PACKAGE INSERT FOR TAXOCAN

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

TAXOCAN 20 solution for infusion

TAXOCAN 80 solution for infusion

COMPOSITION

Each single dose vial of 2 ml contains 20 mg docetaxel anhydrous (10 mg/ml).

Each single dose vial of 8 ml contains 80 mg docetaxel anhydrous (10 mg/ml).

Inactive ingredients

Citric acid, macrogol, polysorbate 80.

Contains 23 % *v/v* dehydrated alcohol.

PHARMACOLOGICAL CLASSIFICATION

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties:

Docetaxel is an antineoplastic medicine which acts by promoting the assembly of tubulin into stable microtubules and inhibits their disassembly which leads to a marked decrease of free tubulin. The binding of docetaxel to microtubules does not alter the number of protofilaments.

Docetaxel has been shown *in vitro* to disrupt the microtubular network in cells, which is essential for vital mitotic and interphase cellular functions. Docetaxel was found to be cytotoxic *in vitro* against various murine and human tumour cell lines and against freshly excised human tumour cells in clonogenic assays.

Docetaxel achieves high intracellular concentrations with a long cell residence time. In addition, docetaxel was found to be active on some, but not all, cell lines overexpressing the para-glycoprotein which is encoded by the multi-medicine resistance gene. *In vivo,* docetaxel is schedule independent.

Pharmacokinetic properties:

The kinetic profile of docetaxel is dose independent and consistent with a three-compartment pharmacokinetic model with half-lives for the alpha, beta and gamma phases of 4 minutes, 36 minutes and 11,1 hours respectively. The late phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment.

Following the administration of 70 – 100 mg/m^2 doses given as one-hour infusions, a mean peak plasma level of 2,57 – 3,67 µg/ml was obtained with a corresponding AUC of 3,13 – 4,83 h·µg/ml. Mean values for total body clearance and steady-state volume of distribution were 21 ℓ/h/m^2 and 113 ℓ, respectively. Docetaxel is more than 95 % bound to plasma proteins.

Faecal excretion is the main route of elimination of docetaxel and its metabolites. The faecal and urinary excretions account for about 75 % and 6 % of the dose, respectively. Only a minor fraction of the dose is excreted as the parent substance. Based on *in vitro* studies, isoenzymes of the cytochrome P450 3A subfamily appear to be involved in docetaxel metabolism. Dexamethasone did not affect protein binding of docetaxel.

When used in combination, docetaxel does not influence the clearance of doxorubicin and the plasma levels of doxorubicinol (a doxorubicin metabolite). However, the clearance of docetaxel was increased.

Clearance of docetaxel in combination therapy with cisplatin, was similar to that observed following monotherapy.

The effect of capecitabine on the pharmacokinetics of docetaxel and *vice versa* showed no effect by capecitabine on the pharmacokinetics of docetaxel (C_{max} and AUC), and no effect by docetaxel on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.

No effect of prednisone on the pharmacokinetics of docetaxel was observed.

INDICATIONS

Breast cancer:

TAXOCAN, in combination with doxorubicin and cyclophosphamide, is indicated for the adjuvant treatment of patients with operable node-positive breast cancer.

TAXOCAN, in combination with doxorubicin, is indicated for the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition.

TAXOCAN monotherapy is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic therapy.

TAXOCAN, in combination with capecitabine, is indicated for the treatment of patients with locally advanced or metastatic breast cancer after failure of cytotoxic chemotherapy. Previous therapy should have included an anthracycline.

Non-small cell lung cancer:

TAXOCAN is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer, even after failure of prior platinum-based chemotherapy.

TAXOCAN, in combination with cisplatin, is indicated for the treatment of patients with unresectable, locally advanced or metastatic non-small cell lung cancer, in patients who have not previously received chemotherapy for this condition.

Ovarian cancer:

TAXOCAN is indicated, after failure of first-line or subsequent chemotherapy, for treatment of metastatic carcinoma of the ovary.

Prostate cancer:

TAXOCAN, in combination with prednisone or prednisolone, is indicated for the treatment of patients with androgen independent (hormone refractory) metastatic prostate cancer.

Head and neck cancer:

TAXOCAN, in combination with cisplatin and 5-fluorouracil, is indicated for the induction treatment of patients with locally advanced squamous cell carcinoma of the head and neck.

