INOTRIX P1532219

INOTRIX P1532219

Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

INOTRIX 40 mg/2 mL concentrate for solution for infusion
INOTRIX 100 mg/5 mL concentrate for solution for infusion
INOTRIX 300 mg/15 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INOTRIX 40 mg/2 mL concentrate for solution for infusion contains 40 mg irinotecan hydrochloride trihydrate.
Contains sugar: 90,0 mg sorbitol.
INOTRIX 100 mg/5 mL concentrate for solution for infusion contains 100 mg irinotecan hydrochloride trihydrate.
Contains sugar: 225,0 mg sorbitol.
INOTRIX 300 mg/15 mL concentrate for solution for infusion contains 300 mg irinotecan hydrochloride trihydrate.
Contains sugar: 675,0 mg sorbitol.
Each mL of solution contains 20 mg irinotecan hydrochloride trihydrate
INOTRIX contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Clear colourless to slightly yellow solution, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

INOTRIX is indicated for the treatment of patients with advanced colorectal cancer with a WHO performance status of 2 or lower:
- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for advanced disease,
- As a single medicine in patients who have failed an established 5-fluorouracil containing treatment regimen.

4.2. Posology and method of administration

Posology

Recommended Dosage:
In monotherapy (for previously treated patient):
The recommended dosage of **INOTRIX** is 350 mg/m² administered as an intravenous infusion over a 30 to 90 minute period every three weeks.

In combination therapy (for previously untreated patient):
Safety and efficacy of **INOTRIX** in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:
1) **INOTRIX** plus 5FU/FA in weekly schedule:
The recommended dose of **INOTRIX** is 80 mg/m² administered as a weekly intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and then by 5-fluorouracil over 6 weeks. This treatment is followed by one week rest.
The full dosage regimen is as follows:
INOTRIX 80 mg/m² as a 30 to 90 minute infusion on Day 1 and then weekly for 6 weeks.
Folinic acid 500 mg/m² intravenous infusion as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m² intravenous infusion as a 24-hour infusion, on Day 1 and then weekly for 6 weeks. The treatment is to be repeated every 7 weeks.

2) **INOTRIX** plus 5FU/FA in every 2 weeks schedule:
The recommended dose of **INOTRIX** is 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 30 to 90 minute period, followed by infusion with folinic acid and 5-fluorouracil.
The full dosage regimen is as follows:
INOTRIX 180 mg/m² intravenous infusion as a 30 to 90 minute infusion on Day 1 only.
Folinic acid 200 mg/m² intravenous infusion as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m² intravenous infusion bolus, followed by 5-fluorouracil 600 mg/m² intravenous infusion as a 22-hour infusion. The folinic acid and 5-fluorouracil are repeated for two consecutive days. Repeat the cycle every two weeks.

Dosage Adjustments:

Delayed Dosing:
INOTRIX should not be administered until the neutrophil count remains above 1 500 cells/mm³. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of **INOTRIX** should be delayed until there has been a full recovery of these effects, especially diarrhoea.

INOTRIX should be administered after appropriate recovery of all adverse events to grade 0 or 1 NCI-CTC grading (National Cancer Institute Common Toxicity Criteria) and when treatment-related diarrhoea is fully resolved. This must be strictly adhered to.
At the start of a subsequent infusion of therapy, the dose of **INOTRIX**, and 5FU when applicable, should be decreased according to the worst grade of adverse events observed in the prior infusion. Treatment should be delayed by 1 to 2 weeks to allow recovery from treatment-related adverse events.

With the following adverse events a dose reduction of 15 to 20 % should be applied for **INOTRIX** and/or 5FU when applicable:
- haematological toxicity [neutropenia grade 4, febrile neutropenia (neutropenia grade 3 - 4 and fever grade 2 - 4)], thrombocytopenia and leukopenia (grade 4);
- non-haematological toxicity (grade 3 - 4).

Treatment Duration:
Treatment with **INOTRIX** should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Method of administration
INOTRIX infusion solution should be infused into a peripheral or central vein.
INOTRIX should not be delivered as an intravenous bolus or an intravenous infusion shorter than 30 minutes or longer than 90 minutes.

For instruction on the preparation of **INOTRIX** see section 6.6.

4.3. Contraindications

Contraindications of **INOTRIX**:
- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of **INOTRIX** (see section 6.1).
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with **INOTRIX** until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving **INOTRIX** should be advised to avoid becoming pregnant and to inform the treating medical practitioner immediately should this occur (see section 4.6).
- Bilirubin > 1,5 times the upper limit of the normal range.
- The safety and efficacy of **INOTRIX** in children have not been established.
- Severe bone marrow failure.
- WHO performance status > 2.
- Concomitant administration of azole antifungals, St. John's Wort (see section 4.5).
- Live attenuated vaccines (see section 4.5).

4.4. Special warnings and precautions for use

INOTRIX should be used in patients with a WHO good performance status of less than 2.

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

It is strongly recommended that **INOTRIX** be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

In all instances where the use of **INOTRIX** is considered for chemotherapy, it is especially important to ensure that the patient understands the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake. In rare cases where it is predictable that the patient would comply poorly with the guidance for the management of side effects, a strict follow-up of the patient by the treating medical practitioner or hospitalisation is recommended.

Given the nature and frequency of adverse events, the expected benefit must be balanced in case of risk factors, especially WHO Performance status ≥ 2 (or Karnofsky Index < 50).

Delayed diarrhoea:
Apart from the diarrhoea shortly after the infusion of **INOTRIX**, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of **INOTRIX** and at any time before the next cycle. In monotherapy, the median time of onset of the first liquid stool was on day 5 after the infusion of **INOTRIX**. Patients should quickly inform their medical practitioner of its occurrence and start appropriate therapy immediately.
Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy, those with baseline leukocytosis and those with performance status ≥ 2. If not properly treated, diarrhoea can be life-threatening, especially if the patient is concomitantly neutropenic.
As soon as the first liquid stool occurs, the patient should start drinking large volumes of beverages containing electrolytes and an appropriate antidiarrhoeal therapy must be initiated immediately.
This antidiarrhoeal treatment will be prescribed by the department where **INOTRIX** has been administered. After discharge from the hospital, the patients should obtain the prescribed medicines so that they can treat the diarrhoea as soon as it occurs. In addition, they must inform their medical practitioner or the department administering **INOTRIX** that diarrhoea is occurring.
The currently recommended antidiarrhoeal treatment is loperamide 4 mg for the first intake and then 2 mg every 2 hours. This therapy should continue for 12 hours after the last liquid stool and should not be modified. In no case should loperamide be administered for more than 48 consecutive hours at these doses, because of the risk of paralytic ileus, nor for less than 12 hours.

