**SCHEDULING STATUS**

S4

## 1. NAME OF MEDICINE:

**INNOTERE 20 mg/1 ml** Concentrate for solution for infusion

**INNOTERE 80 mg/4 ml** Concentrate for solution for infusion

## 2. QUALITATIVE AND QUANTITAVIE COMPOSITION:

**INNOTERE 20 mg/1 ml** each single-dose vial contains docetaxel trihydrate equivalent to 20 mg docetaxel (anhydrous), in 1 ml of concentrate.

**INNOTERE 80 mg/4 ml** each single-dose vial contains docetaxel trihydrate equivalent to 80 mg docetaxel (anhydrous), in 4 ml of concentrate.

Excipients with known effect: ethanol (anhydrous)

Each vial of 1 ml of concentrate contains 0.5 ml of ethanol anhydrous (395 mg).

Each vial of 4 ml of concentrate contains 2 ml of ethanol anhydrous (1.58 g).

**Sugar Free**

For full list of excipients, see **section 6.1**

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.

**INNOTERE** is a clear viscous, colourless to either yellowish or greenish-yellow sterile solution

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

**INNOTERE** is indicated for the following:

**Breast Cancer:**

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

**INNOTERE**, 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.

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

**INNOTERE**, 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 (NSCLC):**

**INNOTERE**, 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.

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

**Ovarian Cancer:**

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

**Prostate Cancer:**

**INNOTERE**, 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:**

**INNOTERE**, 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.

**4.2 Posology and method of administration**

The use of docetaxel 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.

**RECOMMENDED DOSE:**

**INNOTERE** should be administered by intravenous infusion only.

**Dosage:**

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 on day prior to **INNOTERE** 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 **INNOTERE** infusion. Prophylactic G-CSE may be used to mitigate the risk of haematological toxicities.

**INNOTERE** 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 **INNOTERE** dose is 75 mg/m² administered one hour after doxorubicin 50 mg/m² and cyclophosphamide 500 mg/m² every 3 weeks for 6 cycles (see also “Dosage adjustments during therapy”).

In the first-line treatment, **INNOTERE** 75 mg/m² is administered in combination therapy with doxorubicin (50 mg/m²).

For the second-line treatment of breast cancer the recommended dosage of **INNOTERE** therapy is 100 mg/m² in monotherapy.

In combination with capecitabine, the recommended dose of **INNOTERE** is 75 mg/m² every three weeks, combined with capecitabine at 1 250 mg/m² orally twice daily (within 30 minutes after a meal) for 2 weeks followed by 1-week rest period. For capecitabine dose calculation according to body surface area, see the professional information for capecitabine.

**2. Non-small Cell Lung Cancer (NSCLC):**

**In combination therapy (chemotherapy naïve patients):**

The recommended dosage regimen is **INNOTERE** 75 mg/m² immediately followed by cisplatin 75 mg/m² over 30-60 minutes.

**In monotherapy (for previously treated patients):**

The recommended dosage of **INNOTERE** therapy is 100 mg/m² as a single medicine.

**3. Ovarian Cancer:**

The recommended dosage of **INNOTERE** therapy is 100 mg/m².

**4. Prostate Cancer:**

The recommended dose of **INNOTERE** is 75 mg/m². Prednisone or prednisolone 5 mg orally twice daily is administered continuously.

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

**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 **INNOTERE** is 75 mg/m² as a 1-hour infusion followed by cisplatin 75 mg/m² over 1 hour, on day one, followed by 5-fluorouracil as a continuous infusion at 750 mg/m² 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-emetic and appropriate hydration (prior to and after cisplatin administration). Prophylaxis for

neutropenic infections should be administered. For cisplatin and 5-fluorourcil dose modifications, see the professional information for these medicines.

**Dosage adjustments during treatment:**

**General:**

Only the doctor can modify the schedule of administration.

**INNOTERE** should be administered when the neutrophil count is ≥ 1 500 cells/mm³.

Patients who experienced either febrile neutropenia, neutrophil count < 500 cells/mm³ for more than one week, severe or cumulate cutaneous or severe neurosensory signs and/or symptoms, during **INNOTERE** therapy, should have the dosage of **INNOTERE** reduced, during the subsequent cycle, from 100 mg/m² to 75 mg/m² 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 INNOTERE for NSCLC**

For patients who are dosed initially at **INNOTERE** 75 mg/m² in combination with cisplatin, and whose nadir of platelet count during the previous course of therapy is < 25 000 cells/mm³, or in patients who experience febrile neutropenia, or in patients with serious non-haematologic toxicities, the **INNOTERE** dosage in subsequent cycles should be reduced to 65 mg/m².