CONTRAINDICATIONS

- **TAXOCAN** is contraindicated in patients who have a history of hypersensitivity reactions to docetaxel or polysorbate 80 or any of the other ingredients in **TAXOCAN** (see **COMPOSITION**).
- **TAXOCAN** should not be used in patients with baseline neutrophil count of < 1 500 cells/mm^3.
- Pregnancy and lactation, as **TAXOCAN** is teratogenic in animals (see **PREGNANCY AND LACTATION**).
- Children, as the safe use of **TAXOCAN** has not been established.
- **TAXOCAN** should not be used in patients with severe liver impairment since there is no data available (see **WARNINGS AND SPECIAL PRECAUTIONS** and **DOSAGE AND DIRECTIONS FOR USE**).
- Contraindications for other medicines also apply when combined with **TAXOCAN**.

WARNINGS AND SPECIAL PRECAUTIONS

TAXOCAN should be administered under the supervision of a qualified medical practitioner experienced in the use of antineoplastic medicines.
Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with **TAXOCAN** therapy is increased in patients with abnormal liver function and in patients receiving higher doses.

TAXOCAN should generally not be given to patients with serum bilirubin levels > upper limit of normal (ULN), or to patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase levels > 2,5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity and toxic death.

Patients with isolated elevations of transaminase > 1,5 x ULN also had a higher rate of febrile neutropenia grade 4, but did not have an increased incidence of toxic death. Bilirubin, AST or ALT and alkaline phosphatase values should be obtained prior to each cycle of **TAXOCAN** therapy and reviewed by the treating healthcare practitioner.

TAXOCAN therapy should not be given to patients with neutrophil counts of < 1 500 cells/mm^3.

In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving **TAXOCAN**.

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or generalised rash/erythema occurred in patients who received the recommended 3-day dexamethasone premedication.

Hypersensitivity reactions requiring discontinuation of **TAXOCAN** were reported in a small percentage of patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

TAXOCAN must not be given to patients who have a history of severe hypersensitivity reactions to **TAXOCAN** or to other medicines formulated with polysorbate 80.

Severe fluid retention occurred in a number of patients despite use of a 3-day dexamethasone premedication regimen. It was characterised by one or more of the following events: poorly tolerated peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade or pronounced abdominal distension (due to ascites).

The use of **TAXOCAN** should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist. Since significant hypersensitivity reactions may occur, appropriate supportive equipment should be available. During the infusion, it is recommended that vital functions should be closely monitored. Premedication consisting of an oral corticosteroid (see below for prostate) such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **TAXOCAN** administration, unless contraindicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The pre-treatment regimen for prostate cancer is oral dexamethasone 8 mg, administered 12 hours, 3 hours and 1 hour before the **TAXOCAN** regimen.

Haematology:

Neutropenia is the most frequent adverse reaction of **TAXOCAN** and occurs in almost all patients. Severe neutropenia (grade 3 – 4) occurs in a large percentage of patients on combination therapy with doxorubicin. Neutrophil nadirs occur at a median of 7 days but this interval may be shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving **TAXOCAN**. Patients should be retreated with **TAXOCAN** only after neutrophils recover to a level > 1 500 cells/mm^3 (see **DOSAGE AND DIRECTIONS FOR USE**).

In the case of severe neutropenia (< 500 cells/mm^3 for seven days or more) during a course of **TAXOCAN** therapy, a reduction in dose for subsequent courses of therapy and the use of appropriate symptomatic measures are recommended.

In patients treated with **TAXOCAN** in combination with cisplatin and 5-fluorouracil (TCF), febrile neutropenia and neutropenic infection occurred at lower rates when patients received prophylactic G-CSF. Patients treated with TCF should receive prophylactic G-CSF to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TCF should be closely monitored.

In patients treated with **TAXOCAN** in combination with doxorubicin and cyclophosphamide (TAC), febrile neutropenia and/or neutropenic infection occurred at lower rates when patients received primary G-CSF prophylaxis. Primary G-CSF prophylaxis should be considered in patients who receive adjuvant therapy

with TAC for breast cancer to mitigate the risk of complicated neutropenia (febrile neutropenia, prolonged neutropenia or neutropenic infection). Patients receiving TAC should be closely monitored.

Hypersensitivity reactions:

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. The most frequently reported symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and drug fever or chills. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of **TAXOCAN,** thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require interruption of therapy. However, more severe reactions, such as hypotension with a reduction of more than 20 mm Hg, bronchospasm or generalised rash/erythema require immediate discontinuation of the infusion and appropriate symptomatic therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with **TAXOCAN**.

Fluid retention:

Events such as peripheral oedema, pleural effusion, pericardial effusion, ascites, increased capillary permeability and weight gain have been reported. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more after 4 cycles or a cumulative dose > 400 mg/m^2.

