This submission: Closing sequence
Date of submission: 05 March 2026

PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TAXOCAN 20 solution for infusion

TAXOCAN 80 solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

Sugar free.

Excipient with known effect:

Each mL solution contains 0,23 mL dehydrated alcohol (23 % *v/v*).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic 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 inoperable locally advanced squamous cell carcinoma of the head and neck.

Gastric adenocarcinoma

TAXOCAN in combination with cisplatin and 5-fluorouracil is indicated for the palliative treatment of patients with advanced gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction, who have not received prior chemotherapy for advanced disease.

4.2 Posology and method of administration

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.

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

Posology

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.

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 professional information leaflet.

Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of TAXOCAN is 75 mg/m^2 as a 1-hour infusion, followed by cisplatin 75 mg/m^2, as a 1 to 3 hour infusion (both on day 1 only), followed by 5-fluorouracil 750 mg/m^2 per day given as a 24-hour continuous infusion for 5 days, starting at the end of the cisplatin infusion. Treatment is repeated every three weeks. Patients must receive premedication with anti-emetics and appropriate hydration for cisplatin administration. Prophylactic G-CSF should be used to mitigate the risk of haematological toxicities (see Dosage adjustments during treatment below).

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 mg/m² to 60 mg/m². If the patient continues to experience these reactions at 60 mg/m², 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-haematological toxicities, the TAXOCAN dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see the respective professional information leaflet.

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 mg/m^2 to 60 mg/m^2. Patients who experience grade 3 or 4 stomatitis or oesophagitis should have their dose decreased to 60 mg/m^2 while the dose of other concomitant chemotherapy should also be reduced. TAXOCAN should be stopped and not administered again in cases of grade 4 stomatitis or oesophagitis.

For capecitabine dose modifications, see capecitabine professional information leaflet.

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/m².

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

Combination therapy with TAXOCAN for gastric cancer:

Patients treated with TAXOCAN in combination with cisplatin and 5-fluorouracil must receive anti-emetics and appropriate hydration according to current institutional guidelines. G-CSF should be administered to mitigate the risk of complicated neutropenia.

If an episode of febrile neutropenia, prolonged neutropenia or neutropenic infection occurs despite G-CSF use, the TAXOCAN dose should be reduced from 75 mg/m^2 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the TAXOCAN dose should be reduced from 60 mg/m^2 to 45 mg/m^2. In case of grade 4 thrombocytopenia the TAXOCAN dose should be reduced from 75 mg/m^2 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of TAXOCAN until neutrophils recover to a level > 1 500 cells/mm^3 and platelets recover to a level > 100 000 cells/mm^3. Discontinue treatment if these toxicities persist.

Recommended dose modifications for gastrointestinal toxicities in patients treated with TAXOCAN in combination with cisplatin and 5-fluorouracil (5-FU)

Toxicity	**Dose adjustments**
Diarrhoea grade 3	First episode: reduce fluorouracil (5-FU) dose by 20 %. Second episode: then reduce TAXOCAN dose by 20 %.
Diarrhoea grade 4	First episode: reduce TAXOCAN and fluorouracil (5-FU) doses by 20 %. Second episode: discontinue treatment.

Stomatitis grade 3	First episode: reduce fluorouracil (5-FU) dose by 20 %. Second episode: stop fluorouracil (5-FU) only, at all subsequent cycles. Third episode: reduce TAXOCAN dose by 20 %.
Stomatitis grade 4	First episode: stop fluorouracil (5-FU) only, at all subsequent cycles. Second episode: reduce TAXOCAN dose by 20 %.

For cisplatin and fluorouracil dosage adjustments, see local professional information leaflet.

Special populations

Patients with hepatic impairment:

For TAXOCAN dose modifications due to hepatic impairment, see section 4.4.

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 section 4.3).

Children:

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

Elderly patients:

Based on a population pharmacokinetic analysis, there are no special instructions for use in elderly patients. For capecitabine dosage reduction when combined with TAXOCAN, see capecitabine professional information leaflet.

