PROFESSIONAL INFORMATION

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

DOCETERE® 20 mg/1 mL RTU concentrate for solution for infusion

DOCETERE® 80 mg/4 mL RTU concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DOCETERE 20 mg/1 mL RTU:

Each single-dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel (anhydrous), in 1 mL of concentrate.

DOCETERE 80 mg/4 mL RTU:

Each single-dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel (anhydrous), in 4 mL of concentrate.

DOCETERE 20 mg/1 mL RTU contains 395 mg ethanol (anhydrous) and DOCETERE 80 mg/4 mL RTU contains 1,58 g of ethanol (anhydrous) per vial.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Pale yellow to brownish-yellow.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DOCETERE RTU is indicated for the following:

1. Breast cancer

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

DOCETERE RTU, 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.

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

DOCETERE RTU, 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.

2. Non-small cell lung cancer (NSCLC)

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

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

3. Ovarian cancer

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

4. Prostate cancer

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

5. Head and neck cancer

DOCETERE RTU 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.

6. Gastric adenocarcinoma

DOCETERE RTU 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

DOCETERE RTU should be administered by intravenous infusion only.

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

Posology

A premedication consisting of a corticosteroid (see below for prostate cancer), such as oral dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to DOCETERE RTU administration, unless contraindicated, can be used. For prostate cancer, given the concurrent use of prednisone or prednisolone, the recommended premedication regimen is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the DOCETERE RTU infusion.

Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.

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

1. Breast cancer

In the adjuvant treatment of operable node-positive breast cancer, the recommended DOCETERE RTU dose 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 Dosage adjustments during treatment).

In first-line treatment, DOCETERE RTU 75 mg/m^2 is administered in combination therapy with doxorubicin (50 mg/m^2).

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

In combination with capecitabine, the recommended dose of DOCETERE RTU is 75 mg/m^2 every three weeks, combined with capecitabine at 1 250 mg/m^2 orally twice daily (within 30 minutes after a meal) for 2 weeks followed by a 1-week rest period. For capecitabine dose calculation according to body surface area, see capecitabine manufacturers' prescribing information.

2. Non-small cell lung cancer

In combination therapy (chemotherapy naïve patients)

The recommended dosage regimen is DOCETERE RTU 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 DOCETERE RTU therapy is 100 mg/m^2 as a single agent.

3. Ovarian cancer

The recommended dosage of DOCETERE RTU therapy is 100 mg/m^2.

4. Prostate cancer

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

5. 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 DOCETERE RTU 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, patients 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.

6. Gastric adenocarcinoma

For gastric adenocarcinoma, the recommended dose of DOCETERE RTU 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).

Dosage adjustments during treatment

General

ONLY the doctor can modify the schedule of administration.

DOCETERE RTU should be administered when the neutrophil count is ≥ 1 500 cells/mm^3.

Patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions or severe neurosensory signs and/or symptoms during DOCETERE RTU therapy, should have the dosage of DOCETERE RTU reduced, during the subsequent cycle, from 100 mg/m^2 to 75 mg/m^2 and/or from 75 mg/m^2 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 DOCETERE RTU for NSCLC

For patients who are dosed initially at DOCETERE RTU 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-haematologic toxicities, the DOCETERE RTU dosage in subsequent cycles should be reduced to 65 mg/m^2. For cisplatin dosage adjustments, see manufacturers' prescribing information.

Combination therapy with DOCETERE RTU for breast cancer

Patients who receive adjuvant therapy for breast cancer and who experience febrile neutropenia should receive G-CSF in all subsequent cycles. If G-CSF is not used, the DOCETERE RTU dose should be reduced from 75 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. DOCETERE RTU should be stopped and not administered again in cases of grade 4 stomatitis or oesophagitis.

For capecitabine dose modifications when combined with DOCETERE RTU, see capecitabine manufacturers' prescribing information.

For patients developing the first appearance of a grade 2 toxicity which persists at the time of the next DOCETERE RTU/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 DOCETERE RTU 55 mg/m^2. For any subsequent appearances of toxicities, or any grade 4 toxicities, discontinue the DOCETERE RTU dose.

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

Combination therapy with DOCETERE RTU for gastric cancer

Patients treated with DOCETERE RTU 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 DOCETERE RTU dose should be reduced from 75 to 60 mg/m^2. If subsequent episodes of complicated neutropenia occur the DOCETERE RTU dose should be reduced from 60 to 45 mg/m^2. In case of grade 4 thrombocytopenia the DOCETERE RTU dose should be reduced from 75 to 60 mg/m^2. Patients should not be retreated with subsequent cycles of DOCETERE RTU 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 DOCETERE RTU in combination with cisplatin and 5-fluorouracil (5-FU):

Toxicity	Dosage adjustment
Diarrhoea grade 3	First episode: reduce fluorouracil (5-FU) dose by 20 %. Second episode: then reduce DOCETERE RTU dose by 20 %.

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

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

Special populations

Patients with hepatic impairment

Patients with bilirubin > ULN should generally not receive DOCETERE RTU. Also, patients with AST and/or ALT > 1,5 x ULN concomitant with alkaline phosphatase > 2,5 x ULN, should generally not receive DOCETERE RTU (see section 4.3).

Children

The safety and effectiveness of DOCETERE RTU 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 DOCETERE RTU, see capecitabine manufacturers' prescribing information.

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

4.3 Contraindications

DOCETERE RTU is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel, polysorbate 80 or any of the ingredients listed in section 6.1.

DOCETERE RTU should not be used in patients with baseline neutrophil count of < 1 500 cells/mm^3.

Pregnancy and lactation, as DOCETERE RTU is teratogenic in animals (see section 4.6).