**Combination therapy with INNOTERE for Breast Cancer**

Patients who receive adjuvant therapy for breast cancer and who experienced febrile neutropenia may benefit from receiving G-CSF in all subsequent cycles. If G-CSF is not used, the **INNOTERE** dose should be reduced from 75 to 60 mg/m². For capecitabine dose modifications when combined with **INNOTERE**, see the professional information for capecitabine.

For patients developing the first appearance of Grade 2 toxicity which persist at the time of the next **INNOTERE** /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 Grade 2 toxicity, or the first appearance of Grade 3 toxicity, at any time during the treatment cycle, delay treatment until resolved to Grade 0-1, and then resume treatment with **INNOTERE** 55 mg/m². For any subsequent appearance of toxicities, or any Grade 4 toxicities, discontinue the **INNOTERE** dose.

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

**Special Populations:**

**Patients with hepatic impairment:**

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

**Elderly:**

There are no special instructions for the use in the elderly. For capecitabine dosage reduction when combined with **INNOTERE**, see the professional information for

capecitabine.

**Paediatric Population:**

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

**Method of administration:**

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

### 4.3 Contraindications

**INNOTERE** is contraindicated in patients who have a history of hypersensitivity reactions to the active ingredient in **INNOTERE** or polysorbate 80 or any of the ingredients listed in **section 6.1**

**INNOTERE** should not be used in patients with baseline neutrophil count of < 1500 cells/mm³.

**INNOTERE** is contraindicated in pregnancy and lactation as it was found to be teratogenic in animals (see **section 4.6**).

The safe use of **INNOTERE** in children has not been established.

**INNOTERE** 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 **INNOTERE**.

## 4.4 Special warnings and precautions for use

**INNOTERE** (docetaxel) concentrate for solution should be administered under the supervision of a qualified doctor 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 **INNOTERE** therapy is increased in patients with abnormal liver function and in patients receiving higher doses**. INNOTERE** should generally not be given to patients with serum bilirubin levels > upper limits 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 has a higher rate of febrile neutropaenia grade 4, but does not have an increased incidence of toxic death. Bilirubin, AST or ALT and alkaline phosphatase values should be obtained prior to each cycle of **INNOTERE** therapy and reviewed by the treating doctor.

**INNOTERE** therapy should not be given to patients with neutrophil counts of < 1 500 cells/mm³. In order to monitor the occurrence of neutropenia, which may

be severe and results in infections, frequent blood cell counts should be performed on all patients receiving **INNOTERE.**

Severe hypersensitivity reactions characterised by hypotension and/or bronchospasm, or generalised rash/erythema occurs in patients who receive the recommended 3-day dexamethasone premedication. Hypersensitivity reactions requiring discontinuation of the **INNOTERE** infusion were reported. These reactions resolved after discontinuation of the infusion and the administration of appropriate therapy.

**INNOTERE** must not be given to patients who have a history of severe hypersensitivity reactions to docetaxel, as contained in **INNOTERE** or to other medicines formulated with polysorbate 80. Severe fluid retention may occur in patients despite the use of a recommended dexamethasone premedication regimen. It is characterised by one or more of the following events: severe peripheral oedema, generalised oedema, pleural effusion requiring urgent drainage, dyspnoea at rest, cardiac tamponade or pronounced abdominal distention (due to ascites).

The use of **INNOTERE** should be confined to units specialised in the administration of cytotoxic chemotherapy and it should only be administered under the supervision of a qualified oncologist. Since significant hypersensitivity reactions may occur, appropriate

supportive equipment should be available. During the infusion, it is recommended that vital functions should be closely monitored.

Premedication consisting of an oral corticosteroid (see below for prostate) such as dexamethasone 16 mg per day (e.g. 8 mg twice daily) for 3 days, starting one day prior to **INNOTERE** administration, unless contraindicated, may reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. The pre-treatment regiment for prostate cancer is oral dexamethasone 8 mg, 12 hours, 3 hours and 1 hour before the **INNOTERE** regimen.