In addition to the antidiarrhoeal treatment, a prophylactic broad spectrum antibiotic should be given when diarrhoea is associated with severe neutropenia (neutrophil count < 500 cells/mm³).
In addition to the antibiotic treatment, hospitalisation is recommended for management of the diarrhoea in the following cases:
- Diarrhoea associated with fever,
- Severe diarrhoea (requiring intravenous hydration),
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Loperamide should not be given prophylactically, even in patients who experienced delayed diarrhoea at previous cycles.
In patients who experienced severe diarrhoea, a reduction in dose is recommended for subsequent cycles.

Haematology:
Weekly monitoring of complete blood cell counts should be performed during **INOTRIX** treatment.
Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 °C and neutrophil count ≤ 1 000 cells/mm³) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.
INOTRIX administration should be delayed until the neutrophil count is ≥ 1 500 cells/mm³.
In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm³), fever or infections associated with neutropenia, the dose of **INOTRIX** should be reduced.
In patients who experienced severe haematologic events, a dose reduction is recommended for subsequent administration.
There is an increased risk of infections and haematological toxicity in patients with severe diarrhoea.

Patients with hepatic function impairment:
Liver function tests should be performed at baseline and before each cycle.
Patients with impaired liver function (bilirubin > 1,0 and ≤ 1,5 times the upper limit of the normal range [ULN] and transaminases 5 times ULN) are at greater risk of developing severe neutropenia or febrile neutropenia and should be closely monitored, including complete blood counts.
INOTRIX should not be used in patients with a bilirubin > 1,5 times the ULN and the patients with bilirubin > ULN should be followed with caution.
In patients with a bilirubin of < 1,5 times ULN a dose of 350 mg/m² is recommended once every 3 weeks (see section 4.2).

Nausea and vomiting:
Prophylactic treatment with an anti-emetic is recommended before each treatment with **INOTRIX**.
Nausea and vomiting have been frequently reported. Patients with vomiting associated with delayed diarrhoea should be hospitalised as soon as possible for treatment.

Acute cholinergic syndrome:
If an acute cholinergic syndrome appears (defined as early diarrhoea and a group of symptoms such as sweating, abdominal cramping, lacrimation, myosis and salivation), atropine sulphate (0,25 mg subcutaneously) should be administered unless clinically contraindicated. These symptoms may disappear after atropine administration. Caution should be exercised in patients with asthma. In patients who experienced an acute cholinergic syndrome, the use of prophylactic atropine sulphate is recommended with subsequent doses of **INOTRIX**.

Immunosuppressant effects/increased susceptibility to infections:
Administration of live or live-attenuated vaccines in patients immunocompromised by **INOTRIX**, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving **INOTRIX**. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Elderly:
Due to the greater frequency of decreased hepatic, renal or cardiac function in an elderly patient, dose selection with **INOTRIX** should be cautious in this population.

Respiratory disorders:
Interstitial lung disease presenting as lung infiltration is uncommon during **INOTRIX** therapy. Interstitial lung disease can be fatal. Risk factors possibly associated with the development of interstitial lung disease include the use of pneumotoxic medicinal products, radiation therapy and colony stimulating factors. Patients with risk factors should be closely monitored for respiratory symptoms before and during irinotecan therapy

Extravasation:
While **INOTRIX** is not a known vesicant, care should be taken to avoid extravasation and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site and application of ice is recommended.

Chronic inflammatory bowel disease and/or bowel obstruction:
Patients must not be treated with **INOTRIX** until resolution of the bowel obstruction (see section 4.3).

Renal function:
Increases in serum creatinine or blood urea have been observed. There have been cases of acute renal failure. These events have generally been attributed to complications of infection or to dehydration related to nausea, vomiting, or diarrhoea. Instances of renal dysfunction due to tumour lysis syndrome have also been reported.
No specific pharmacokinetic studies have been performed in patients with renal impairment.

Irradiation therapy:
Patients who have previously received pelvic/abdominal irradiation are at increased risk of myelosuppression following the administration of **INOTRIX**. Medical practitioners should use caution in treating patients with extensive prior irradiation (e.g., > 25 % of bone marrow irradiated and within 6 weeks prior to start of treatment with irinotecan as in **INOTRIX**). Dosing adjustment may apply to this population.

Cardiac disorders:
Myocardial ischaemic events have been observed following **INOTRIX** therapy predominately in patients with underlying cardiac disease, other known risk factors for cardiac disease, or previous cytotoxic chemotherapy (see section 4.8). Consequently, patients with known risk factors should be closely monitored, and action should be taken to try to minimise all modifiable risk factors (e.g. smoking, hypertension, and hyperlipidaemia).

Vascular disorders:
INOTRIX has been associated with thromboembolic events (pulmonary embolism, venous thrombosis, and arterial thromboembolism) in patients presenting with multiple risk factors in addition to the underlying neoplasm.

Others:
Cases of renal insufficiency, hypotension or circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.
Concomitant administration of **INOTRIX** with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbitone, phenytoin) of CYP3A4 may alter the metabolism of **INOTRIX** and should be avoided (see section 4.5).
Since **INOTRIX** contains sorbitol, patients with rare hereditary problems of fructose intolerance should not be given **INOTRIX**.

Paediatric population
The safety and efficacy of **INOTRIX** in children have not yet been established. No data are available.

4.5 Interaction with other medicines and other forms of interaction

Pharmacokinetic parameters of **INOTRIX** combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy.

Neuromuscular blocking medicines:
Interaction between **INOTRIX** and neuromuscular blocking medicines cannot be ruled out. Medicines with anticholinesterase activity may prolong the neuromuscular blocking effects of suxamethonium and the neuromuscular blockade of non-depolarising medicines may be antagonised. Excess acetylcholine may impair the muscle relaxant action of the non-depolarising medicines and may impair the return of normal muscle tone at the end of anaesthesia.

Antineoplastic medicines:
The adverse effects of **INOTRIX**, such as myelosuppression and diarrhoea, is expected to be exacerbated by other antineoplastic medicines having a similar adverse-effect profile.

Dexamethasone:
Lymphocytopenia has been reported in patients receiving **INOTRIX**, and it is possible that the administration of dexamethasone as antiemetic prophylaxis may have enhanced the likelihood of lymphocytopenia. Hyperglycaemia has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of **INOTRIX**. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives:
Laxative use during therapy with **INOTRIX** is expected to worsen the incidence or severity of diarrhoea.

