PROFESSIONAL INFORMATION

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE

Accord Paclitaxel 30 (concentrate solution for infusion)

Accord Paclitaxel 100 (concentrate solution for infusion)

Accord Paclitaxel 300 (concentrate solution for infusion)

"This product is a sterile solution"

Warning: Accord Paclitaxel (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 **Accord Paclitaxel.** Patients receiving **Accord Paclitaxel** 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 **Accord Paclitaxel** should not be rechallenged with the medicine.

Accord Paclitaxel 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 **Accord Paclitaxel.**

The polyoxyethylated castor oil in **Accord Paclitaxel** 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 **Accord Paclitaxel** should be carried out by using non-plasticised PVC-containing equipment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

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

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

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

Excipients with known effect:

Contains anhydrous ethanol 39,1 % m/v and polyoxyl castor oil 527,0 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:

Accord Paclitaxel 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

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

Indication 2 and 3: Secondary treatment of ovarian carcinoma: Accord Paclitaxel 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 Accord Paclitaxel is 175 mg/m^2 administered intravenously over a period of 3 hours, with a 3 week interval between courses.

Accord Paclitaxel 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 Accord Paclitaxel is 175 mg/m^2 administered over a period of 3 hours; followed by a platinum compound, with a 3 week interval between courses. Accord Paclitaxel should not be re-administered until the neutrophil count is at least 1 500/mm^3 and the platelet count is at least 100 000/mm^3. Patients who experience severe neutropenia (neutrophil count <500/mm^3) or moderate to severe peripheral neuropathy should receive a dose reduction of 20 % for subsequent courses (see section 4.4).

The incidence and severity of neurotoxicity and haematological toxicity increases with dose. All patients must be premedicated prior to Accord Paclitaxel administration to reduce the risk of severe hypersensitivity reactions. Such premedications may be corticosteroids, antihistamines, and H_2 antagonists prior to Accord Paclitaxel administration, e.g. dexamethasone 20 mg orally approximately 12 and 6 hours before Accord Paclitaxel or 20 mg IV approximately 30-60 minutes prior to Accord Paclitaxel, and cimetidine 300 mg or ranitidine 50 mg, IV 30 to 60 minutes before Accord Paclitaxel. Accord Paclitaxel 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 Accord Paclitaxel dose (b)**
24 hour infusion		
< 2 x ULN and	≤ 1,5 mg/dl	135 mg/m^2
2-< 10 x ULN and	≤ 1,5 mg/dl	100 mg/m^2
< 10 x ULN and	1,6-7,5 mg/dl	50 mg/m^2
≥ 10 x ULN or	> 7,5 mg/dl	Not recommended
3 hour infusion		

< 10 x ULN and	≤ 1,25 x ULN	175 mg/m^2
< 10 x ULN and	1,26 – 2,0 x ULN	135 mg/m^2
< 10 x ULN and	2,01 – 5,0 x ULN	90 mg/m^2
≥ 10 x ULN or	> 5,0 ULN	Not recommended

(a) Differences in criteria for bilirubin levels between the 3 and 24 hour infusion are due to differences in clinical trial design.

(b) Dosage recommendations are for the first course of therapy: further dose reduction in subsequent courses should be based on individual tolerance.

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 Accord Paclitaxel in children has not been established (see section 4.4)

Method of administration

For intravenous use.

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

4.3 CONTRA-INDICATIONS:

- Accord Paclitaxel is contra-indicated in patients who have a history of severe hypersensitivity reactions to paclitaxel, ~~or~~ other medicines formulated with polyoxyethylated castor oil or to any of the excipients listed in section 6.1.
- Accord Paclitaxel should not be used in patients with baseline neutrophils < 1500 /mm^3.
- Pregnancy and lactation (see section 4.6).
- The safety and effectiveness of Accord Paclitaxel in children has not been established.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Accord Paclitaxel 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. Accord Paclitaxel should be administered as a diluted infusion. Accord Paclitaxel should be given before cisplatin when used in combination.