The safe use of DOCETERE RTU in children has not been established.

DOCETERE RTU should not be used in patients with severe liver impairment since there is no data available (see section 4.4 and section 4.2).

Contraindications for other medicines also apply when combined with DOCETERE RTU.

4.4 Special warnings and precautions for use

DOCETERE RTU (docetaxel) concentrate for solution for infusion should be administered under the supervision of a qualified doctor experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

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

DOCETERE RTU 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 DOCETERE RTU therapy and reviewed by the treating doctor.
DOCETERE RTU 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 DOCETERE RTU.
Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or generalised rash/erythema occurred in 2,2 % (2/92) of patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the DOCETERE RTU infusion were reported in five patients who did not receive premedication. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.
DOCETERE RTU must not be given to patients who have a history of severe hypersensitivity reactions to DOCETERE RTU or to other medicines formulated with polysorbate 80.
Severe fluid retention occurred in 6,5 % (6/92) of patients despite the use of a recommended 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 DOCETERE RTU 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 cancer) such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to DOCETERE RTU 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, 12 hours, 3 hours and 1 hour before the DOCETERE RTU regimen.

Neutropenia

Neutropenia is the most frequent adverse reaction of DOCETERE RTU and occurs in almost all patients. Severe neutropenia (grade 3 – 4) occurred in 99 % of patients on combination therapy with doxorubicin.

Neutrophil nadirs occurred 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 DOCETERE RTU. Patients should be re-treated with DOCETERE RTU 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 DOCETERE RTU therapy, a reduction in dose for subsequent courses of therapy and the use of appropriate symptomatic measures are recommended.

In patients treated with DOCETERE RTU in combination with cisplatin and 5-fluorouracil (TCF), febrile neutropenia and/or 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.

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. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCETERE RTU, 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 DOCETERE RTU.

Patients who have previously experienced a hypersensitivity reaction to paclitaxel may develop a potentially fatal hypersensitivity reaction to DOCETERE RTU.

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 DOCETERE RTU 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.

Fluid retention

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

Patients with liver impairment

In patients treated with DOCETERE RTU 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 DOCETERE RTU 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 DOCETERE RTU should not be used unless strictly indicated.

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

Nervous system

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

Cardiac toxicity

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

Eye disorders

Cystoid macular oedema (CMO) has been reported in patients treated with docetaxel. Patients with impaired vision should undergo a prompt and complete ophthalmologic examination. In case CMO is diagnosed, DOCETERE RTU treatment should be discontinued and appropriate treatment initiated (see section 4.8, Post-marketing experiences).

Second primary malignancies

Second primary malignancies have been reported when DOCETERE RTU 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 DOCETERE RTU (see section 4.8 – Post-marketing experiences)**.** 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**.**

Interactions

The concomitant use of DOCETERE RTU with strong CYP3A4 inhibitors (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) should be avoided (see section 4.5).

Excipients

The amount of ethanol in DOCETERE RTU may be harmful in patients suffering from alcoholism and should also be taken into account in high-risk groups such as patients with liver disease or epilepsy.
Consideration should be given to possible effects on the central nervous system.
The amount of ethanol in DOCETERE RTU may alter the effects of other medicines.
The amount of ethanol in DOCETERE RTU may impair the ability to drive or use machines (see section 4.7).

Elderly

An analysis of safety data in patients equal to or greater than 60 years of age treated with DOCETERE RTU 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 DOCETERE RTU 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.

Others

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

4.5 Interaction with other medicines and other forms of interaction

There have been no formal clinical studies to evaluate the medicine interactions of DOCETERE RTU.

In vitro studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds which induce, inhibit or are metabolised by (and thus may inhibit the enzyme competitively) cytochrome P450-3A, such as ciclosporin, 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 case of combination with CYP3A4 inhibitors, the occurrence of DOCETERE RTU adverse reactions may increase, as a result of reduced metabolism. If the concomitant use of a strong CYP3A4 inhibitor (e.g. ketoconazole, itraconazole, clarithromycin, indinavir, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of DOCETERE RTU may be suitable during the treatment with the strong CYP3A4 inhibitor (see section 4.4). In a pharmacokinetic study with 7 patients, the co-administration of docetaxel with the strong CYP3A4 inhibitor ketoconazole leads to a significant decrease in docetaxel clearance by 49 %.

Docetaxel is highly protein bound (> 95 %). Although the possible *in vivo* interaction of DOCETERE RTU 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 docetaxel. In addition, dexamethasone did not affect protein binding of docetaxel. Docetaxel did not influence the binding of digoxin.

In the doxorubicin/docetaxel combination, the clearance of docetaxel was increased.

4.6 Fertility, pregnancy and lactation

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

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. The amount of ethanol in DOCETERE RTU may impair the patient's ability to drive or use machines (see section 4.4 - Excipients). Therefore, patients should be warned of the potential impact of the side effects of the product on the ability to drive or use machines, and be advised not to drive or use machines if they experience these side effects during treatment.

4.8 Undesirable effects

Blood and lymphatic system disorders

The most frequent adverse reaction to DOCETERE RTU was neutropenia (in patients who did not receive G-CSF), which was reversible and not cumulative. The median day to nadir was 7 days and the median duration of severe neutropenia (< 500 cells/mm^3) was 7 days.
Fever in absence of infection, in patients with non-small cell lung cancer, was reported in 17,2 % (1,2 % severe) of patients treated in combination with cisplatin.

Bleeding episodes have occurred and were infrequently associated with severe thrombocytopenia (< 50 000 cells/mm^3).