Diuretics:
Dehydration secondary to vomiting and/or diarrhoea may be induced by **INOTRIX**. The medical practitioner may wish to withhold diuretics during dosing with **INOTRIX** and during periods of active vomiting or diarrhoea.

Anticonvulsants:
Concomitant administration of CYP3A enzyme-inducing anticonvulsant medicines (e.g. carbamazepine, phenobarbitone or phenytoin) leads to reduced exposure to the active metabolite SN-38. Consideration should be given to starting or substituting non-enzyme inducing anticonvulsants at least one week prior to initiation of **INOTRIX** therapy in patients requiring anticonvulsant treatment.

Azole antifungals:
INOTRIX clearance is greatly reduced in patients receiving concomitant azole antifungals, leading to increased exposure to the active metabolite, SN-38. Azole antifungals should be discontinued at least 1 week prior to starting **INOTRIX** therapy and should not be administered during **INOTRIX** therapy (see section 4.3).

St. John's Wort (Hypericum perforatum):
Exposure to the active metabolite of **INOTRIX** is reduced in patients taking concomitant St. John's Wort. St. John's Wort should be discontinued at least 1 week prior to the first cycle of **INOTRIX** and should not be administered during **INOTRIX** therapy (see section 4.3).

Atazanavir sulphate:
Co-administration of atazanavir sulphate, a CYP3A4 and UGT1A1 inhibitor has the potential to increase systemic exposure to SN-38, the active metabolite of **INOTRIX**.
Atazanavir should not be used with **INOTRIX**.

Bevacizumab:
In one study, **INOTRIX** plasma concentrations were similar in patients receiving **INOTRIX**/5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of **INOTRIX**, were analysed in a subset of patients. Concentrations of SN-38 were on average 33 % higher in patients receiving **INOTRIX**/5-FU/FA in combination with bevacizumab compared with **INOTRIX**/5-FU/FA alone. Due to high inter-patient variability and limited sampling, it is uncertain if the increase in SN-38 levels observed was due to bevacizumab. There was a small increase in diarrhoea and leukopenia adverse events. More dose reductions of **INOTRIX** were reported for patients receiving
INOTRIX/5-FU/FA in combination with bevacizumab.
Loperamide should not be given prophylactically.

Vaccines:
Yellow fever vaccine: Risk of fatal generalised reaction to vaccine.
Live attenuated vaccines: Risk of generalised reaction to vaccines, possibly fatal. Concomitant use is contraindicated during treatment with **INOTRIX** and for 6 months following discontinuation of chemotherapy.
Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Vitamin K antagonists:
Increased risk of haemorrhage and thrombotic events in tumoral diseases. If vitamin K antagonists are indicated, an increased frequency in the monitoring of INR (International Normalised Ratio) is required.

Immunodepressant medicines:
Immunodepressant medicines (e.g. ciclosporin, tacrolimus) may result in excessive immunosuppression with risk of lymphoproliferation.

4.6. Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and female
Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with **INOTRIX**. Women of childbearing potential and men have to use effective contraception during and up to 3 months after treatment.

Pregnancy
INOTRIX is contraindicated during pregnancy as it may cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of **INOTRIX** in pregnant women. If **INOTRIX** is used during pregnancy, or if the patient becomes pregnant, while receiving **INOTRIX**, the patient should be apprised of the potential hazard to the foetus (see section 4.3).

Breastfeeding
In lactating rats, 14C-irinotecan was detected in milk. It is unknown whether **INOTRIX** is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breastfeeding should be discontinued for the duration of **INOTRIX** therapy (see section 4.3)

Fertility
There is no human data on the effect of **INOTRIX** on fertility. In animals, adverse effects of **INOTRIX** on the fertility of offspring has been documented

4.7 Effects on ability to drive and use machines

INOTRIX has moderate influence on the ability to drive and use machines. Patients should be warned about the potential for dizziness or visual disturbances which may occur within 24 hours following the administration of **INOTRIX** and advised not to drive or operate machinery if these symptoms occur.

4.8 Undesirable effects

a. Summary of the safety profile
The most frequent, dose-limiting adverse reactions of **INOTRIX** are delayed diarrhoea (occurring more than 24 hours after administration) and blood disorders including neutropenia, anaemia and thrombocytopenia.

b. Tabulated list of adverse reactions
Frequencies are defined as: Frequent (more frequent, very common, common), Less frequent (single report, isolated report, uncommon, rare, very rare)
The following adverse reactions considered to be possibly or probably related to the administration of **INOTRIX** have been reported from patients at the recommended dose of 350 mg/m² in monotherapy.
Frequencies from post-marketing surveillance are not known (cannot be estimated from available data).

MedDRA System Organ Class	Frequency	Preferred Term
Blood and lymphatic system disorders	Frequent	Leukopenia, neutropenia*, anaemia, thrombocytopenia, febrile neutropenia
	Frequency unknown	Thrombocytopenia with antiplatelet antibodies
Immune system disorders	Frequency unknown	Hypersensitivity, anaphylactic reaction

DETACH BEFORE DISPENSING

SCHEDULING STATUS

S4

PATIENT INFORMATION LEAFLET
INOTRIX 40 mg/2 mL concentrate for solution for infusion
INOTRIX 100 mg/5 mL concentrate for solution for infusion
INOTRIX 300 mg/15 mL concentrate for solution for infusion
(Irinotecan hydrochloride trihydrate)
(Contains sugar: Sorbitol)

Read all of this leaflet carefully before INOTRIX is administered to you
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist, nurse or other healthcare provider.

What is in this leaflet:

1. What **INOTRIX** is and what it is used for
2. What you need to know before you are given **INOTRIX**
3. How **INOTRIX** will be administered to you
4. Possible side effects
5. How to store **INOTRIX**
6. Contents of the pack and other information

1. What INOTRIX is and what it is used for

INOTRIX belongs to a group of medicines called cytostatics (anti-cancer medicines).
INOTRIX is used to treat cancer of the lower bowel, alone or in combination with two other medicines (5-fluorouracil and folinic acid).

2. What you need to know before INOTRIX is administered to you

INOTRIX should not be administered to you:
- If you are hypersensitive (allergic) to irinotecan hydrochloride trihydrate or any of the ingredients of **INOTRIX** (listed in section 6).
- If you are pregnant or breastfeeding or if you think you may be pregnant.
- If you have severe bone marrow failure.
- If your WHO performance status > 2 (i.e. if your general health status does not allow you to carry out general activities of daily living).
- If you have a disease involving frequent inflammation of the intestine (chronic inflammatory bowel disease) or blockage of the intestine (ileus).
- If your bilirubin (breakdown product of red blood cells) level is high.
- If you are a child or adolescent.
- If you are taking azole antifungal medication (used to treat fungal infections).
- If you are taking St John's Wort (a herbal supplement).
- If you are having any live attenuated vaccinations. Speak to your healthcare provider before any vaccination.