**Haematology:**

Neutropenia is the most frequent adverse reaction of **INNOTERE** and occurs in almost all patients. Severe neutropenia (grade 3-4) occurs frequently in patients on combination therapy with doxorubicin. Neutrophil nadirs occurred at a median of 7 days but this interval maybe shorter in heavily pre-treated patients. Frequent monitoring of complete blood counts should be conducted on all patients receiving **INNOTERE**. Patients should be re-treated with **INNOTERE** only after neutrophils recover to level ≥ 1 500 cells/mm³ (see "**Section 4.2**").

In the case of severe neutropenia (< 500 cells/mm³ for seven days or more) during a course of **INNOTERE** therapy, a reduction in dose for subsequent courses of therapy and the use of appropriate symptomatic measures are recommended.

**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 **INNOTERE**, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or cutaneous reactions do not require interruption of therapy. However more severe reactions, such as hypotension with a reduction of more than 20 mmHg, 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 **INNOTERE**.

**Fluid Retention:**

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

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

**Patients with Liver Impairment:**

In patients treated with **INNOTERE** at 100 mg/m² who have serum transaminase levels (ALT and/or AST) greater than 1,5 times the upper limits of the normal range (ULN) concurrent with serum alkaline phosphatase levels greater than 2,5 times the upper limits of the normal range (ULN), there is a higher risk of developing severe adverse reactions such as toxic deaths, sepsis and gastrointestinal haemorrhage which can be fatal febrile neutropenia, infections, thrombocytopenia, stomatitis and asthaenia. Therefore, the

recommended dose of **INNOTERE** in patients with elevated liver function tests (LFTs) is 75 mg/m² 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 **INNOTERE** should not be used unless strictly indicated.

**Cutaneous Reactions:**

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

**Nervous System Disorders:**

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

**Elderly:**

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

**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 **INNOTERE** therapy is recommended until diagnosis is available. Early use of supportive care measures may help improve the condition. The benefit of resuming docetaxel treatment must be carefully evaluated.

**Patients with renal impairment**

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

**Eye disorders**

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

**Others:**

Contraceptive measures must be taken during and for at least four months after cessation of **INNOTERE** therapy for men and at least seven months after cessation of **INNOTERE** therapy for women.

**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 (see section 4.2).

***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 (CHF)***

Patients should be monitored for symptoms of congestive heart failure during therapy and during the follow up period. In patients treated with the TAC regimen for node positive breast cancer, the risk of CHF has been shown to be higher during the first year after treatment (see section 4.8 and 5.1).

***Leukaemia***

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

***Patients with 4+ nodes***

As the benefit observed in patient with 4+ nodes was not statistically significant on disease-free survival (DFS) and overall survival (OS), the positive benefit/risk ratio for TAC in patients with 4+ nodes was not fully demonstrated at the final analysis (see section 5.1).

***Older people***

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

Of the 333 patients treated with **INNOTERE** every three weeks in a prostate cancer study, 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with **INNOTERE** every three weeks, the incidence of related nail changes occurred at a rate ≥ 10% higher in patients who were 65 years of age or greater compared to younger patients. The incidence of related fever, diarrhoea, anorexia, and peripheral oedema occurred at rates ≥ 10% higher in patients who were 75 years of age or greater versus less than 65 years.

Among the 300 (221 patients in the phase III part of the study and 79 patients in the phase II part) patients treated with docetaxel in combination with cisplatin and 5 fluorouracil in the gastric cancer study, 74 were 65 years of age or older and 4 patients were 75 years of age or older. The incidence of serious adverse events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, 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.

Contains alcohol. **INNOTERE** is harmful for those suffering from alcohol.

**4.5 Interaction with other medicines and other forms of interaction**

There have been no formal clinical studies to evaluate the interactions of docetaxel, as contained in **INNOTERE**

In *vitro* studies show that the metabolism of docetaxel 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, 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 **INNOTERE** 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, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole) cannot be avoided, a close clinical surveillance is warranted and a dose-adjustment of **INNOTERE** may be suitable during the treatment with the strong CYP3A4 inhibitor.

The co-administration of **INNOTERE** with the strong CYP3A4 inhibitor ketoconazole may lead to a significant decrease in docetaxel clearance (by 49%).

Docetaxel is highly protein bound (> 95 %). Although the possible *in vivo* interaction of **INNOTERE** with concomitantly administered medicine 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 **INNOTERE**.

When used in combination with doxorubicin, **INNOTERE** clearance is increased.