Fluid retention is cumulative in incidence and severity. The onset of moderate and severe retention is delayed and less frequent in patients with premedication compared with patients without premedication. However, it has been reported in some patients during the early courses of therapy.

A premedication consisting of a corticosteroid such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **TAXOCAN** administration, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions (see **DOSAGE AND DIRECTIONS FOR USE**).

Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely.

Respiratory disorders:

Acute respiratory distress syndrome, interstitial pneumonia/pneumonitis, interstitial lung disease, pulmonary fibrosis and respiratory failure have been reported and may be associated with fatal outcome. Cases of radiation pneumonitis have been reported in patients receiving concomitant radiotherapy.

If new or worsening pulmonary symptoms develop, patients should be closely monitored, promptly investigated, and appropriately treated. Interruption of **TAXOCAN** therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming **TAXOCAN** treatment must be carefully evaluated.

Patients with liver impairment:

In patients treated with **TAXOCAN** at 100 mg/m^2 who have serum transaminase levels (ALT and/or AST) greater than 1,5 times the upper limit of the normal range (ULN) concurrent with serum alkaline phosphatase levels greater than 2,5 times the upper limit of the normal range (ULN), there is a higher risk of developing severe adverse reactions such as toxic deaths, including sepsis and gastrointestinal haemorrhage which can be fatal, febrile neutropenia, infections, thrombocytopenia, stomatitis and asthenia. Therefore, the recommended dose of **TAXOCAN** in patients with elevated liver function tests (LFTs) is 75 mg/m^2 and LFTs should be measured at baseline and before each cycle (see **DOSAGE AND DIRECTIONS FOR USE**).

For patients with serum bilirubin levels > ULN and/or ALT and AST > 3,5 times the ULN concurrent with serum alkaline phosphatase levels > 6 times the ULN, no dose reduction can be recommended and **TAXOCAN** should not be used unless strictly indicated.

Patients with renal impairment:

There are no data available in patients with severely impaired renal function treated with **TAXOCAN**.

Cutaneous reactions:

Localised skin erythema of the extremities (palms of the hands and soles of the feet), with oedema followed by desquamation, has been observed. This type of toxicity can lead to the interruption or discontinuation of treatment.

Nervous system:

The development of severe peripheral neurotoxicity including paraesthesia, dysaesthesia and pain has been observed in patients and requires a reduction of dose. When symptoms persist, treatment should be stopped.

Elderly patients:

An analysis of safety data in patients equal to or greater than 60 years of age treated with **TAXOCAN** and capecitabine combination therapy, showed an increase in the incidence of treatment-related grade 3 and 4 adverse events, treatment-related serious adverse events and early withdrawals from treatment due to adverse events compared to patients less than 60 years of age. In patients treated with **TAXOCAN** every three weeks the incidence of anaemia, infection, nail changes, anorexia and weight loss occurred at a rate ≥ 10 % in patients who were 65 years of age.

Eyes:

Excessive tear formation (epiphora), severe enough to interfere with reading and driving has been experienced in patients treated with **TAXOCAN**. Epiphora are more severe and occur more frequently in patients receiving **TAXOCAN** weekly. Epiphora is generally reversible 4 – 6 weeks after stopping **TAXOCAN** treatment.

Cystoid macular oedema (CMO) has been reported in patients treated with **TAXOCAN**. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, **TAXOCAN** treatment should be discontinued and appropriate treatment initiated.

Dehydration:

Occurrences of dehydration as a consequence of gastrointestinal events, gastrointestinal perforation, ischaemic colitis, colitis and neutropenic enterocolitis may occur (see **SIDE EFFECTS**).

Others:

Contraceptive measures must be taken during, and for at least three months after cessation of therapy.

Additional cautions for use in adjuvant treatment of breast cancer:

Complicated neutropenia:

For patients who experience complicated neutropenia (prolonged neutropenia, febrile neutropenia or infection), G-CSF and dose reduction should be considered.

Leukaemia:

In the **TAXOCAN**, doxorubicin and cyclophosphamide (TAC) treated patients, the risk of delayed myelodysplasia or myeloid leukaemia requires haematological follow-up.

Gastrointestinal reactions:

Symptoms such as early abdominal pain and tenderness, fever, diarrhoea, with or without neutropenia, may be early manifestations of serious gastrointestinal toxicity and should be evaluated and treated promptly.

Congestive heart failure:

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow-up period.

Elderly patients:

There are limited data available in patients > 70 years of age on **TAXOCAN** use in combination with doxorubicin and cyclophosphamide.