Patients should be pre-treated with corticosteroids, antihistamines and H_2 antagonists before receiving Accord Paclitaxel.

Hypersensitivity reactions

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 Accord Paclitaxel. These reactions are probably histamine-mediated. Rare fatal reactions have occurred in patients despite pre-treatment. In cases of severe hypersensitivity reactions, Accord Paclitaxel infusion should be immediately discontinued, symptomatic therapy should be initiated and the patient should not be rechallenged with the agent. Minor hypersensitivity reactions such as flushing, skin reactions, and not requiring treatment do not require interruption of therapy.

Bone marrow suppression

Bone marrow suppression (primary neutropenia) is the principal dose-limiting toxicity. Frequent monitoring of blood counts should be instituted during Accord Paclitaxel treatment. Patients should not be retreated until neutrophils recover to a level >1500/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 Accord Paclitaxel, 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 Accord Paclitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with Accord Paclitaxel. 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 Accord Paclitaxel but generally do not require treatment. In severe cases, Accord Paclitaxel 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 Accord Paclitaxel infusion, is recommended. Continuous cardiac monitoring is not required except for patients with serious conduction abnormalities.

Cases of myocardial infarction have been reported. Congestive heart failure has been reported typically in patients who have received other chemotherapy, notably anthracyclines. Patients may experience severe cardiovascular events possibly related to Accord Paclitaxel administration. Included are hypertension, venous thrombosis, ventricular tachycardia, and atrioventricular conduction block.

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

When Accord Paclitaxel is used in combination with doxorubicin or trastuzumab for treatment of metastatic breast cancer, monitoring of cardiac function is recommended.

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 medical practitioners 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, 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). For more details see professional information of trastuzumab or doxorubicin.

Neurologic

Neurological symptoms may occur following the first course and the frequency of symptoms may increase with increasing exposure to paclitaxel. Sensory symptoms have usually improved or resolved within several months of paclitaxel discontinuation. Pre-existing neuropathies resulting from prior therapies are not a contraindication for Accord Paclitaxel therapy.

Cross-study comparison of neurotoxicity suggests that when Accord Paclitaxel is given in combination with cisplatin 75 mg/m^2, the incidence of severe neurotoxicity is more common at an Accord Paclitaxel 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 moderate to severe symptomatology is unusual and requires a dose reduction of 20 % for all subsequent courses of Accord Paclitaxel.

Hepatic

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

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 Accord Paclitaxel 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 Accord Paclitaxel 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 Accord Paclitaxel 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 Accord Paclitaxel for use in this population.

Pseudomembranous colitis

Pseudomembranous colitis has been reported, rarely, including cases in patients who have not received concurrent antibiotic treatment. This reaction should be considered in the differential diagnosis of severe or persistent cases of diarrhoea occurring during or shortly after treatment with 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. Patients with visual impairment during paclitaxel treatment should seek a prompt and complete ophthalmologic examination. Discontinue paclitaxel treatment if a CME diagnosis is confirmed.

Excipients

Accord Paclitaxel contains dehydrated alcohol, 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.

Accord Paclitaxel contains polyoxyl castor oil which may cause severe allergic reactions.

4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Paclitaxel clearance is not affected by cimetidine premedication.

Cisplatin: The recommended regimen of Accord Paclitaxel administration for the primary treatment of ovarian carcinoma is for Accord Paclitaxel to be given before cisplatin. When Accord Paclitaxel is given before cisplatin, the safety profile of Accord Paclitaxel is consistent with that reported for single product use.

When Accord Paclitaxel 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 gynaecological cancers.

Ketoconazole: Medications concomitantly administered with Accord Paclitaxel (e.g. corticosteroids, antihistamines, and H_2 antagonists) did not appear to interact adversely; however, possible interactions of Accord Paclitaxel with concomitantly administered medications have not been formally investigated. Based on *in vitro* data, there is the possibility of the inhibition of Accord Paclitaxel metabolism in patients treated with ketoconazole. As a result, caution should be exercised when treating patients with Accord Paclitaxel when they are receiving ketoconazole as concomitant therapy.