Bone marrow suppression and other haematological adverse reactions to DOCETERE RTU include:

	% Patients with haematological events			
	Single agent		**Combination with doxorubicin**	**Combination with cisplatin**
Number of patients	**n = 1 312**	**n = 121**	**n = 258**	**n = 406**
	100 mg/m²	**75 mg/m²**	**75 mg/m²**	**75 mg/m²**
Neutropenia: All	96,6	89,8	99,2	91,1
Severe **				74,8
Severe *	76,4	54,2	91,7	51,5
Febrile neutropenia:				
All	11,8	8,3	34,1	4,9
Severe	4,6			
Thrombocytopenia:				
All	7,8	10	28,1	14,9
Severe **				2,7
Severe *	0,2	1,7	0,8	0,5
Anaemia: All	90,4	93,3	96,1	88,6
Severe **	8,9	10,8	9,4	6,9
Infections: All	20	10,7	35,3	14,3
Severe **	5,7	5	7,8	5,7

* NCI grade 4

** NCI grade 3 – 4

Immune system disorders

Hypersensitivity reactions may occur, usually within a few minutes following the start of the infusion of DOCETERE RTU.

The most frequently reported symptoms are flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and medicine fever or chills.

Severe anaphylactic reactions characterised by hypotension and/or bronchospasm or generalised rash/erythema, requiring therapeutic intervention may occur. These may resolve after discontinuing the infusion and appropriate therapy.

	% Patients with anaphylactic reactions			
	Single agent		**Combination with doxorubicin**	**Combination with cisplatin**
	100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
All	25,9	2,5	4,7	10,6
Severe *	5,3	0	1,2	2,5

* NCI grade 3 – 4

Nervous system disorders

Neurosensory signs characterised by paraesthesia, dysaesthesia or pain including burning, may occur.

Neuromotor events, mainly characterised by weakness, may occur.

These events were spontaneously reversible within 3 months in 35,3 % of patients with neurotoxicity following DOCETERE RTU treatment at 100 mg/m^2 as a single agent.

	% Patients with neurological events			
	Single agent		Combination with doxorubicin	Combination with cisplatin
	100 mg/m²	**75 mg/m²**	**75 mg/m²**	**75 mg/m²**
Neurosensory: All	50	24	30,2	40,4
Severe *	4,1	0,8	0,4	3,7
Neuromotor: All	13,8	9,9	2,3	12,8
Severe **	4	2,5	0,4	2,0

* NCI grade 3

** NCI grade 3 – 4

Cardiac disorders

Hypertension has been reported.

	% Patients with cardiovascular events		
	Single agent		Combination with doxorubicin
	100 mg/m²	**75 mg/m²**	**75 mg/m²**
Hypotension	3,8	1,7	0,4
Cardiac dysrhythmia:			
All	4,1	2,5	1,2
Severe *	0,7	0	0
Heart failure	0,5	0	2,3

* NCI grade 3 – 4

Vascular disorders

Fluid retention: Events such as peripheral oedema and less frequently, 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 in patients with premedication compared with patients without premedication, however, it has been reported in some patients during the early courses of therapy. The median time to fluid retention reversibility was 16,4 weeks (range 0 to 42 weeks) in patients receiving the recommended premedication.

Fluid retention has not been accompanied by acute episodes of oliguria or hypotension.

Fluid retention has been less frequently reported in patients receiving the recommended premedication compared with patients without premedication.

	% Patients with fluid retention			
	Single agent		**Combination with doxorubicin**	**Combination with cisplatin**
	100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
All	64,1	24,8	35,7	25,9
Severe	6,5	0,8	1,2	0,7

Gastrointestinal disorders

Gastrointestinal effects such as nausea, vomiting, diarrhoea, abdominal pain and constipation may occur.

Stomatitis, oesophagitis and taste perversion may occur.

Gastrointestinal bleeding may occur.

Anorexia may occur and may be severe.

	% Patients with gastrointestinal events			
	Single agent		**Combination with doxorubicin**	**Combination with cisplatin**
	100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**	**75 mg/m^2**
Nausea: All	40,5	28,9	64	69,0
Severe *	4	3,3	5	9,6
Vomiting: All	24,5	16,5	45	53,4
Severe*	3	0,8	5	7,6
Diarrhoea: All	40,6	11,6	45,7	41,1
Severe *	4	1,7	6,2	6,4
Anorexia	16,8	19,0	8,5	28,8
Constipation	9,8	6,6	14,3	9,4
Stomatitis: All	41,8	24,8	58,1	23,4
Severe *	5,3	1,7	7,8	2,0

* NCI grade 3 – 4

Hepato-biliary disorders

In patients treated at 100 mg/m^2 as a single agent, increases in serum levels of AST, ALT, bilirubin and alkaline phosphatase greater than 2,5 times the ULN were observed.

In patients treated at 75 mg/m^2 as a single agent, no NCI grade 3 – 4 increases in serum levels of AST, ALT and alkaline phosphatase were observed and less than 2 % of the patients experienced grade 3 – 4 increase in bilirubin.

In patients treated in combination with doxorubicin at 75 mg/m^2, less than 1 % of patients experienced grade 3 – 4 increases in AST and ALT. Grade 3 – 4 increase in bilirubin and alkaline phosphatase were observed in less than 2,5 % of the patients.

	% Patients with hepatic events		
	Single agent		Combination with doxorubicin
	100 mg/m^2	**75 mg/m^2**	**75 mg/m^2**
AST increase: Severe *	< 3,0	0	< 1,0
ALT increase: Severe *	< 2,0	0	< 1,0
Bilirubin increase: Severe *	< 5,0	< 2,0	< 2,5
Alkaline phosphatase increase: Severe *	< 4,0	0	< 2,5

* NCI grade 3 – 4

Skin and subcutaneous tissue disorders

Reversible cutaneous reactions may occur. The majority of these events were reversible within 21 days. The cutaneous reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand-foot syndrome), but also on the arms, face or thorax and frequently associated with pruritus. Eruptions generally occurred within one week after the DOCETERE RTU infusion.