In addition, dexamethasone did not affect protein binding of **INNOTERE**.

**INNOTERE** does not influence the binding of digoxin.

Clearance of **INNOTERE** in combination therapy with cisplatin is similar to that observed following monotherapy. The pharmacokinetic profile of cisplatin administered shortly after **INNOTERE** infusion is similar to that observed with cisplatin alone. There is no effect by capecitabine on the pharmacokinetics of **INNOTERE** (Cmax and AUC) and no effect by **INNOTERE** on the pharmacokinetics of the main capecitabine metabolite 5'-DFUR.

There is no effect of prednisone on the pharmacokinetics of **INNOTERE**.

**INNOTERE** should be administered with caution in patients concomitantly receiving potent CYP3A4 inhibitors (e.g. protease inhibitors like ritonavir and azole antifungals like ketoconazole or itraconazole). A medicine interaction study performed in patients receiving ketoconazole and docetaxel as contained in **INNOTERE**, showed that the clearance of **INNOTERE** was reduced by half by ketoconazole, probably because the metabolism of **INNOTERE** involves CYP3A4 as a major (single) metabolic pathway. Reduced tolerance of **INNOTERE** may occur, even at lower doses.

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

## 4.6 Fertility, pregnancy and lactation

**Pregnancy**

Pregnancy is contraindicated as **INNOTERE** is teratogenic in animals (see section 4.3).

**Breast feeding**

Lactation is contraindicated during treatment with **INNOTERE** (see section 4.3).

**Women of childbearing potential/Contraception in males and females**

Women of childbearing age receiving docetaxel should be advised to avoid becoming pregnant, and to inform the treating doctor immediately should this occur.

Contraceptive measures must be taken during treatment and for at least four months after cessation of **INNOTERE** therapy for men and at least seven months after cessation of **INNOTERE** therapy for women.

**Fertility**

In non-clinical studies, docetaxel, as contained in **INNOTERE,** had genotoxic effects and may alter male fertility. Therefore, men being treated with **INNOTERE** are advised not to father a child during and up to 4 to 6 months after treatment and to seek advice on conservation of sperm prior to treatment.

**4.7 Effects on ability to drive and use machines**

There are no results on studies performed on the effects on the ability to drive and use machines. The amount of alcohol in this medicine may impair the ability to drive or use machines (see section 4.4).

**4.8 Undesirable effects**

a. **Summary of the safety profile**

In clinical trials with docetaxel, as contained in **INNOTERE**, the most commonly reported adverse reactions of **INNOTERE** alone were: neutropenia (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), anaemia, alopecia, nausea, vomiting, stomatitis, diarrhoea and asthenia. The severity of adverse events of **INNOTERE** may be increased when it is given in combination with other chemotherapeutic medicines.

The following undesirable effects are frequently observed with **INNOTERE**:

*Immune system disorders*

Hypersensitivity reactions have occurred within a few minutes following the start of the infusion of **INNOTERE** and were usually mild to moderate. The most frequently reported symptoms were flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills. Severe reactions were characterised by hypotension and/or bronchospasm or generalised rash/erythema (see **section** 4.4).

*Nervous system disorders*

The development of severe peripheral neurotoxicity requires a reduction of dose (see **sections 4.2 and 4.4**). Mild to moderate neuro-sensory signs are characterised by paraesthesia, dysesthesia or pain including burning. Neuro-motor events are mainly characterised by weakness.

*Skin and subcutaneous tissue disorders*

Reversible cutaneous reactions have been observed and were generally considered as mild to moderate. Reactions were characterised by a rash including localised eruptions mainly on the feet and hands (including severe hand and foot syndrome), but also on the arms, face or thorax, and frequently associated with pruritus. Eruptions occurs within one week after the **INNOTERE** infusion. Less frequently, severe symptoms such as eruptions followed by desquamation which may lead to interruption or discontinuation of **INNOTERE** treatment are reported (see **sections 4.2 and 4.4**). Severe nail disorders are characterised by hypo- or hyperpigmentation and sometimes pain and onycholysis.

*General disorders and administration site conditions:*

Infusion site reactions are generally mild and consisted of hyper pigmentation, inflammation, redness or dryness of the skin, phlebitis or extravasation and swelling of the vein.