In elderly patients treated with **TAXOCAN** every three weeks, the incidence of related nail changes occurred at a rate ≥ 10 % higher in patients who were 65 years of age or older compared to younger patients. The incidence of related fever, diarrhoea, anorexia, and peripheral oedema occurred at rates ≥ 10 % higher in patients who were 75 years of age or older versus less than 65 years.

Effects on ability to drive and use machines:

The amount of alcohol in **TAXOCAN** may impair the patient's ability to drive or use machines. **TAXOCAN** can also cause excessive tear formation which may interfere with driving.

Patients should be advised not to drive or operate machines until it is established that their ability to perform such activities is not affected.

Alcohol

TAXOCAN contains 23 % *v/v* dehydrated alcohol (see **COMPOSITION** and **Effects on ability to drive and use machines** above). **TAXOCAN** may be harmful for those suffering from alcoholism. The amount of alcohol should be taken into account in high-risk groups, such as patients with liver disease or other diseases affecting the central nervous system (e.g. epilepsy).

The amount of alcohol in **TAXOCAN** may alter the effects of other medicines.

INTERACTIONS

There have been no formal clinical studies to evaluate the interactions of **TAXOCAN**.

In vitro studies have shown that the metabolism of **TAXOCAN** may be modified by the concomitant administration of medicines which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450 3A, such as ciclosporin, tacrolimus, cyclophosphamide, midazolam, ketoconazole, erythromycin and troleandomycin. As a result, caution should be exercised when treating patients with these medicines as concomitant therapy, since there is a potential for a significant interaction.

In combination with CYP3A4 inhibitors, the occurrence of **TAXOCAN** side effects may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a dose reduction of **TAXOCAN** may be suitable during treatment.

TAXOCAN is highly protein bound (> 95 %). Although the possible *in vivo* interaction of **TAXOCAN** with concomitantly administered medication has not been investigated formally, *in vitro* interactions with tightly protein-bound medicines such as erythromycin, diphenhydramine, propranolol, propafenone, phenytoin, salicylate, sulfamethoxazole and sodium valproate did not affect protein binding of **TAXOCAN**. In addition, dexamethasone did not affect protein binding of **TAXOCAN**. **TAXOCAN** did not influence the binding of digoxin.

In the doxorubicin/**TAXOCAN** combination, the clearance of **TAXOCAN** was increased.

PREGNANCY AND LACTATION

Pregnancy and lactation are contraindicated, as **TAXOCAN** is teratogenic in animals (see **CONTRAINDICATIONS**).

DOSAGE AND DIRECTIONS FOR USE

The use of **TAXOCAN** should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a medical practitioner qualified in the use of anticancer chemotherapy.

TAXOCAN should be administered by intravenous (IV) infusion only.

Dosage:

For breast, non-small cell lung, ovarian, and head and neck cancers, premedication consisting of an oral corticosteroid, such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days starting 1 day prior

to **TAXOCAN** administration, unless contraindicated, can be used. Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg, administered 12 hours, 3 hours and 1 hour before the **TAXOCAN** infusion. Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

TAXOCAN is administered as a one-hour infusion every three weeks.

Care should be taken with administration of the infusion to avoid extravasation.

Breast cancer:

In the adjuvant treatment of operable node-positive breast cancer, the recommended dose of **TAXOCAN** is 75 mg/m^2 administered one hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for 6 cycles (see also **Dose adjustments during treatment** below).

In first-line treatment, **TAXOCAN** 75 mg/m^2 is given in combination therapy with doxorubicin (50 mg/m^2).

For the second-line treatment of breast cancer the recommended dosage of **TAXOCAN** therapy is 100 mg/m^2 in monotherapy.

In combination with capecitabine, the recommended dose of **TAXOCAN** is 75 mg/m^2 every three weeks, combined with capecitabine at 1 250 mg/m^2 twice daily (within 30 minutes after a meal) for two weeks followed by a one week rest period. For capecitabine dose calculation according to body surface area, see capecitabine package insert.

Non-small cell lung cancer (NSCLC):

In combination therapy (chemotherapy naïve patients):

The recommended dose regimen is **TAXOCAN** 75 mg/m^2 immediately followed by cisplatin 75 mg/m^2 over 30 – 60 minutes.

In monotherapy (for previously treated patients):

The recommended dosage of **TAXOCAN** therapy is 100 mg/m^2 as a single medicine.

Ovarian cancer:

The recommended dosage of **TAXOCAN** therapy is 100 mg/m^2.

Prostate cancer:

The recommended dose of **TAXOCAN** is 75 mg/m^2. Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

Patients should be observed closely, especially during the first and second infusion of **TAXOCAN**, because of the risk of hypersensitivity reactions.