Nail disorders may occur. These were characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

Less frequently, severe symptoms such as eruptions followed by desquamation which may rarely lead to interruption or discontinuation of DOCETERE RTU treatment, may occur.

	% Patients with cutaneous events			
	Single agent		Combination with doxorubicin	Combination with cisplatin
	100 mg/m^2	75 mg/m^2	75 mg/m^2	75 mg/m^2
Cutaneous: All	56,6	15,7	13,6	11,1
Severe *	5,9	0,8	0	0,2
Nail changes: All	27,9	9,9	20,2	13,3
Severe	2,6	0,8	0,4	0,7

* NCI grade 3 – 4

Other

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

In patients treated with 100 mg/m^2 as single agent, alopecia has been observed in 79 % of patients. Alopecia was considered severe in about 0,5 % of the patients.

Asthenia has been observed in 62,6 % of patients. Asthenia was severe in 11,2 % of the patients.

Arthralgias and myalgia may occur.

Dyspnoea may occur and is frequently associated with acute hypersensitivity reactions, respiratory infections and cancerous lung involvement.

Generalised or localised pain may occur, including chest pain without any cardiac or respiratory involvement.

	% Patients with other events			
	Single agent		Combination with doxorubicin	Combination with cisplatin
	100 mg/m^2	75 mg/m^2	75 mg/m^2	75 mg/m^2
Alopecia: All	79	38	94,6	73,6
Severe*	0,5			
Asthenia: All	62,6	48,8	54,7	51,5
Severe	11,2	12,4	8,1	9,9
Myalgia: All	20	5,8	8,5	13,8
Severe	1,4	0	0	0,5
Infusion site reactions	5,6	0	3,1	6,2
Pain	16,5	10,7	17,1	5,4

* NCI grade 3 – 4

COMBINATION THERAPY WITH DOCETERE RTU IN THE ADJUVANT TREATMENT OF BREAST CANCER

Clinically important treatment-related adverse events in patients receiving DOCETERE RTU in combination with doxorubicin and cyclophosphamide (TAC):

Of the 744 patients treated with TAC, 36,7 % experienced severe adverse events during the treatment period compared to 13,8 % during the follow-up period. Dose reductions due to haematological toxicity occurred in 1 % of cycles during the treatment period. Six per cent of patients discontinued treatment due to adverse events; fever in the absence of infection and allergy being the most common reasons for withdrawal. Two patients died within 30 days of their last study treatment; death was considered to be related to study medication.

	DOCETERE RTU 75 mg/m^2+ doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 n = 744	
Body system **Adverse event**	**All grades (%)**	**Grade 3/4 (%)**
Infections and infestations		
Infection	29,2	3,2
Neutropenic infection	17,3	3,6
Blood and lymphatic system disorders		
Anaemia	92,1	4,2
Neutropenia	71,8	65,3
Thrombocytopenia	39,5	2,0
Febrile neutropenia	24,6	N/A
Immune system disorders		
Hypersensitivity reactions	9,0	0,9
Metabolism and nutrition disorders		
Anorexia	19,9	2,2
Nervous system disorders		
Dysgeusia	27,3	0,7
Peripheral sensory neuropathy	23,1	0,0
Peripheral motor neuropathy	2,7	0,0
Syncope	0,4	0,0
Somnolence	0,3	0,0
Eye disorders		
Conjunctivitis	3,8	0,0
Increased lacrimation	10,1	0,1

Cardiac disorders		
Cardiac dysrhythmias	2,8	0,3
Vascular disorders		
Hot flush	21,4	0,9
Hypotension	1,5	0,0
Phlebitis	0,9	0,0
Lymphoedema	0,3	0,0
Respiratory, thoracic and mediastinal disorders		
Cough	3,0	0,0
Gastrointestinal disorders		
Nausea	80,4	5,1
Stomatitis	68,4	7,1
Vomiting	42,5	4,3
Diarrhoea	30,9	3,2
Constipation	24,5	0,4
Abdominal pain	6,5	0,5
Skin and subcutaneous tissue disorders		
Alopecia	97,7	N/A
Skin disorder	16,1	0,7
Nail disorders	18,4	0,4
Musculoskeletal and connective tissue disorders		
Myalgia	22,8	0,8
Arthralgia	15,1	0,4
Reproductive system and breast disorders		
Amenorrhoea	26,2	N/A
General disorders and administration site conditions		
Asthenia	79,2	11,0

Fever in absence of infection	36,6	N/A
Peripheral oedema	26,6	0,4
Investigations		
Weight increased	12,5	0,0
Weight decreased	2,6	0,3

Infections and infestations

Fever in the absence of infection was seen in 36,6 % of patients and infection was seen in 29,2 % (grade 3/4: 3,2 %) of patients during the study period. There were no deaths due to sepsis during the study period.

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

Acute myeloid leukaemia (AML)/myelodysplastic syndrome:

After 10 years of follow-up in study TAX316, AML occurred in 3 of the 744 (0,4 %) patients who received DOCETERE RTU, doxorubicin and cyclophosphamide and in 1 of 736 (0,1 %) patients who received fluorouracil, doxorubicin and cyclophosphamide. One patient died due to AML during the follow-up period (median follow-up time of 8 years). Myelodysplastic syndrome occurred in 2 of 744 (0,3 %) patients who received DOCETERE RTU, doxorubicin, and cyclophosphamide.