Warnings and precautions
Tell your doctor or healthcare professional before being given the **INOTRIX** concentrate for solution for infusion if:
- you have impaired liver function you are at greater risk of developing severe decrease in white blood cells or fever.
- you experience nausea and vomiting. If you experience vomiting together with delayed diarrhoea, you should be hospitalised for treatment.
- you experience early diarrhoea together with a group of symptoms such as sweating, abdominal cramping, watery eyes and salivation. If this occurs, inform your doctor as a specific medication is required in order for these symptoms to disappear.
- you are an elderly patient, the dose may have to be adjusted accordingly.
- if you have recently had or are due to have vaccinations.
- if you have previously received pelvic/abdominal radiotherapy you may be at increased risk of developing bone marrow suppression.
- if you suffer/suffered from heart disease Your doctor will monitor you closely and discuss with you how risk factors (for example smoking, high blood pressure and to high fat content) can be reduced.
- if you have a type of lung disease that causes scarring of lungs.

INOTRIX should only be administered under the supervision of a qualified medical doctor in units specialised in the administration of chemotherapy. It is recommended that **INOTRIX** be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

Some people will need special care from their doctors when they are on **INOTRIX**. It is especially important that your doctor explains the need for sufficiently prolonged antidiarrhoeal treatment and abundant fluid intake if you require it.

You may develop diarrhoea soon after treatment or delayed diarrhoea, which if not properly treated can be life-threatening. As soon as the first liquid stool occurs please consult your doctor or healthcare professional immediately for appropriate treatment. You may need an antibiotic or hospitalisation.

Your blood cell count should be monitored weekly as infection may occur due to a decrease in white blood cells. Fever together with a decrease in white blood cells should be urgently treated in hospital. The **INOTRIX** dose should be delayed or reduced accordingly.

INOTRIX is rarely associated with blood flow disorders (blood clots in the vessels of your legs and lungs) and it may occur rarely in patients with multiple risks factors.
If you are not sure if any of the above apply to you, talk to your doctor or pharmacist before being given **INOTRIX**.

Children and adolescents
INOTRIX has not been studied in children or adolescents and therefore should not be used in this patient population.

Other medicine and INOTRIX:
Always tell your healthcare professional if you are taking any other medicine (this includes complementary or traditional medicines).
The use of **INOTRIX** with these medicines may cause undesirable interactions.

In particular tell your doctor if you are using medicines containing the following active substances:
- Medicines used to cause muscle paralysis/anaesthesia during surgery (neuromuscular blocking medicines). The effect of these medicines may be prolonged when administered together with **INOTRIX**.
- Other medicines used for cancer therapy (antineoplastic medicines). When administered together with **INOTRIX**, these medicines may worsen diarrhoea and blood disorders that may be experienced.
- A cortisone medicine known as dexamethasone used to treat inflammation and also cancer. When administered together with **INOTRIX**, dexamethasone may enhance (increase) the chances of experiencing a decrease in a type of white blood cells (a blood disorder known as lymphocytopenia).
- Laxatives, as these can worsen the incidence or severity of diarrhoea.
- Medicines that increase urination (diuretics) as this, together with the vomiting and diarrhoea that may be experienced with **INOTRIX**, can result in dehydration.
- Medicines used to treat epilepsy (i.e. anticonvulsants e.g. carbemazepine, phenobarbitone or phenytoin) which may decrease the effect of **INOTRIX**.
- Medicines used to treat fungal infection, known as azole antifungals (e.g. ketoconazole), as these may increase the effect of **INOTRIX**.
- A HIV medicine known as atazanavir may increase the effects of **INOTRIX**.
- A cancer medicine known as bevacizumab may increase the effects of **INOTRIX**.
- St. John's Wort (a herbal medication used to treat depression). When administered together with **INOTRIX**, the effect of **INOTRIX** is reduced.
- Ciclosporin or tacrolimus which are immunosuppressants (used to dampen down your body's immune system).
- A medicine which works against vitamin K , as this may increase your risk of bleeding. You may need to have more frequent checks.

Pregnancy, breastfeeding and fertility
If you are pregnant or breastfeeding, think you may be pregnant or are planning to have a baby, please consult your doctor, pharmacist or other healthcare provider for advice before being administered **INOTRIX**.

You should not be administered with **INOTRIX** if you are pregnant or breastfeeding your baby. It could harm your baby.

Women of childbearing age as well as men who have been administered with **INOTRIX**, must use contraceptive measures during the period of treatment and for at least 3 months after stopping treatment.

Driving and using machines
INOTRIX might cause dizziness or blurred vision. Do not drive or operate tools or machines if you experience such side effects.
It is not always possible to predict to what extent **INOTRIX** may interfere with the daily activities of a patient. Patients should ensure that they do not engage in the above activities until they are aware of the measure to which **INOTRIX** affects them.
INOTRIX contains sorbitol (a sugar), If your doctor has told you that you have an intolerance to some sugars, talk to your doctor before you receive **INOTRIX**.
INOTRIX contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How INOTRIX will be administered

You will not be expected to give yourself **INOTRIX**. It will be given to you by a person who is qualified to do so.-
Your doctor will calculate the exact dosage for you based on your weight and height.
When **INOTRIX** is administered on it's own, the usual dose is 350 mg/m² given as an intravenous infusion over 30 to 90 minutes every three weeks.
When **INOTRIX** is to be used together with 5-fluorouracil and folinic acid, the usual dose is 80 mg/m² given as an intravenous infusion over 30 to 90 minutes, followed by an infusion of folinic acid and the 5-fluorouracil over six weeks. After this period there will be one weeks rest.

The usual dose will be adjusted or delayed if you have neutropenia (very low blood count of a type of white blood cells), severe diarrhoea, vomiting or if you are elderly.
Your doctor will tell you how long your treatment with **INOTRIX** will last. Do not stop any treatment unless your doctor tells you to do so.
If you have the impression that the effect of **INOTRIX** is too strong or too weak, tell your doctor.

If you are administered more INOTRIX than you should
Since a healthcare professional will administer **INOTRIX**, he/she will control the dosage. However, in the event of overdosage, your doctor will manage the overdosage.

If your dose of INOTRIX is missed
Your doctor will administer **INOTRIX** so this should not happen. In the event a dose is missed, your doctor will not give you a double dose to make up for the missed doses.
Do not miss your doctor's appointments. Your doctor will tell you when treatment is to be stopped.