Head and neck cancer:

For the induction treatment of locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), the recommended dose of **TAXOCAN** is 75 mg/m^2 as a 1-hour infusion followed by cisplatin 75 mg/m^2 over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m^2 per day for five days. This regimen is administered every 3 weeks for 4 cycles. Following chemotherapy, the patient should receive radiotherapy.

Patients must receive premedication with anti-emetics and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for neutropenic infections should be administered. For cisplatin and 5-fluorouracil dose modifications, see local package insert.

Dose adjustments during treatment:

General:

Only the medical practitioner can modify the schedule of administration.

TAXOCAN should be administered when the neutrophil count is ≥ 1 500 cells/mm^3. In patients who experienced either febrile neutropenia, neutrophil < 500 cells/mm^3 for more than one week, severe or

cumulative cutaneous reactions or severe peripheral neuropathy during **TAXOCAN** therapy, the dose of **TAXOCAN** should be reduced from 100 mg/m^2 to 75 mg/m^2 and/or from 75 to 60 mg/m^2. If the patient continues to experience these reactions at 60 mg/m^2, the treatment should be discontinued.

*Combination therapy with **TAXOCAN** for NSCLC:*

For patients who are dosed initially at **TAXOCAN** 75 mg/m^2 in combination with cisplatin and whose nadir of platelet count during the previous course of therapy is < 25 000 cells/mm^3, or in patients who experience febrile neutropenia, or in patients with serious non-haemotological toxicities, the **TAXOCAN** dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see package insert.

*Combination therapy with **TAXOCAN** for breast cancer:*

Patients who received adjuvant therapy for breast cancer and who experience febrile neutropenia may benefit from receiving G-CSF in all subsequent cycles. If G-CSF is not used, the **TAXOCAN** dose should be reduced from 75 to 60 mg/m^2.

For capecitabine dose modifications, see capecitabine package insert.

For patients developing the first appearance of a grade 2 toxicity, which persists at the time of the next **TAXOCAN**/capecitabine treatment, delay treatment until resolved to grade 0-1, and resume at 100 % of the original dose.

For patients developing the second appearance of a grade 2 toxicity, or the first appearance of a grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to grade 0-1, then resume treatment with **TAXOCAN** 55 mg/m^2.

For any subsequent appearances of toxicities, or any grade 4 toxicities, discontinue the **TAXOCAN** dose.

Special populations:

Patients with hepatic impairment:

For **TAXOCAN** dose modifications due to hepatic impairment see **WARNINGS AND SPECIAL PRECAUTIONS**.

Patients with bilirubin > ULN should generally not receive **TAXOCAN**. Also, patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase > 2,5 x ULN, should generally not receive **TAXOCAN** (see **CONTRAINDICATIONS**).

Children:

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

Elderly:

Based on a population pharmacokinetic analysis, there are no special instructions for use in the elderly. For capecitabine dosage reduction when combined with **TAXOCAN**, see capecitabine package insert.

Recommendations for safe handling:

Handling precautions for cytostatic medicines should be followed:

- Only trained personnel should handle the antineoplastic medicine in a designated area.
- **TAXOCAN** is an antineoplastic medicine and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing **TAXOCAN** infusion solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If **TAXOCAN** should come into contact with the skin, wash immediately and thoroughly with soap and water. If **TAXOCAN** should come into contact with the eyes or mucous membranes wash immediately and thoroughly with water.
- The cytotoxic preparation must not be handled by pregnant staff.
- Adequate care and precautions should be taken in the disposal of items used to dilute **TAXOCAN**.
- **TAXOCAN** requires dilution prior to administration. Please follow preparation instructions provided below.

Dilution for infusion:

- Aseptically withdraw the required amount of **TAXOCAN** solution with a calibrated syringe and inject into a 250 ml infusing bag or bottle of either 0,9 % sodium chloride intravenous infusion or 5 % dextrose intravenous infusion to produce a final concentration of 0,3 to 0,74 mg/ml. If a dose greater than 200 mg **TAXOCAN** is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/ml is not exceeded.
- Thoroughly mix the infusion by manual rotation.
- Do not admix with other medications.
- **TAXOCAN** infusion is compatible with commonly available administration sets, including PVC sets.
- **TAXOCAN** should be visually inspected for particulate matter or discolouration prior to administration.
- If the **TAXOCAN** solution or dilution for infusion is not clear or appears to have precipitation, it should be discarded.

The **TAXOCAN** dilution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature and lighting conditions. Administration should be completed within 4 hours from the start of the preparation of the solution.