Cardiac disorders

The following treatment emergent cardiovascular events were reported during the study period: dysrhythmias, all grades (6,2 %), hypotension, all grades (1,9 %) and congestive heart failure (3,5 %). Twenty-six patients developed congestive heart failure during the study period, with most cases reported in the follow-up period. Congestive heart failure lead to death in 2 patients.

Gastrointestinal disorders

In addition to gastrointestinal events reflected in the above table, 7 patients were reported to have colitis/enteritis/large intestine perforation. Two of these patients required treatment discontinuation; no deaths due to these events occurred during the treatment period.

Other persistent reactions

The most common adverse events that started during the treatment period and persisted into the follow-up period are described in the table below (median follow-up time of 8 years). The majority of the events that had persisted resolved during the follow-up period.

Persistent reactions in patients receiving DOCETERE RTU in combination with doxorubicin and cyclophosphamide:

	DOCETERE RTU 75 mg/m^2+ doxorubicin 50 mg/m^2 + cyclophosphamide 500 mg/m^2 n = 744	
Body system **Adverse event**	Persisting from the treatment period into the follow-up period n (%)	Ongoing at the end of the follow-up period n (%)
Alopecia	92,3	3,9
Asthenia	31,7	3,9
Amenorrhoea	27,2	16,3
Lymphoedema	1,5	0,8
Peripheral oedema	16,0	2,6
Peripheral sensory neuropathy	11,3	1,3

COMBINATION THERAPY WITH DOCETERE RTU AND CAPECITABINE FOR BREAST CANCER

Summary of at least remotely related adverse events reported in ≥ 5 % of patients treated with DOCETERE RTU and capecitabine in combination:

Body system Adverse event	**Capecitabine with DOCETERE RTU (n = 251)**	
	Total **%**	**Grade 3/4** **%**
Gastrointestinal		
Stomatitis	67	18
Diarrhoea	64	14
Nausea	43	6
Vomiting	33	4
Constipation	14	1
Abdominal pain	14	2
Dyspepsia	12	-
Abdominal pain upper	9	-
Dry mouth	5	-
Skin and subcutaneous		
Hand-foot syndrome*	63	24
Alopecia	41	6
Nail disorder	14	2
Dermatitis	8	-
Rash erythema	8	< 1
Nail discolouration	6	-

Onycholysis	5	1
General		
Asthenia	23	3
Pyrexia	21	1
Fatigue	21	4
Weakness	13	1
Pain in limb	9	< 1
Lethargy	6	-
Pain	6	-
Neurological		
Taste disturbance	15	< 1
Paraesthesia	11	< 1
Dizziness	9	-
Headache	7	< 1
Peripheral neuropathy	5	-
Metabolism		
Anorexia	12	1
Decreased appetite	10	-
Dehydration	8	2
Decreased weight	6	-
Eye		
Increased lacrimation	12	-
Musculoskeletal		
Myalgia	14	2
Arthralgia	11	1
Back pain	7	1

Cardiovascular		
Lower limb oedema	14	1
Respiratory		
Sore throat	11	2
Dyspnoea	7	1
Cough	6	< 1
Epistaxis	5	< 1
Infection		
Oral candidiasis	6	< 1

- Not observed

* Grade 3 only

Frequent grade 3 and 4 laboratory abnormalities were:

Adverse event	**Capecitabine with DOCETERE RTU (n = 251)**
Laboratory abnormalities (according to NCI/CTC)	**Grade 3/4 %**
Neutropenia	63
Anaemia	10
Thrombocytopenia	3
Hyperbilirubinaemia	9

Summary of at least remotely related adverse events reported in < 5 % of patients treated with DOCETERE RTU and capecitabine in combination (n = 251); listed according to MedDRA system organ class (SOC), in order of decreasing frequency within each particular SOC:

Infections and infestations

Urinary tract infection* (grade 3/4: 0,4 %), neutropenic sepsis (grade 3/4: 2,4 %), tonsillitis*, upper respiratory tract infection*, herpes simplex, herpes zoster, cellulitis (grade 3/4: 0,4 %), cystitis*, pharyngitis* (grade 3/4: 0,4 %), pneumonia*, fungal infection*, laryngitis*, localised infection, lower respiratory tract infection* (grade 3/4: 0,4 %), nail bed infection*, otitis media* (grade 3/4: 0,4 %), sepsis* (grade 3/4: 0,4 %), tooth abscess, bladder infection*, bronchitis*, bronchopneumonia* (grade 3/4: 0,4 %), *Candida**, pseudomembranous colitis, erysipelas, eye infection*, gastrointestinal infection*, gingivitis infection*, serous otitis media*, peritonsillar abscess*, *Pseudomonas* infection*, skin and subcutaneous tissue abscess, skin candidiasis*, vaginal candidiasis, vaginitis, vulvitis and vulvovaginitis*.

Blood and lymphatic system disorders

Leucopenia* (grade 3/4: 2,8 %), decreased white blood cell count (grade 3/4: 0,8 %), agranulocytosis (grade 3/4: 0,4 %), increased international normalised ratio, leucocytosis*, decreased prothrombin (grade 3/4: 0,4 %) and thrombocytopenia (grade 3/4: 0,4 %).

Immune system disorders

Hypersensitivity* (grade 3/4: 1,2 %), anaphylactoid reaction and hypersensitivity to the medicine.

Metabolism and nutrition disorders

Hyperlipidaemia*, hypokalaemia, hypomagnesaemia and increased weight.

Psychiatric disorders

Depression*, anxiety, confusion, delusion and mood alteration*.