Method of administration

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

For recommendations on safe handling and instructions on preparation and administration of TAXOCAN, see section 6.6.

4.3 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 listed in section 6.1.
- 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 section 4.6).
- Children, as the safe use of TAXOCAN has not been established.
- TAXOCAN should not be used in patients with severe liver impairment since there are no data available (see sections 4.4 and 4.2).
- Contraindications for other medicines also apply when combined with TAXOCAN.

4.4 Special warnings and precautions for use

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 health care 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 with a corticosteroid

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 pretreatment 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 pretreated 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 section 4.2).

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.

Gastrointestinal reactions

Caution is recommended for patients with neutropenia, particularly at risk for developing gastrointestinal complications. Enterocolitis could develop at any time and could lead to death as early as on the first day of onset. Patients should be closely monitored for early manifestations of serious gastrointestinal toxicity (see Neutropenia above, and section 4.8).

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. Patients with severe fluid retention such as pleural effusion, pericardial effusion and ascites should be monitored closely. See Premedication with a corticosteroid, above.

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 section 4.2).

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.

The amount of ethanol in TAXOCAN should be taken into account when given to patients with hepatic impairment (see Excipients below).

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.

Severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP) have been reported in association with TAXOCAN treatment. Patients should be informed about the signs and symptoms of serious skin manifestations and monitored closely. In case SCARs are observed, treatment discontinuation should be considered.

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.

Cardiac toxicity

Ventricular dysrhythmia including ventricular tachycardia (sometimes fatal) has been reported in patients treated with TAXOCAN in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide (see section 4.8). Baseline cardiac assessment is recommended.

Second primary malignancies

Second primary malignancies have been reported when TAXOCAN was given in combination with anticancer treatments known to be associated with second primary malignancies. Second primary malignancies (including acute myeloid leukaemia, myelodysplastic syndrome, non-Hodgkin lymphoma and renal cancer) may occur several months or years after docetaxel-containing therapy. Patients should be monitored for second primary malignancies (see section 4.8).

Tumour lysis syndrome

Tumour lysis syndrome has been reported with TAXOCAN (see section 4.8, Post-marketing experience). Patients at risk of tumour lysis syndrome (i.e. with renal impairment, hyperuricaemia, bulky tumour) should be closely monitored in order to properly manage this syndrome. Correction of dehydration and treatment of high uric acid levels are recommended prior to initiation of treatment.

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 or greater compared to younger patients.

Eye disorders

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 have been reported (see section 4.8).

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 docetaxel, 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:

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 rates ≥ 10 % higher in patients who were 65 years of age or greater compared to younger patients.

The incidence of the following adverse events (all grades): lethargy, stomatitis, diarrhoea, febrile neutropenia/neutropenic infection, occurred at rates ≥ 10 % higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Excipients

TAXOCAN contains 23 % *v/v* dehydrated alcohol (see section 2). 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 and impair the ability to drive and use machines (see section 4.7).

4.5 Interaction with other medicines and other forms of interaction

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.

4.6 Fertility, pregnancy and lactation

Pregnancy and lactation are contraindicated, as TAXOCAN is teratogenic in animals (see section 4.3).

There are no available data on the effect of TAXOCAN on fertility.

4.7 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.

4.8 Undesirable 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 and connective tissue disorders

Frequent: arthralgia or myalgia

General disorders and administration 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 and connective tissue disorders

Frequent: arthralgia, myalgia

Reproductive system and breast disorders

Frequent: amenorrhoea

General disorders and administration 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 and connective tissue 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 administration 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 and connective tissue disorders

Frequent: myalgia, arthralgia

General disorders and administration 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 and connective tissue disorders

Frequent: myalgia

General disorders and administration site conditions

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

Less frequent: infusion site conditions, pain.

Post-marketing experience

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Second primary malignancies, including non-Hodgkin lymphoma and renal cancer, have been reported in association with TAXOCAN when used in combination with other anticancer treatments known to be associated with second primary malignancies.