From a microbiological point of view, the diluted product should be used immediately after preparation. 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 – 8 °C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

SIDE EFFECTS

TAXOCAN 100 mg/m^2 and 75 mg/m^2 or TAXOCAN 75 mg/m^2 in combination with doxorubicin and cisplatin:

Infections and infestations:

Frequent: infections

Blood and lymphatic system disorders:

Frequent: anaemia, neutropenia, febrile neutropenia, thrombocytopenia

Less frequent: bleeding episodes, bone marrow suppression

Bleeding episodes may be associated with severe thrombocytopenia (< 50 000 cells/mm^3).

Immune system disorders:

Frequent: anaphylactic reactions, hypersensitivity reactions

Metabolism and nutrition disorders:

Frequent: anorexia

Nervous system disorders:

Frequent: neurosensory signs characterised by paraesthesia, dysaesthesia or pain including burning, neuromotor events mainly characterised by weakness

Less frequent: convulsions, transient loss of consciousness

Eye disorders:

Less frequent: lacrimal duct obstruction resulting in excessive tearing, lacrimation with or without conjunctivitis, transient visual disturbances

Cardiac disorders:

Frequent: cardiac dysrhythmia, heart failure

Less frequent: pericardial effusion, myocardial infarction

Vascular disorders:

Frequent: hypotension

Less frequent: hypertension, venous thromboembolic events

Respiratory, thoracic and mediastinal disorders:

Less frequent: dyspnoea

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, vomiting, constipation, stomatitis.

Less frequent: colitis, gastrointestinal bleeding, gastrointestinal perforation, ileus, intestinal obstruction, ischaemic colitis, neutropenic enterocolitis, abdominal pain, oesophagitis, taste perversion

Hepato-biliary disorders:

Less frequent: hepatitis, ascites

Skin and subcutaneous tissue disorders:

Frequent: cutaneous reaction, alopecia

Less frequent: severe cutaneous reaction, nail changes, erythema multiforme, Stevens-Johnson syndrome, a rash including localised eruptions mainly on the feet and hands, but also on the arms, face or thorax and frequently associated with pruritus

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia or myalgia

General disorders and administrative site conditions:

Frequent: asthenia, fever, infusion site reactions, pain, fluid accumulation

Generalised or localised pain (including chest pain without any cardiac or respiratory involvement.

Infusion site reactions may consist of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Investigations:

Frequent: increased serum level of bilirubin, increased serum levels of AST, ALT and alkaline phosphatase

Less frequent: increased capillary permeability.

Combination therapy with TAXOCAN in the adjuvant treatment of breast cancer:

Clinically important treatment related adverse events in patients receiving **TAXOCAN** 75 mg/m^2 in combination with doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2:

Infections and infestations:

Frequent: infections

Blood and lymphatic system disorders:

Frequent: anaemia, neutropenia, thrombocytopenia, febrile neutropenia, neutropenic infection

Less frequent: lymphoedema, leukaemia

Immune system disorders:

Frequent: hypersensitivity reactions

Metabolism and nutrition disorders:

Frequent: anorexia, weight gain or loss

Nervous system disorders:

Frequent: sensory neuropathy, motor neuropathy, neuro-cerebellar and neuro-cortical disorders

Less frequent: syncope

Eye disorders:

Frequent: lacrimation disorder, conjunctivitis

Cardiac disorders:

Frequent: cardiac dysrhythmia, congestive heart failure

Vascular disorders:

Frequent: hypotension, vasodilatation

Less frequent: phlebitis

Respiratory, thoracic and mediastinal disorders:

Frequent: cough

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, stomatitis, vomiting, taste perversion, constipation, abdominal pain

Less frequent: colitis, enteritis, large intestine perforation

Skin and subcutaneous tissue disorders:

Frequent: alopecia, skin toxicity, nail disorders

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia, myalgia

Reproductive system and breast disorders:

Frequent: amenorrhoea

General disorders and administrative site conditions:

Frequent: asthenia, fever in absence of infection, peripheral oedema.