4. Possible side effects

INOTRIX can have side effects.
Not all side effects reported for **INOTRIX** are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking **INOTRIX**, please consult your doctor, pharmacist or other healthcare professional for advice.

If any of the following happens, tell your doctor immediately or go to the casualty department at your nearest hospital:
- Swelling around the eyes or face or tongue, (which may rarely be a serious allergic reaction)
- Swelling in the ankles, wrists, arms and legs
- Difficulty breathing
- Severe nausea, vomiting
- Fever
- Severe diarrhoea

These are all very serious side effects. If you have them, you may have had a serious reaction to **INOTRIX**. You may need urgent medical attention or hospitalisation.
A frequent side-effect with **INOTRIX** is diarrhoea. Please take note of the following important information:

Diarrhoea
INOTRIX may cause you to have diarrhoea. There are two types of diarrhoea, which can be distinguished by when they start. "Early" diarrhoea starts less than 24 hours after the infusion and "delayed" diarrhoea starts more than 24 hours after the infusion.
If you have ANY DIARRHOEA it is IMPORTANT that you tell your doctor or healthcare professional immediately.

Patients with an increased risk of diarrhoea are those who had a previous abdominal/pelvic radiotherapy and initial raised white blood cells.

Early diarrhoea (Frequent)
- if diarrhoea starts less than 24 hours after the infusion ("early diarrhoea") you should contact your doctor IMMEDIATELY.

This "early diarrhoea" may be accompanied by a group of other symptoms listed below. This is known as acute cholinergic syndrome occurring during or within the first 24 hours after the infusion of INOTRIX. The symptoms may be:

Frequent:
- abdominal pain/cramping

Less frequent:
- chills
- lacrimation (watery eyes)
- rhinitis (irritation and inflammation inside the nose which may result in stuffy nose, runny nose and/or post-nasal drip)
- dizziness
- hypotension (low blood pressure)
- malaise (lack of well being)
- increased salivation (mouth watering)
- myosis (constriction to the pupil of the eyes)

Frequency unknown:
- sweating
- visual disturbances
- conjunctivitis (inflammation of the eye)
- vasodilation (widening of blood vessels)

Delayed diarrhoea (Frequent)
- if your diarrhoea starts more than 24 hours after the infusion ("delayed diarrhoea") you should IMMEDIATELY contact your doctor.

You must tell your doctor if:
- you have nausea and vomiting as well as diarrhoea
- you have any fever as well as the diarrhoea
- you still have diarrhoea 48 hours after starting the diarrhoea treatment

Do not take any treatment for diarrhoea other than that given to you by your doctor.

Decrease in white blood cells (Frequent)

INOTRIX may cause a decrease in the number of some of your white blood cells, which play an important role in fighting infections. This is called neutropenia.
If you have any fever, this may be an indication of infection associated with this neutropenia.
Contact your doctor or healthcare provider immediately.

Nausea and vomiting (Frequent)
If you have any fever, and particularly if you also have diarrhoea and/or nausea and/or vomiting contact your doctor or healthcare provider IMMEDIATELY.
Tell your doctor if you notice any of the following IMMEDIATELY:

Frequent side effects:
- difficulty in breathing
- dehydration
- change in kidney function tests
- excessive bilirubin (breakdown product of red blood cells) in the blood
- low blood volume resulting in dizziness or fainting
- inflammation and ulceration of the membranes lining the digestive tract
- infection
- anaemia which is decreased number of red blood cells which may lead to a feeling of weakness, fatigue or poor concentration
- leucopenia which is too few white blood cells which results in greater risk of infection
- thrombocytopenia which is too few platelets in the blood which may result in bleeding into the skin, bruising or prolonged bleeding after injury
- blockage of blood vessels that can result in severe chest pain, stroke, inflammation of a vein with formation of a clot, heart attack, heart arrest, sudden death

Other side-effects have also been reported with INOTRIX
Frequent:
- loss of hair
- lack of appetite
- constipation
- inflammation of the mouth
- decreased weight
- pain
- lack of energy

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects via https://www.sahpra.org.za/Publications/Index/8. By reporting side effects, you can help provide more information on the safety of **INOTRIX**.

5. How to store INOTRIX

STORE ALL MEDICINES OUT OF REACH OF CHILDREN.
INOTRIX will be stored in the pharmacy
Store at or below 25 °C.
After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours at a temperature at or below 25 ºC for 4 days under refrigeration (between 2 and 8 ºC). Discard any unused portion thereafter. Do not freeze.
Keep the container in the outer carton in order to protect from light.
Do not use after the expiry date stated on the vial and the carton.

Return all unused medicine to your pharmacist.
Do not dispose of unused medicine in drains or sewerage systems (e.g. toilets).

6. Contents of the pack and other information

What INOTRIX contains
The active substance is irinotecan hydrochloride trihydrate.
Each mL of solution contains 20 mg irinotecan hydrochloride trihydrate

INOTRIX 40 mg/2 mL concentrate for solution for infusion contains 40 mg irinotecan hydrochloride trihydrate.
Contains 90,0 mg sorbitol.
INOTRIX 100 mg/5 mL concentrate for solution for infusion contains 100 mg irinotecan hydrochloride trihydrate.
Contains 225,0 mg sorbitol.
INOTRIX 300 mg/15 mL concentrate for solution for infusion contains 300 mg irinotecan hydrochloride trihydrate.
Contains 675,0 mg sorbitol.

The other ingredients of **INOTRIX** are Sorbitol, Lactic acid, Sodium hydroxide, Hydrochloric acid, Water for injection.

What INOTRIX looks like and contents of the pack
INOTRIX concentrate for solution for infusion is a clear colourless to slightly yellow solution, essentially free from visible particles.
The diluted infusion solution is a pale yellow clear, sterile, pyrogen-free solution, free from visible particles.

INOTRIX 40 mg/2 mL concentrate for solution for infusion is marketed in Type – I, 2 R amber BB tubular glass vial with 13 mm neck stoppered with 13 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having Taxim blue colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

INOTRIX 100 mg/5 mL concentrate for solution for infusion is marketed in Type – I, 6 R amber BB tubular glass vial with 20 mm neck stoppered with 20 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having Dark green colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

INOTRIX 300 mg /15 mL concentrate for solution for infusion is marketed in Type – I, 20 R amber BB tubular glass vial with 20 mm neck stoppered with 20 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having sky blue colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

Not all packs and pack sizes are necessarily marketed.