Fluid retention includes events such as peripheral oedema and less frequently pleural effusion, pericardial effusion, ascites and weight gain. The peripheral oedema usually starts at the lower extremities and may become generalised with a weight gain of 3 kg or more. Fluid retention is cumulative in incidence and severity (see **section 4.4).**

b. **Tabulated summary of adverse reactions**

| **MedDRA system organ classes** | **Frequent undesirable effects** | **Less frequent undesirable effects** |
|---|---|---|
| **Infections and infestations** | **oral candiasis,** Infection, fever in the absence of infection, neutropenic infection | |
| **Blood and lymphatic system disorders** | Neutropenia, febrile neutropenia, thrombocytopenia, anaemia, infections, fever in absence of infection, neutropenic infection, hyperbilirubinemia | severe anaphylactic reaction (characterised by hypotension and/or bronchospasm or generalised rash/erythema) |

| | | | |
|---|---|---|---|
| | | | |
| **Immune system disorders:** | Flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea, drug fever, chills, hypersensitivity reaction | | |
| **Metabolism and nutrition disorders** | anorexia, weight gain, decreased appetite, dehydration, decreased weight. | | |
| **Nervous system disorders** | Paraesthesia, dysaesthesia, pain, weakness, neuropathy sensory, neuro-cortical, neuropathy motor, neuro-cerebellar, taste disturbance, dizziness, headache, peripheral neuropathy. | syncope | |
| **Eye disorders** | Lacrimation, conjunctivitis | | |

| | | | |
|---|---|---|---|
| **Cardiac disorders** | Hypotension, cardiac dysrhythmias, vasodilation cardiac left ventricular function, ischaemic myocardial, venous, lower limb oedema, cardiac left ventricular function | Heart failure, venous thromboembolic events, myocardial infarction | |
| **Vascular disorders** | peripheral oedema, pleural effusion, pericardial effusion, ascites, increased capillary permeability, weight gain, fluid retention | | |
| **Respiratory, thoracic and mediastinal disorders** | cough, sore throat, dyspnoea, epistaxis | | |
| **Gastrointestinal disorders:** | Nausea, vomiting, diarrhoea, anorexia, constipation, stomatitis, taste perversion, upper abdominal pain, dry mouth, pharyngitis, | dehydration, gastrointestinal perforation, ischemic colitis, colitis, and neutropenic enterocolitis | |

| | | | |
|---|---|---|---|
| | odynophagia, gastrointestinal pain/cramping, heartburn, gastrointestinal bleeding, oesophagitis/dysphagia | | |
| **Hepatobiliary disorders:** | ALT increase, AST increase, bilirubin increase, alkaline phosphatase increase. | Hepatitis | |
| **Skin and subcutaneous disorders:** | Rash (including local eruptions), pruritis, nail disorders (including pain and onycholysis for the nails), alopecia, nail disorders, skin toxicity, hand-foot syndrome, nail discolouration, onycholysis, desquamation, dry skin | | |

| | | | |
|---|---|---|---|
| **Musculoskeletal, connective tissue and bone disorders**: | *A*sthenia, myalgia, arthralgia, back pain | | |
| **Renal and urinary disorders** | | Dysuria, haematuria, oliguria, urinary incontinence, enuresis, nocturia, renal failure and urethral pain. | |
| **Reproductive system and Breast disorders** | Amenorrhoea | Breast pain, pelvic pain, vaginal discharge, vaginal discomfort, vaginal dryness, vaginal haemorrhage and vulval disorders | |
| **General disorders and administrative site conditions:** | Alopecia, asthenia, myalgia, infusion site reactions, pain, pyrexia, fatigue, weakness, pain in limb, lethargy, taste, sense of smell altered, altered hearing, cancer | | |

| | | |
|---|---|---|
| | pain, weight loss | |
| **Investigations:**<br><br>**Injury and poisoning:** | | Decreased haemoglobin<br><br>Oesophageal burn and neurotoxicity |

**Reporting of suspected adverse reactions**

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

Suspected adverse reactions can also be reported directly to the HCR via email: pv@innovata.co.za or tel: +27 86 999 0912

**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 **INNOTERE** 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

Category and class of medicine: Cytostatic agents A 26

Pharmacotherapeutic group: Taxanes.

ATC code: L01CD02.

Mechanism of action:

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.

Pharmacodynamic effects:

Docetaxel is 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 concentration 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 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 is obtained with a corresponding AUC of
4,6 h. µg/mL. Mean values for total body clearance and steady-state volume of distribution are 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. 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

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

**INNOTERE 20 mg/1 ml:**

Excipients are polysorbate 80, citric acid monohydrate and ethanol (anhydrous).