Combination therapy with TAXOCAN and capecitabine for breast cancer:

Infections and infestations:

Frequent: oral candidiasis, urinary tract infection, neutropenic sepsis, tonsillitis, upper respiratory tract infection, herpes simplex, herpes zoster, cellulitis, cystitis, pharyngitis, pneumonia, fungal infection, laryngitis, localised infection, lower respiratory tract infection, nail bed infection, otitis media, sepsis, tooth abscess, bladder infection, bronchitis, bronchopneumonia, pseudomembranous colitis, erysipelas, eye infection, gastrointestinal infection, gingivitis, otitis media, peritonsillar abscess, *Pseudomonas* infection, skin and subcutaneous tissue abscess, skin *Candida*, vaginal candidiasis, vaginitis, vulvitis, vulvovaginitis

Blood and lymphatic system disorders:

Frequent: neutropenia, anaemia, thrombocytopenia, leucopenia, decreased white blood cell count, agranulocytosis, increased international normalised ratio (INR), leucocytosis, decreased prothrombin, lymphoedema

Immune system disorders:

Frequent: anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders:

Frequent: anorexia, decreased appetite, dehydration, decreased or increased weight, hyperlipidaemia, hypokalaemia, hypomagnesaemia

Psychiatric disorders:

Frequent: depression, anxiety, confusion, delusion, mood alteration, hoarseness, throat tightness

Nervous system disorders:

Frequent: taste disturbance, paraesthesia, dizziness, headache, peripheral neuropathy, insomnia, hypaesthesia, polyneuropathy, syncope, hyperaesthesia, parosmia,

sedation, ataxia, migraine, movement disorder, nightmares, sensory disturbance, vasovagal attack, neurotoxicity, neuralgia

Eye disorders:

Frequent: increased lacrimation, eye irritation, conjunctivitis, xerophthalmia, eye disorder, ocular hyperaemia, red eye, blurred vision, reduced visual acuity and visual disturbance

Ear and labyrinth disorders:

Frequent: earache, impaired hearing, tinnitus, vertigo

Cardiac disorders:

Frequent: tachycardia, palpitations, supraventricular tachycardia, atrial fibrillation, cardiac murmur, extrasystoles, pericardial effusion, pulmonary oedema, chest pressure sensation

Vascular disorders:

Frequent: flushing, venous phlebitis, thrombophlebitis, hypotension, hypertension, postural hypotension, vein disorder, superficial venous phlebitis, hyperaemia, hot flushes

Respiratory, thoracic and mediastinal disorders:

Frequent: sore throat, dyspnoea, cough, epistaxis, rhinorrhoea, productive cough, nasopharyngitis, rhinitis, chest wall pain, exertional dyspnoea, nasal ulcer, nasal passage irritation, throat swelling, chest tightness, dyspnoea, haemoptysis, nasal dryness, pleural effusion, seasonal rhinitis, sinus congestion, sinusitis, chest pain (non-cardiac)

Gastrointestinal disorders:

Frequent: stomatitis, diarrhoea, nausea, vomiting, constipation, abdominal pain (general, upper and lower), dyspepsia, dry mouth, abdominal distension, oral pain, dysphagia, flatulence, haemorrhoids, cheilitis, haemorrhagic diarrhoea, dry throat, feeling of gastrointestinal fullness, frequent motions, gastritis, gingival bleeding, glossodynia, haematemesis, mouth haemorrhage, oesophageal pain, rectal bleeding, retching, tenesmus, tongue oedema, abdominal tenderness, defaecation urgency, eructation, discoloured faeces, hiatus hernia, ileus, lip ulceration, loose stools, melaena, necrotising enterocolitis, oesophageal ulcer, oesophagitis, oral mucosal eruption, salivary hypersecretion, tongue discolouration, tongue ulceration, oesophageal burn, hiccups

Hepato-biliary disorders:

Frequent: ascites, hepatic coma, hepatic failure, abnormal hepatic function, hepatotoxicity, jaundice, hyperbilirubinaemia

Skin and subcutaneous tissue disorders:

Frequent: hand-foot syndrome (grade 3 only), alopecia, nail disorder, dermatitis, rash erythema, nail discolouration, onycholysis, dry skin, facial oedema, exfoliative dermatitis, pigmentation disorder, pruritus, skin hyperpigmentation, pruritic rash, red face, skin discolouration, blister, increased sweating, acne, brittle nails, eczema, eyelid oedema, localised exfoliation, localised skin reaction, nail dystrophy, paronychia, macular rash, maculopapular rash, papular rash, pustular rash, skin inflammation, skin necrosis, skin ulcer, sloughing of skin, keratosis, subcutaneous nodule and toxicoderma, palmar erythema

Musculoskeletal, connective tissue and bone disorders:

Frequent: arthralgia, myalgia, back pain, bone pain, muscle cramps, musculoskeletal pain, joint stiffness, muscle spasms, muscle weakness, pain in limb, rigors, loin pain, pain in the face, shoulder blade pain

Renal and urinary disorders:

Frequent: dysuria, haematuria, oliguria, urinary incontinence, enuresis, nocturia, renal failure, urethral pain

Reproductive system and breast disorders:

Frequent: Breast pain, pelvic pain, vaginal discharge, vaginal discomfort, vaginal dryness, vaginal haemorrhage and vulval disorder

General disorders and administrative site conditions:

Frequent: asthenia, pyrexia, fatigue, weakness, lethargy, pain, oedema, peripheral oedema, upper limb oedema, lower limb oedema, influenza-like illness, injection site reaction, fluid retention, malaise, swelling, feeling jittery, clamminess, extravasation, inflammatory oedema reaction, injection site infection, mucous membrane disorder

Investigations:

Frequent: decreased haemoglobin.