Nervous system disorders

Peripheral neuropathy*, insomnia, taste loss (grade 3/4: 0,8 %), hypo-aesthesia, polyneuropathy* (grade 3/4: 0,4 %), syncope (grade 3/4: 1,2 %), hyperaesthesia, parosmia, sedation, ataxia* (grade 3/4: 0,4 %), burning sensation skin, dystonia, encephalopathy*, abnormal gait*, oral hypo-aesthesia*, insomnia exacerbated, migraine (grade 3/4: 0,4 %), movement disorder*, nightmares, sensory disturbance* and vasovagal attack.

Eye disorders

Eye irritation, conjunctivitis*, xerophthalmia, eye disorder*, ocular hyperaemia, red eye, blurred vision, reduced visual acuity and visual disturbance*.

Ear and labyrinth disorders

Earache, impaired hearing, tinnitus and vertigo*.

Cardiac disorders

Oedema*, peripheral oedema, upper limb oedema (grade 3/4: 0,4 %), tachycardia*, palpitations, supraventricular tachycardia (grade 3/4: 0,4 %), atrial fibrillation, cardiac murmur*, extrasystoles*, pericardial effusion and pulmonary oedema (grade 3/4: 0,4 %).

Vascular disorders

Flushing, venous phlebitis and thrombophlebitis* (grade 3/4: 0,4 %), hypotension (grade 3/4: 1,2 %), increased blood pressure (grade 3/4: 0,4 %), postural hypotension (grade 3/4: 0,8 %), lymphoedema, vein disorder* and superficial venous phlebitis and thrombophlebitis.

Respiratory, thoracic and mediastinal disorders

Epistaxis (grade 3/4: 0,4 %), rhinorrhoea, productive cough, nasopharyngitis, rhinitis*, chest wall pain, exertional dyspnoea, nasal ulcer, nasal passage irritation, throat swelling*, chest tightness, dyspnoea exacerbated, haemoptysis, nasal dryness, pleural effusion, seasonal rhinitis, sinus congestion and sinusitis*.

Gastrointestinal disorders

Abdominal distension, oral pain, dysphagia, flatulence, haemorrhoids (grade 3/4: 0,4 %), lower abdominal pain (grade 3/4: 0,4 %), cheilitis, haemorrhagic diarrhoea (grade 3/4: 0,8 %), 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, ascites, defaecation urgency, eructation, faeces discoloured, hiatus hernia, ileus (grade 3/4: 0,4 %), lip ulceration, loose stools, melaena, necrotising enterocolitis (grade 3/4: 0,4 %), oesophageal ulcer (grade 3/4: 0,4 %), oesophagitis, oral mucosal eruption, salivary hypersecretion, tongue discolouration and tongue ulceration.

Hepatobiliary disorders

Hepatic coma (grade 3/4: 0,4 %), hepatic failure (grade 3/4: 0,4 %), abnormal hepatic function* (grade 3/4: 0,4 %), hepatotoxicity* (grade 3/4: 0,4 %) and jaundice* (grade 3/4: 0,4 %).

Skin and subcutaneous tissue disorders

Dry skin, facial oedema (grade 3/4: 0,4 %), nail abnormality* (grade 3/4: 0,8 %), exfoliative dermatitis*, pigmentation disorder* (grade 3/4: 0,4 %), pruritus, skin hyperpigmentation, pruritic rash, atopic dermatitis, 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, popular rash, pustular rash, skin inflammation*, skin necrosis (grade 3/4: 0,4 %), skin ulcer*, sloughing of skin, solar keratosis (grade 3/4: 0,4 %), subcutaneous nodule and toxicoderma.

Musculoskeletal, connective tissue and bone disorders

Bone pain (grade 3/4: 0,4 %), muscle cramps, musculoskeletal pain, joint stiffness, muscle spasms and muscle weakness.

Renal and urinary disorders

Dysuria, haematuria, oliguria, urinary incontinence, enuresis, nocturia, renal failure* (grade 3/4: 0,4 %) and urethral pain.

Reproductive system and breast disorders

Breast pain, pelvic pain*, vaginal discharge, vaginal discomfort, vaginal dryness, vaginal haemorrhage and vulval disorder*.

General disorders and administration site conditions

Influenza-like illness, rigors (grade 3/4: 0,4 %), injection site reaction*, chest pain (non-cardiac) (grade 3/4: 0,4 %), fluid retention, hyperaemia, malaise, palmar erythema, hot flushes*, loin pain (grade 3/4: 0,4 %), swelling*, feeling jittery, chest pain* (grade 3/4: 0,4 %), chest pressure sensation, clamminess, extravasation*, hiccups, hoarseness, inflammatory oedema reaction, injection site infection (grade 3/4: 0,4 %), intermittent pyrexia, mucous membrane disorder*, neuralgia* (grade 3/4: 0,4 %), pain in the face, shoulder blade pain and throat tightness.

Investigations

Decreased haemoglobin (grade 3/4: 0,4 %).

Injury and poisoning

Oesophageal burn and neurotoxicity*.

** = not otherwise specified*

COMBINATION THERAPY WITH DOCETERE RTU IN PROSTATE CANCER PATIENTS

The following data are based on the experience of 332 patients, who were treated with DOCETERE RTU 75 mg/m^2 every 3 weeks in combination with prednisone or prednisolone 5 mg orally twice daily.