**INNOTERE 80 mg/4 ml**

Excipients are polysorbate 80, citric acid monohydrate and ethanol (anhydrous).

**6.2 Incompatibilities**

**INNOTERE** must not be mixed with other medicinal products except those mentioned in **section 6.6.**

**6.3 Shelf life**

Unopened vial: 24 months

***After opening of the vial***

Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions must be controlled by the user.

***Once added to the infusion bag***

Reconstitution/dilution must take place in a controlled and under aseptic conditions and the medicine should be used immediately. If it is not used immediately, in use storage times and conditions must be controlled by the user.

Once added as recommended into the infusion bag (PP) or infusion bottle (PE), the **INNOTERE** infusion solution, if stored below 25°C, is stable for 8 hours in infusion bottle or for 6 hours in infusion bag. It should be used within 6-8 hours (which includes the one-hour infusion IV administration).

In addition, physical and chemical in-use stability of the infusion solution prepared as recommended has been demonstrated in non-PVC bags up to 48 hours when stored between 2 to 8°C.

**INNOTERE** infusion solution is a supersaturated solution. It may crystallize over time. If crystallisation takes place, the solution must not be used and it must be discarded.

**6.4 Special Precautions for storage**

Single-dose vials of **INNOTERE** concentrate for infusion should be stored at or below 25 °C and protected from light.

The INNOTERE infusion solution should preferably be used immediately. It may, however, be stored at room temperature (not exceeding 25 °C) for a maximum of 8 hours (this includes the one-hour infusion time for administration of the infusion, under room temperature and normal lighting conditions). It may also be stored for 48 hours in refrigerator conditions (2-8 °C). Discard any unused solution. (See section 6.3)

**6.5 Nature and contents of container**

**INNOTERE 20 mg/1 ml:**

Concentrate for solution for infusion is filled in a 1 ml colourless type-I glass vial, closed with a 13 mm grey chlorobutyl rubber stopper and a flip-off seal consisting of an aluminium shell and a plastic flip-off button.

The rubber stopper is coated with a Teflon® barrier film.

**INNOTERE 80 mg/4 ml:**

Concentrate for solution for infusion is filled in a 4 ml colourless type-I glass vial, closed with a 20 mm grey chlorobutyl rubber stopper and a flip-off seal consisting of an aluminium shell and a plastic flip-off button.

The rubber stopper is coated with a Teflon® barrier film.

The sealed vial is labelled with a pre-printed label and packed into a pre-printed carton together with the package insert.

**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 reconstitute the medicine in a designated area.
- **INNOTERE** is an antineoplastic medicine and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing **INNOTERE** solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn
- If **INNOTERE** concentrate or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water. If **INNOTERE** concentrate or infusion solution should come into contact with the eyes or 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 **INNOTERE**.
- Any unused product or waste material should be disposed of in accordance with local requirements.
- Preparation for intravenous administration:
- Preparation of the infusion solution:

- DO NOT use the two-vial formulation (injection concentrate and diluent) with the one-vial formulation.
- The vials are stored under refrigeration conditions. The required number of **INNOTERE** boxes must therefore be allowed to stand at room temperature (below 25 °C) for 5 minutes before use.
- More than one **INNOTERE** concentrate vial may be necessary to obtain the required dose for the patient. Based on the required dose for the patient expressed in mg, aseptically withdraw the required amount of **INNOTERE** 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 INNOTERE is required, use a large volume of the infusion vehicle so that a concentration of 0,74 mg/ml **INNOTERE** is not exceeded.
- Mix the infusion bag or bottle manually using a rocking motion.
- The **INNOTERE** infusion 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.
- **INNOTERE** infusion solution should be visually inspected prior to use. Solutions containing a precipitate should be discarded.

**7.HOLDER OF CERTIFICATE OF REGISTRATION**

Innovata Pharmaceuticals (Pty) LTD

Crownwood office Park

100 Northern Parkway

Ormonde

Johannesburg

2091

SOUTHAFRICA

Tel: +27 86 999 0912

**8. REGISTRATION NUMBERS**

**INNOTERE 20:** 52/26/0202

**INNOTERE 80:** 52/26/0203

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

14 July 2020

**10. DATE OF REVISION OF THETEXT**

18 September 2026