Combination therapy with TAXOCAN in prostate cancer patients:

Clinically important treatment related adverse events in patients with prostate cancer who received **TAXOCAN** 75 mg/m^2 every three weeks in combination with prednisone or prednisolone 5 mg twice daily:

Blood and lymphatic system disorders:

Frequent: anaemia, neutropenia, infection, thrombocytopenia, febrile neutropenia

Immune system disorders:

Frequent: allergic reactions

Metabolism and nutrition disorders:

Frequent: fluid retention, anorexia

Nervous system disorders:

Frequent: sensory neuropathy, motor neuropathy, taste disturbances

Eye disorders:

Frequent: tearing

Cardiac disorders:

Frequent: decreased cardiac left ventricular function

Respiratory, thoracic and mediastinal disorders:

Frequent: epistaxis, cough, dyspnoea

Gastrointestinal disorders:

Frequent: nausea, diarrhoea, stomatitis/pharyngitis, vomiting

Skin and subcutaneous tissue disorders:

Frequent: alopecia, nail changes, rash/desquamation

Musculoskeletal, connective tissue and bone disorders:

Frequent: myalgia, arthralgia

General disorders and administrative site conditions:

Frequent: fatigue.

Combination therapy with TAXOCAN in head and neck cancer:

Clinically important treatment related adverse events in patients receiving **TAXOCAN** 75 mg/m^2 in combination with cisplatin and 5-fluorouracil:

Infections and infestations:

Frequent: infections, neutropenic infection

Blood and lymphatic system disorders:

Frequent: anaemia, neutropenia, febrile neutropenia, thrombocytopenia

Immune system disorders:

Frequent: allergic reactions

Metabolism and nutrition disorders:

Frequent: weight gain, weight loss, anorexia

Nervous system disorders:

Frequent: neurosensory signs characterised by paraesthesia, dysaesthesia or pain including burning, dizziness, altered taste and sense of smell

Eye disorders:

Frequent: tearing, conjunctivitis

Ear and labyrinth disorders:

Frequent: altered hearing

Cardiac disorders:

Frequent: myocardial ischaemia

Less frequent: dysrhythmia

Vascular disorders:

Frequent: venous disease

Gastrointestinal disorders:

Frequent: diarrhoea, nausea, vomiting, stomatitis, constipation, oesophagitis, dysphagia, odynophagia, gastrointestinal pain, cramping, heartburn, gastrointestinal bleeding

Skin and subcutaneous tissue disorders:

Frequent: alopecia, rash/itch, dry skin, desquamation

Musculoskeletal, connective tissue and bone disorders:

Frequent: myalgia

General disorders and administrative site conditions:

Frequent: lethargy, cancer pain, fever in absence of infection, oedema

Less frequent: infusion site conditions, pain.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

See **SIDE EFFECTS**.

Symptoms of overdose:

In case of overdose, the patient should be kept in a specialised unit and vital functions closely monitored. There is no known antidote for **TAXOCAN** overdosage. The primary anticipated complications of overdosage would consist of neutropenia, mucositis, cutaneous reactions and paraesthesia.

Treatment of overdose:

Patients should receive therapeutic G-CSF as soon as possible after discovery of overdose. Other appropriate symptomatic measures should be taken, as needed.

IDENTIFICATION

Clear, colourless to pale yellow solution, free from visible particles.

PRESENTATION

TAXOCAN 20 is packed into 2 ml, 13 mm Type 1, transparent, clear tubular glass vials, with grey sil 1 closure and 13 mm aluminium seal with a green flip off top.

Each vial is packed into an outer carton.

TAXOCAN 80 is packed into 10 ml, 20 mm Type 1, transparent, clear tubular glass vials, with grey sil 1 closure and 20 mm aluminium seal with a red flip off top.

Each vial is packed into an outer carton.

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Protect from light.

Keep the vial in the outer carton until required for use.

Discard any unused portion.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS

TAXOCAN 20: 46/26/0265

TAXOCAN 80: 46/26/0264

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

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