Doxorubicin: Plasma levels of doxorubicin and doxorubicinol may be increased when Accord Paclitaxel and doxorubicin are used in combination. Sequence effects characterised by more profound neutropenic and stomatitis episodes, have been observed with combination use of Accord Paclitaxel and doxorubicin, when Accord Paclitaxel was administered before doxorubicin and using longer than recommended infusion times.

Active substances metabolised in the liver: The metabolism of paclitaxel is catalysed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical interaction studies, caution should be exercised when administering Accord Paclitaxel concomitantly with known substrates, inducers or inhibitors of these isoenzymes, e.g., ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, clopidogrel, cimetidine, ritonavir, saquinavir, indinavir, and_nelfinavir) because toxicity of 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.

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

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

Breastfeeding

It is not known whether Accord Paclitaxel is excreted in human milk.

Breast feeding should be discontinued for the duration of Accord Paclitaxel therapy.

Fertility

Accord Paclitaxel 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 medicine contains alcohol, which may impair the ability to drive or operate machines.

4.8 UNDESIRABLE EFFECTS

a. Summary of the safety profile

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

b. Tabulated list of adverse reactions

System organ class	Frequency	Adverse reaction
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, sepsis, pseudomembranous colitis
Blood and lymphatic system disorders	Frequent	Myelosuppression, neutropenia, anaemia, thrombocytopenia, leukopenia, bleeding
	Less Frequent	Febrile neutropenia, acute myeloid leukaemia, myelodysplastic syndrome
	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, angioedema, respiratory distress, generalised urticaria, oedema, back pain, chills, chest pain, tachycardia, abdominal pain, pain in extremity, diaphoresis, and hypertension), anaphylactic reactions (with fatal outcome), anaphylactic shock
	Frequency unknown	Bronchospasm
Metabolism and nutrition disorders	Less Frequent	Anorexia, dehydration
	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 Frequency unknown	Reversible optic nerve and/or visual disturbances (scintillating scotomata), particularly in patients who have received higher doses than recommended Macular oedema, photopsia, vitreous floaters
Ear and labyrinth disorders	Less Frequent	Hearing loss, tinnitus, vertigo, ototoxicity
Cardiac disorders	Frequent Less Frequent	Abnormal ECG, bradycardia Cardiomyopathy, asymptomatic ventricular tachycardia, tachycardia with bigeminy, AV block and syncope, myocardial infarction, cardiac failure, atrial fibrillation, supraventricular tachycardia
Vascular disorders	Frequent Less Frequent Frequency unknown	Hypotension, hypertension, thrombosis, thrombophlebitis Shock Phlebitis
Respiratory, thoracic and mediastinal disorders	Less Frequent	Dyspnoea, pleural effusion, respiratory failure, interstitial pneumonia, lung fibrosis, pulmonary embolism, cough

Gastro-intestinal disorders	Frequent Less Frequent	Nausea, vomiting, diarrhoea, mucosal inflammation. Bowel obstruction, bowel perforation, ischaemic colitis, pancreatitis, mesenteric thrombosis, neutropenic colitis oesophagitis, constipation, ascites
Hepato-biliary disorders	Less Frequent	Hepatic necrosis (with fatal outcome), hepatic encephalopathy (with fatal outcome)
Skin and subcutaneous tissue disorders	Frequent Less Frequent Frequency unknown	Alopecia, transient and mild nail and skin changes Pruritus, rash, erythema, 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). Palmar-plantar erythrodysesthesia syndrome
Musculoskeletal, connective tissue and bone disorders	Frequent Frequency unknown	Arthralgia, myalgia Systemic lupus erythematosus, scleroderma
General disorders and administration site conditions	Frequent	Mucosal inflammation, injection site reactions (including localised oedema,

	Less Frequent	pain, erythema, induration, on occasion extravasations can result in cellulitis). Asthenia, malaise, pyrexia, oedema
Investigations	Frequent Less Frequent	Severe elevation in AST (SGOT), severe elevation in alkaline phosphatase Severe elevation in bilirubin, increase in blood creatinine.

c. Description of selected adverse reactions

Unless otherwise noted, the following discussion refers to the overall safety database of 812 patients with solid tumours treated with single-agent Accord 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.