Clinically important treatment-related adverse events in patients with prostate cancer who received DOCETERE RTU in combination with prednisone or prednisolone:

	DOCETERE RTU 75 mg/m^2 every three weeks + prednisone (or prednisolone) 5 mg twice daily n = 332 %	
Adverse event	**Any**	**Grade 3/4**
Blood disorders		
Anaemia	66,5	4,9
Infection	12,0	3,3
Neutropenia	40,9	32,0
Thrombocytopenia	3,4	0,6
Febrile neutropenia	2,7	-
Immune system		
Allergic reactions	6,9	0,6
Fluid retention		
Fluid retention	24,4	0,6
Neurological		
Sensory neuropathy	27,4	1,2
Motor neuropathy	3,9	0,0
Skin and subcutaneous		
Alopecia	65,1	-
Nail changes	28,3	0,0
Rash/desquamation	3,3	0,3
Gastrointestinal		
Nausea	35,5	2,4

Diarrhoea	24,1	1,2
Stomatitis/pharyngitis	17,8	0,9
Taste disturbance	17,5	0,0
Vomiting	13,3	1,2
Anorexia	12,7	0,6
Respiratory		
Epistaxis	3,0	0,0
Cough	1,2	0,0
Dyspnoea	4,5	0,6
Cardiovascular		
Cardiac left ventricular function	3,9	0,3
Eye		
Tearing	9,3	0,6
General		
Fatigue	42,8	3,9
Musculoskeletal		
Myalgia	6,9	0,3
Arthralgia	3,0	0,3

COMBINATION THERAPY WITH DOCETERE RTU IN HEAD AND NECK CANCER

The following table summarises the safety data obtained in 174 patients with locally advanced inoperable squamous cell carcinoma of the head and neck (SCCHN), who were treated with DOCETERE RTU 75 mg/m^2 in combination with cisplatin and 5-fluorouracil.

Clinically important treatment-related adverse events in patients with SCCHN receiving DOCETERE RTU in combination with cisplatin and 5-fluorouracil (TAX323):

	DOCETERE RTU 75 mg/m^2 + cisplatin 75 mg/m^2 + 5-fluorouracil 750 mg/m^2 n = 174	
Adverse event	**Any %**	**Grade 3/4 %**
Blood disorders		
Neutropenia	93,1	76,3
Anaemia	89,1	9,2
Thrombocytopenia	23,6	5,2
Febrile neutropenia*	5,2	0
Infections		
Infection	15,5	6,3
Fever in the absence of infection	14,4	0,6
Neutropenic infection	11,0	0
Immune system		
Allergy	2,9	0
Fluid retention		
Oedema only	20,1	0
Weight gain only	12,6	5,7
Neurological		
Neurosensory	16,7	0,6
Dizziness	1,1	-
Skin and subcutaneous		
Alopecia	79,9	10,9

Rash/itch	8,6	0
Dry skin	5,2	0
Desquamation	4,0	0,6
Gastrointestinal		
Nausea	43,7	0,6
Stomatitis	42,0	4,0
Diarrhoea	29,3	2,9
Vomiting	25,9	0,6
Anorexia	15,5	0,6
Constipation	6,9	0
Oesophagitis/dysphagia/ odynophagia	5,7	0,6
Gastrointestinal pain/cramping	5,2	-
Heartburn	4,0	-
Gastrointestinal bleeding	1,1	0,6
Cardiovascular		
Cardiac dysrhythmia	0,6	0,6
Myocardial ischaemia	1,7	1,7
Venous disorder	1,1	0,6
Eye		
Tearing	1,7	0
Conjunctivitis	1,1	0
General		
Lethargy	37,9	3,4
Taste, sense of smell altered	10,3	-
Altered hearing	5,7	0

Cancer pain	1,1	0,6
Weight loss	9,8	0
Musculoskeletal		
Myalgia	6,3	0,6

* Febrile neutropenia: grade ≥ 2 fever concomitant with grade 4 neutropenia requiring IV antibiotics and/or hospitalisation.

COMBINATION THERAPY WITH DOCETERE RTU IN GASTRIC ADENOCARCINOMA

Data in the following table are based on the experience of 221 patients with advanced gastric adenocarcinoma and no history of prior chemotherapy for advanced disease, who were treated with DOCETERE RTU 75 mg/m^2 in combination with cisplatin and 5-fluorouracil.

Clinically important treatment-related adverse events in gastric adenocarcinoma patients receiving DOCETERE RTU in combination with cisplatin and 5-fluorouracil (TAX 325):

	DOCETERE RTU 75 mg/m^2 + cisplatin 75 mg/m^2 + 5-fluorouracil 750 mg/m^2 n = 221	
Adverse event	**Any %**	**Grade 3/4 %**
Blood disorders		
Anaemia	96,8	18,2
Neutropenia	95,5	82,3
Fever in the absence of infection	30,8	1,8
Thrombocytopenia	25,5	7,7
Infection	16,7	12,7
Febrile neutropenia	15,9	N/A

Neutropenic infection	14,1	N/A
Immune system		
Allergic reactions	9,0	1,8
Fluid retention		
Fluid retention	14,9	0,0
Neurological		
Neurosensory disorder	38,0	7,7
Neuromotor disorder	6,3	1,8
Dizziness	8,1	2,7
Skin and subcutaneous		
Alopecia	66,5	5,0
Rash/itch	8,1	0,5
Nail changes	8,1	0,0
Skin desquamation	1,8	0,0
Gastrointestinal		
Nausea	71,9	14,5
Vomiting	61,1	14,5
Anorexia	44,8	10,4
Stomatitis	59,3	20,8
Diarrhoea	74,7	19,5
Constipation	10,0	0,9
Oesophagitis/dysphagia/ odynophagia	9,0	0,9
Gastrointestinal pain/cramping	7,7	1,4
General		
Lethargy	56,1	18,6

Cardiac		
Cardiac dysrhythmias	1,8	0,9
Eye		
Tearing	8,1	0,0
Ear and labyrinth		
Altered hearing	4,1	0,0

Febrile neutropenia or neutropenic infection

Febrile neutropenia and/or neutropenic infection occurred in 28,6 % of patients, regardless of G-CSF use. G-CSF was used for secondary prophylaxis in only 18,6 % of patients (10 % of cycles) for the TCF arm. Febrile neutropenia and/or neutropenic infection occurred at lower rates; 12,2 % when patients received prophylactic G-CSF, and 26,9 % without prophylactic G-CSF.