NAME, BUSINESS ADDRESS AND TELEPHONE NUMBER OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION
AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1, First Floor
53 Phillip Engelbrecht Avenue
Meyersdal, Ext. 12, 1448
Johannesburg
South Africa

This leaflet was last revised in
31 May 2022

REGISTRATION NUMBER
INOTRIX 40 mg/2 ml 55/26/0362
INOTRIX 100 mg/5 ml 55/26/0363
INOTRIX 300 mg/15 ml 55/26/0364

MedDRA System Organ Class	Frequency	Preferred Term
Gastrointestinal disorders	Frequent	Late diarrhoea, nausea, vomiting, early diarrhoea, abdominal cramping/pain, anorexia, stomatitis, constipation, mucositis
	Less frequent	Rectal disorder, GI monilia
	Frequency unknown	Intestinal obstruction, Ileus: cases of ileus without preceding colitis have also been reported, megacolon, gastrointestinal haemorrhage, colitis; in some cases, colitis was complicated by ulceration, bleeding, ileus, or infection, typhlitis, colitis ischaemic, colitis ulcerative, symptomatic or asymptomatic pancreatic enzymes increased, intestinal perforation
Metabolism and nutrition disorders	Frequent	Decreased weight, decreased appetite, dehydration, hypovolaemia
	Less frequent	Hypokalaemia, hypomagnesaemia
	Frequency unknown	Dehydration (due to diarrhoea and vomiting)
Skin and subcutaneous tissue disorders	Frequent	Alopecia
	Less frequent	Rash, cutaneous signs such as dry skin, pruritus, skin discolouration
	Frequency unknown	Sweating , skin reactions
Vascular disorders	Frequent	Venous and arterial thromboembolic events which includes –, arterial thrombosis, deep vein thrombophlebitis, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder
	Less frequent	Flushing
	Frequency unknown	Vasodilation, hypotension‡
Infections and infestations	Frequent	Infection
	Less frequent	Sepsis
	Frequency unknown	Pseudomembranous colitis one of which has been documented bacteriologically (Clostridium difficile), sepsis, fungal infections*, viral infections†
Hepatobiliary disorders	Frequent	Hyperbilirubinaemia
	Frequency unknown	Steatohepatitis, hepatic steatosis
Respiratory, thoracic and mediastinal disorders	Frequent	Dyspnoea
	Less frequent	Rhinitis
	Frequency unknown	Interstitial lung disease presenting as lung infiltration is uncommon during irinotecan therapy; early effects such as dyspnoea have been reported (see section 4.4), dyspnoea (see section 4.4), hiccups
Nervous system disorders	Less frequent	Abnormal gait, confusion, headache, dizziness
	Frequency unknown	Speech disorder generally transient in nature, in some cases, the event was attributed to the cholinergic syndrome observed during or shortly after infusion of irinotecan, paraesthesia, muscular contractions involuntary
Cardiac disorders	Frequent	Angina pectoris, cerebral infarct, cerebrovascular accident, heart arrest, myocardial infarct, myocardial ischaemia, sudden death
	Less frequent	Syncope, bradycardia
	Frequency unknown	Cardiac disorders, hypertension (during or after infusion), cardio circulatory failure‡
Renal and urinary disorders	Less frequent	Urinary tract infection
	Frequency unknown	Renal impairment and acute renal failure generally in patients who become infected and/or volume depleted from severe gastrointestinal toxicities‡, renal insufficiency‡
Reproductive system and breast disorders	Less frequent	Breast pain
Endocrine disorders	Less frequent	Diaphoresis, increased salivation
General disorders and administrative site conditions	Frequent	Asthenia, fever, mucosal inflammation, pain
	Less frequent	Chills, malaise, extravasation, tumour-lysis syndrome
	Frequency unknown	Infusion site reaction
Investigations	Frequent	Increased serum creatinine, blood bilirubin increase, increase serum alkaline phosphatase
	Less frequent	Increased GGTP (gamma-glutamyl transpeptidase), increase in amylase, increase in lipase
	Frequency unknown	Amylase increased, hypokalaemia, hyponatraemia mostly related with diarrhoea and vomiting, transaminases increased (i.e. AST and ALT) in the absence of progressive liver metastasis have been very rarely reported
Musculoskeletal and connective tissue disorders	Frequency unknown	Cramps

* Neutropenia was reversible and not cumulative; the median day to nadir was 8 days and total recovery was usually reached by day 22 in monotherapy and within 7 - 8 days in combination therapy. Infectious episodes resulted in death in 2 cases.

**e.g. Pneumocystis jirovecii pneumonia, bronchopulmonary aspergillosis, systemic candida.

† e.g. Herpes zoster, influenza, hepatitis B reactivation, cytomegalovirus colitis.

‡ Infrequent cases of renal insufficiency, hypotension or cardio circulatory failure have been observed in patients who experienced episodes of dehydration associated with diarrhoea and/or vomiting, or sepsis.

INOTRIX has been studied in combination with 5-FU and FA for metastatic colorectal cancer. Safety data of adverse reactions from clinical studies demonstrate very commonly observed NCI Grade 3 or 4 possibly or probably-related adverse events in the blood and the lymphatic system disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders MedDRA System Organ Classes. The following adverse reactions considered to be possibly or probably related to the administration of **INOTRIX** have been reported from patients treated by **INOTRIX** in combination therapy with 5FU/FA in every 2 weeks schedule at the recommended dose of 180 mg/m^2.

MedDRA System Organ Class	Frequency	Preferred Term
Infections and infestations	Frequent	Infection
Blood and lymphatic system disorders	Frequent	Thrombocytopenia, neutropenia, anaemia
	Frequent	Febrile neutropenia
Metabolism and nutrition disorders	Frequent	Decreased appetite
Nervous system disorders	Frequent	Cholinergic syndrome
Gastrointestinal disorders	Frequent	Diarrhoea, vomiting, nausea
	Frequent	Abdominal pain, constipation
Skin and subcutaneous tissue disorders	Frequent	Alopecia (reversible)

MedDRA System Organ Class	Frequency	Preferred Term
General disorders and administration site conditions	Frequent	Mucosal inflammation, asthenia
	Frequent	Pyrexia
Investigations	Frequent	Transaminases (ALT and AST) increased, blood bilirubin increased, blood alkaline phosphatase increased

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8

4.9 Overdose

Symptoms

There have been reports of overdosage at doses up to approximately twice the recommended therapeutic dose, which may be fatal. The most significant adverse reactions reported were severe neutropenia and diarrhoea.