Haematological toxicities: Bone marrow suppression was the major dose-limiting toxicity of Accord Paclitaxel.

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 Accord Paclitaxel dose and schedule.

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

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

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

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

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 Accord Paclitaxel alone and in combination with other chemotherapeutic agents.

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

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse 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 Accord Paclitaxel 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.

In case of overdose, the patient should be closely monitored. Treatment should be directed at the primary anticipated toxicities.

Treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification: A 26 Cytostatic agents

Pharmacotherapeutic group: antineoplastic agents (taxanes), ATC code: L01C D01.

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

Kolliphor ELP (Polyoxyl 35 castor oil)

Anhydrous ethanol

6.2 Incompatibilities

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

Polyoxyl castor oil) can result in di-(2-ethylhexyl)phthalate [DEHP] leaching from plasticized polyvinyl chloride (PVC) containers, at levels which increase with time and concentration. Consequently, the preparation, storage, and administration of paclitaxel should be carried out in non-PVC-containing equipment such as glass, polypropylene, or polyolefin.

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. Other in-use storage times and conditions are the responsibility of the user.

After dilution:

Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2 – 8 °C and at 25 °C for 7 days when diluted in 5 % Dextrose Injection, and for 14 days when diluted in 0,9 % Sodium Chloride Injection, or 5 % Dextrose and 0,9 % Sodium Chloride Injection or 5 % Dextrose in Ringer's 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 children.

See section 6.3 for storage of unopened vials and diluted solutions.

6.5 Nature and contents of container

Accord Paclitaxel injection 6 mg/ml is presented as follows:

- **Accord Paclitaxel 30:** 5 ml filled in a 5 ml clear glass vial with an omniflex rubber stopper sealed with an aluminium seal and red coloured flip off top.
- **Accord Paclitaxel 100:** 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.
- **Accord Paclitaxel 300:** 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

Directions for use/handling: Handling: Caution should be exercised when handling Accord Paclitaxel. This includes all handling activity in clinical settings, pharmacies, store rooms 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 extravasations, it is advisable to closely monitor the injection site for possible infiltration during medicines administration.

Preparation for IV administration: Accord Paclitaxel must be diluted prior to infusion. Accord Paclitaxel 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. Chemical and physical in-use stability of the solution prepared for infusion has been demonstrated at 2 – 8 °C and at 25 °C for 7 days when diluted in 5 % Dextrose Injection, and for 14 days when diluted in 0,9 % Sodium Chloride Injection, or 5 % Dextrose and 0,9 % Sodium Chloride Injection or 5 % Dextrose in Ringer's Injection. There have been rare 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 Accord Paclitaxel since they can cause the stopper to collapse resulting in loss of sterile integrity of the Accord Paclitaxel solution. Parenteral medicines 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. Accord Paclitaxel should be administered through an in-line filter with a microporus 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-ethylhexyl)phthalate], which may be leached from plasticised PVC infusion bags or sets, diluted Accord Paclitaxel 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 Accord Paclitaxel should undergo disposal according to local guidelines for the handling of cytotoxic compounds.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Accord Healthcare (Pty) Ltd

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6 Coombe Place

Rivonia

Gauteng

South Africa

8. REGISTRATION NUMBER:

Accord Paclitaxel 30: 44/26/0377

Accord Paclitaxel 100: 44/26/0378

Accord Paclitaxel 300: 44/26/0379

9. DATE OF FIRST AUTHORISATION

2 March 2012

10. DATE OF REVISION OF THE TEXT

05 February 2015