Post-marketing experiences:

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 DOCETERE RTU 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 DOCETERE RTU 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 DOCETERE RTU.

Nervous system disorders

Cases of convulsion or transient loss of consciousness have been observed with DOCETERE RTU 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 DOCETERE RTU.

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 DOCETERE RTU in combination regimens including doxorubicin, 5-fluorouracil and/or cyclophosphamide.

Vascular disorders

Dehydration and pulmonary oedema have been reported.

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

Enterocolitis, including colitis, ischaemic colitis, and neutropenic enterocolitis have been reported with a potential 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 DOCETERE RTU. 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 DOCETERE RTU 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 DOCETERE RTU is important. It allows continued monitoring of the benefit/risk balance of DOCETERE RTU. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications: https://www.sahpra.org.za/Publications/Index/8, or to the Pharmacovigilance Unit at Sanofi at za.drugsafety@sanofi.com (email) or 011 256 3700 (tel).

4.9 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 DOCETERE RTU overdosage. The primary anticipated complications of overdosage would consist of neutropenia, mucositis, cutaneous reactions and paraesthesia.

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

Docetaxel belongs to the medicine class A 26 Cytostatic agents.

Pharmacotherapeutic group: Taxanes, ATC Code: L01CD02.

Docetaxel is an antineoplastic agent 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 multidrug resistance gene.

5.2 Pharmacokinetic properties

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 – 115 mg/m^2 in Phase I studies. 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 a 100 mg/m^2 dose given as a one-hour infusion, a mean peak plasma level of 3,7 µg/mL was obtained with a corresponding AUC of 4,6 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 compound. 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 pharmacokinetic profile of cisplatin administered shortly after docetaxel infusion is similar to that observed with cisplatin alone.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

polysorbate 80

ethanol (anhydrous) (395 mg/mL).

6.2 Incompatibilities

Do not admix with other medications.

6.3 Shelf life

DOCETERE 20 mg/1 mL RTU: 24 months.

DOCETERE 80 mg/4 mL RTU: 36 months.

6.4 Special precautions for storage

Unopened vials should be stored at or below 25 °C, protected from light. Freezing does not adversely affect the product.

The DOCETERE RTU infusion solution should preferably be used immediately. It may however be stored at room temperature (not exceeding 25 °C) for a maximum of 4 hours (this includes the one-hour infusion time for administration of the infusion, under room temperature and normal lighting conditions).

Discard any unused solution.

6.5 Nature and contents of container

DOCETERE 20 mg/1 mL RTU: Carton containing one clear glass vial of DOCETERE 20 mg/1 mL RTU (green seal with green flip-off cap).

DOCETERE 80 mg/4 mL RTU: Carton containing one clear glass vial of DOCETERE 80 mg/4 mL RTU (magenta seal with magenta flip-off cap).

6.6 Special precautions for disposal and other handling

Recommendations for safe handling

Handling precautions for cytostatic agents should be followed:

- Only trained personnel should reconstitute the agent in a designated area.
- DOCETERE RTU is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing DOCETERE RTU solutions.

- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If DOCETERE RTU concentrate or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If DOCETERE RTU concentrate or infusion solution 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 reconstitute DOCETERE RTU.

Preparation for intravenous administration

Preparation of the infusion solution:

DO NOT use the two-vial formulation (injection concentrate and diluent) with the one-vial (RTU) formulation.

If the vials are stored under refrigeration, allow the required number of DOCETERE RTU cartons to stand at room temperature (below 25 °C) for 5 minutes before use.

More than one DOCETERE RTU concentrate vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, use a 21 gauge needle and aseptically withdraw the required amount of DOCETERE RTU concentrate solution using a calibrated syringe.

Inject the required concentrate volume into a 250 mL infusion bag or bottle containing either 5 % glucose solution or 0,9 % sodium chloride solution. If a dose greater than 200 mg of DOCETERE RTU is required, use a larger volume of the infusion vehicle so that a concentration of 0,74 mg/mL docetaxel is not exceeded.

Mix the infusion bag or bottle manually using a rocking motion.

The DOCETERE RTU infusion solution should be aseptically administered intravenously as soon as possible after preparation as a one-hour infusion, under room temperature and normal lighting conditions. The total duration of manipulation from start of the preparation of the bag to the end of the infusion must not exceed 4 hours.

DOCETERE RTU infusion solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

Do not admix with other medications.

DOCETERE RTU infusion is compatible with commonly available administration sets, including PVC sets.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

sanofi-aventis south africa (pty) ltd.
Hertford Office Park, Building I, 5th Floor
90 Bekker Road, Vorna Valley
Midrand 2196
Tel: 011 256 3700

8. REGISTRATION NUMBERS

DOCETERE 20 mg/1 mL RTU: 44/26/0098

DOCETERE 80 mg/4 mL RTU: 44/26/0099

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2012

10. DATE OF REVISION OF THE TEXT

03 October 2022

NAMIBIA

Scheduling status: NS2

Registration No.:

DOCETERE 20 mg/1 mL RTU – 14/26/0009

DOCETERE 80 mg/4 mL RTU – 14/26/0008