Treatment

There is no known antidote for **INOTRIX**. Maximum supportive care should be instituted to prevent dehydration due to diarrhoea and to treat any infectious complications.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cytostatic topoisomerase I inhibitor. ATC Code: L01XX19

Mechanism of action

Irinotecan is a semi-synthetic derivative of camptothecin. It is an antineoplastic medicine, which acts as a specific inhibitor of DNA topoisomerase I. It is metabolised by carboxylesterase in most tissues to SN-38, which was found to be more active than irinotecan in purified topoisomerase I and more cytotoxic than irinotecan against several murine and human tumour cell lines. The inhibition of DNA topoisomerase I by irinotecan or SN-38 induces single-strand DNA lesions which blocks the DNA replication fork and are responsible for the cytotoxicity. This cytotoxic activity was found to be time-dependent and was specific to the S phase.

In vitro, irinotecan and SN-38 were found not to be significantly recognised by the P-glycoprotein^{MDR}, and displays cytotoxic activities against doxorubicin and vinblastine resistant cell lines.

Furthermore, irinotecan has a broad antitumour activity *in vivo* against murine tumour models (P03 pancreatic ductal adenocarcinoma, MA16/C mammary adenocarcinoma, C38 and C51 colon adenocarcinoma) and against human xenografts (Co-4 colon adenocarcinoma, Mx-1 mammary adenocarcinoma, ST-15 and SC-16 gastric adenocarcinomas). Irinotecan is also active against tumours expressing the P-glycoprotein^{MDR} (vincristine- and doxorubicin-resistant P388 leukaemias).

Beside the antitumour activity of irinotecan, the most relevant pharmacological effect of irinotecan is the inhibition of acetylcholinesterase.

5.2 Pharmacokinetic properties

Absorption

At the recommended dose of 350 mg/m^2, the mean irinotecan and SN-38 peak plasma concentrations were 7,7 µg/ml and 56 ng/ml, respectively and were reached at the end of the infusion. The mean area under the curve (AUC) values were 34 µg.h/ml and 451 ng.h/ml, respectively. A large inter-individual variability in pharmacokinetic parameters is generally observed for SN-38.

Distribution

A population pharmacokinetic analysis of irinotecan has been performed in patients with metastatic colorectal cancer, treated with various schedules and at different doses in phase II trials. Pharmacokinetic parameters estimated with a three-compartment model were similar to those observed in phase I studies.

All studies have shown that CPT-11 and SN-38 pharmacokinetics are independent of the administered dose, of the number of previous cycles and of the administration schedule.

In vitro, plasma protein binding for irinotecan and SN-38 was approximately 65 % and 95 %, respectively.

Biotransformation

Mass balance and metabolism studies with 14C-labelled medicine have shown that more than 50 % of an intravenously administered dose of irinotecan is excreted as unchanged substance, with 33 % in the faeces mainly via the bile and 22 % in urine.

Two metabolic pathways, each representing at least 12 % of the dose, have been identified: oxidative metabolism at the terminal piperidine ring by cytochrome P450 3A enzymes which results in an aminopentanoic acid derivative (APC) and a primary amine derivate and hydrolysis by carboxylesterases into the active metabolite SN-38. SN-38 is mainly eliminated by glucuronidation and further by biliary and renal excretion (less than 0,5 % of the irinotecan dose). Unchanged irinotecan is the major entity in plasma followed by APC, SN-38 glucuronide and SN-38. Only SN-38 has significant cytotoxic activity and no other circulating metabolites have been detected. Irinotecan clearance is decreased by about 40 % in patients with bilirubinaemia between 1,5 and 3 times the upper normal limit. In these patients a 200 mg/m^2 irinotecan dose leads to plasma irinotecan exposure comparable to that observed at 350 mg/m^2 in cancer patients with normal liver parameters. Coadministration of 5-fluorouracil/folinic acid in the combination regimen does not change the pharmacokinetics of irinotecan.

Elimination

In a study in 60 patients with a dosage regimen of a 30-minute intravenous infusion of 100 to 750 mg/m^2 every three weeks, irinotecan showed a biphasic or triphasic elimination profile. The mean plasma clearance was 15 L/h/m^2 and the volume of distribution at steady state (Vss) quite large: 157 l/m^2. The mean plasma half-life of the first phase of the triphasic model was 12 minutes, of the second phase 2,5 hours, and the terminal phase half-life was 14,2 hours. SN-38 showed a biphasic elimination profile with a mean terminal elimination half-life of 13,8 hours.

Pharmacokinetic/Pharmacodynamic relationship(s):

The intensity of the major toxicities encountered with irinotecan (e.g. leukoneutropenia and diarrhoea) are related to the exposure (AUC) to parent drug and metabolite SN-38. Significant correlations were observed between haematological toxicity (decrease in white blood cells and neutrophils at nadir) or diarrhoea intensity and both irinotecan and metabolite SN-38 AUC values in monotherapy.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

INOTRIX concentrate for infusion contains the following inactive ingredients:

Sorbitol, Lactic acid, Sodium hydroxide, Hydrochloric acid, Water for injection.

6.2 Incompatibilities

None known.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 months

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8 °C, unless reconstitution/ dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store at or below 25 °C.

After dilution in either 0,9 % sodium chloride or 5 % dextrose, the diluted solution is stable for 24 hours at a temperature at or below 25 ºC for 4 days under refrigeration (between 2 and 8 ºC). Discard any unused portion thereafter. See section 6.3 for shelf life after dilution.

Do not freeze.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

INOTRIX 40 mg/2 mL concentrate for solution for infusion is marketed in Type – I, 2 R amber BB tubular glass vial with 13 mm neck stoppered with 13 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having Taxim blue colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

INOTRIX 100 mg/5 mL concentrate for solution for infusion is marketed in Type – I, 6 R amber BB tubular glass vial with 20 mm neck stoppered with 20 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having Dark Green colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

INOTRIX 300 mg /15 mL concentrate for solution for infusion is marketed in Type – I, 20 R amber BB tubular glass vial with 20 mm neck stoppered with 20 mm Omniflex plus coated dark grey colour bromobutyl rubber stopper and sealed with cleared lacquered aluminium seal having sky blue colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

Not all packs and pack sizes are necessarily marketed.

6.6 Special precautions for disposal and handling

Preparation for the Intravenous Infusion Administration:

Aseptically withdraw the required amount of **INOTRIX** solution from the vial with a calibrated syringe and inject into a 250 mL infusion bag or bottle containing either 0,9 % sodium chloride solution or 5 % dextrose solution. The infusion should then be thoroughly mixed by manual rotation.

If any precipitate is observed in the vials before or after reconstitution, the product should be discarded according to standard procedures for cytotoxic medicines.

Do not admix with other medications.