Blood and lymphatic system disorders:

Disseminated intravascular coagulation (DIC), often in association with sepsis, or multiorgan failure, may occur.

Immune system disorders:

Rare cases of anaphylactic shock have been reported. Very rarely these cases resulted in a fatal outcome in patients who received premedication.

Hypersensitivity reactions with potentially fatal outcome have been reported with TAXOCAN in patients who previously experienced hypersensitivity reactions to paclitaxel.

Metabolism and nutrition disorders:

Cases of electrolyte imbalance have been reported. Cases of hyponatraemia have been reported, mostly associated with dehydration, vomiting and pneumonia. Hypokalaemia, hypomagnesaemia, and hypocalcaemia were observed, usually in association with gastrointestinal disorders and in particular with diarrhoea. Tumour lysis syndrome, sometimes fatal, has been reported.

Musculoskeletal disorders:

Myositis has been reported with TAXOCAN.

Nervous system disorders:

Cases of convulsion or transient loss of consciousness have been observed with TAXOCAN

administration. These reactions may appear during the infusion of the medicine.

Ear and labyrinth disorders:

Rare cases of ototoxicity, hearing disorders and/or hearing loss have been reported, including cases associated with other ototoxic medicines.

Eye disorders:

Cases of lacrimation, with or without conjunctivitis, have been reported and individual cases of lacrimal duct obstruction resulting in excessive tearing have been reported.
Cases of transient visual disturbances (flashes, flashing lights, scotomata) typically occurring during the medicine infusion and in association with hypersensitivity reactions have been reported. These were usually reversible upon discontinuation of the infusion.
Cases of cystoid macular oedema (CMO) have been reported in patients treated with TAXOCAN.

Cardiac disorders:

Venous thromboembolic events and myocardial infarction have rarely been reported. Ventricular dysrhythmia including ventricular tachycardia, sometimes fatal, has been reported in patients treated with TAXOCAN in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide.

Gastrointestinal disorders:

Enterocolitis, including colitis, ischaemic colitis, and neutropenic enterocolitis have been reported with a potentially fatal outcome.
Occurrences of dehydration have been reported as a consequence of gastrointestinal events, including enterocolitis and gastrointestinal perforation.
Cases of ileus and intestinal obstruction may occur.

Hepato-biliary disorders:

Cases of hepatitis, sometimes fatal primarily in patients with pre-existing liver disorders, have been reported.

Skin and subcutaneous tissue disorders:

Cases of cutaneous lupus erythematosus, bullous eruptions such as erythema multiforme, severe cutaneous adverse reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis have been reported with TAXOCAN. Scleroderma-like changes and permanent alopecia have been reported.

Renal and urinary disorders:

Renal insufficiency and renal failure have been reported; the majority of these cases were associated with concomitant nephrotoxic medicines.

General disorders and administration site conditions:

Injection site recall reaction (recurrence of skin reaction at a site of previous extravasation following administration of TAXOCAN at a different site) has been observed at the site of previous extravasation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of TAXOCAN is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

See section 4.8.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Taxanes.

ATC code: L01CD02.

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.

5.2 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Citric acid

Macrogol

Polysorbate 80

Dehydrated alcohol.

6.2 Incompatibilities

TAXOCAN should not be mixed with other medicines.

6.3 Shelf life

Unopened vials:

24 months.

After opening of the vial:

See section 6.6 below.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

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

Discard any unused portion.

6.5 Nature and contents of container

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.

6.6 Special precautions for disposal and other handling

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 mg/mL 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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Zydus Healthcare SA (Pty) Ltd

Southdowns Office Park

Building B, Ground Floor

22 Karee Street

Centurion 0157

Tel: 012 748 6400

8. REGISTRATION NUMBERS

TAXOCAN 20: 46/26/0265

TAXOCAN 80: 46/26/0264

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

16 February 2017

10. DATE OF REVISION OF THE TEXT

19 February 2026