of a used medicine

The product should be used immediately after opening.

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used. If no safety box is available, the equipment should be supplemented with a mask and protective glasses.

If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Discard after single use.

Discard any unused portion.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (Pty) Ltd

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

INDAXOL 30: 55/26/0437

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