INOTRIX reconstituted and diluted infusion solution is a pale-yellow clear, sterile, pyrogen-free solution, free from visible particles.

Medicine handling precautions for cytostatic medicines should be followed:

- Only trained personnel should reconstitute the medicine in a designated area.
- **INOTRIX** is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing **INOTRIX** solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If **INOTRIX** solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water.
- If **INOTRIX** solution 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 and any unused medicine.

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

AUROGEN SA (PTY) LTD
Woodhill Office Park, Building 1, First Floor
53 Phillip Engelbrecht Avenue
Meyersdal, Ext. 12, 1448
Johannesburg
South Africa

8 REGISTRATION NUMBER

INOTRIX 40 mg/2 ml 55/26/0362
INOTRIX 100 mg/5 ml 55/26/0363
INOTRIX 300 mg/ 15 ml 55/26/0364

9 DATE OF FIRST AUTHORISATION

31 MAY 2022

P1532219

⬆DETACH BEFORE DISPENSING

SKEDULERINGSTATUS

S4

PASIËNTINLIGTINGSBLAD
INOTRIX 40 mg/2 mL konsentraat vir oplossing vir infusie
INOTRIX 100 mg/5 mL konsentraat vir oplossing vir infusie
INOTRIX 300 mg/15 mL konsentraat vir oplossing vir infusie
(Irinotekaanhidrochloriedtrihidraat)
(Bevat suiker: Sorbitol)

Lees asseblief hierdie inligtingsblad noukeurig deur voordat INOTRIX aan jou toegedien word

- Hou hierdie inligtingsblad. Dit mag nodig wees dat jy dit weer lees.
- Indien jy enige verdere vrae het, vra jou dokter, apteker, verpleegster of ander gesondheidsorgverskaffer.

Wat is in hierdie inligtingsblad:

1. Wat is **INOTRIX** en waarvoor word dit gebruik
2. Wat jy moet weet voordat **INOTRIX** aan jou toegedien word
3. Hoe **INOTRIX** aan jou toegedien sal word
4. Moontlike newe-effekte
5. Hoe om **INOTRIX** te bêre
6. Inhoud van die pak en ander inligting.

1. Wat is INOTRIX en waarvoor word dit gebruik

INOTRIX behoort aan 'n groep medisyne wat sitosatiese middels (antikankermedisynes) genoem word.

INOTRIX word gebruik vir die behandeling van kolorektale kanker, as monoterapie of in kombinasie met twee ander medisynes (5-fluoorurasiel en foliniensuur).

2. Wat jy moet weet voordat INOTRIX aan jou toegedien word

INOTRIX moenie aan jou toegedien word nie:

- Indien jy hipersensitief (allergies) is vir irinotekaanhidrochloriedtrihidraat of vir enige van die bestanddele van **INOTRIX** (gelys by afdeling 6).
- Indien jy swanger is of jou baba borsvoed, of vermoed dat jy swanger kan wees.
- Indien jy erge beenmurgversaking het.
- Indien jou WGO-prestasiestatus > 2 is (d.i. indien jou algemene gesondheidstoestand sodanig is dat jy nie algemene aktiwiteite van die daaglikse lewe kan uitvoer nie).
- Indien jy 'n siekte het waar die derms gereeld ontsteek is (chroniese inflammatoriese dermsiekte) of wat blokkasie van die derm (ileus) behels.
- Indien jou bilirubienvlak (afbraakproduk van rooibloedselle) hoog is.
- Indien jy 'n kind of adolessent is.
- Indien jy asool-tipe antifungale medikasie (gebruik om swaminfeksies te behandel) neem.
- Indien jy johanneskruid ('n kruieaanvulling) neem.
- Indien jy enige inentings met lewendige, verswakte (geattenueerde) entstowwe moet ontvang. Bespreek dit met jou gesondheidsorgverskaffer voor enige inenting gedoen word.

Waarskuwings en voorsorgmaatreëls

Sê vir jou dokter of gesondheidsorgdeskundige voordat die **INOTRIX** konsentraat vir oplossing vir infusie aan jou gegee word indien:

- jy belemmerde lewerfunksie het, aangesien jy dan 'n groter risiko het om erge verlaging van witbloedselle of koors te ontwikkel.
- jy naarheid en braking ondervind. Indien jy braking saam met vertraagde diarree ervaar, behoort jy in die hospitaal opgeneem te word vir behandeling.
- jy vroeë diarree gepaardgaande met 'n groep simptome soos sweting, buikkrampe, oë wat water en speekselafskeiding ervaar. Indien dit voorkom, lig jou dokter in want 'n spesifieke medikasie is nodig om hierdie simptome te beheer.
- jy 'n bejaarde pasiënt is; dit mag nodig wees om die dosis dienooreenkomstig aan te pas.
- Indien jy onlangs ingeënt is of binnekort entstowwe behoort te ontvang.

INOTRIX behoort slegs toegedien te word onder toesig van 'n gekwalifiseerde mediese dokter en by eenhede wat gespesialiseerd is in die toediening van chemoterapie. Dit word aanbeveel dat **INOTRIX** slegs toegedien word in gesondheidsorginstellings met fasiliteite wat voldoende toegerus is, insluitende 'n intensiewesorgeenheid.

Party mense sal spesiale sorg van hul dokters benodig terwyl hulle met **INOTRIX** behandel word. Dit is veral belangrik dat jou dokter die noodsaaklikheid van voldoende verlengde antidiarreïese behandeling en oorvloedige vloeistofinname, indien nodig, aan jou verduidelik.

Jy mag kort na behandeling diarree ontwikkel, of vertraagde diarree, wat lewensbedreigend mag wees indien dit nie behoorlik behandel word nie. Sodra die eerste waterige ontlasting voorkom, konsulteer asseblief onmiddellik jou dokter of gesondheidsorgdeskundige vir toepaslike behandeling. Behandeling met 'n antibiotikum of hospitalisasie mag nodig wees.

Jou bloedseltelling moet weekliks gemonitor word, aangesien infeksie weens 'n vermindering van witbloedselle opgedoen mag word. Indien koors gepaardgaande met 'n verlaging van die witbloedseltelling voorkom, moet dit dringend in die hospitaal behandel word. Die **INOTRIX**-dosis moet dienooreenkomstig uitgestel of verlaag word.

Indien jy onseker is of enige van bogenoemde op jou van toepassing is, bespreek dit met jou dokter of apteker voordat **INOTRIX** aan jou toegedien word.

Kinders en adolessente

INOTRIX is nie by kinders of adolessente bestudeer nie en moet gevolglik nie in hierdie pasiëntpopulasie gebruik word nie.

Ander medisyne en INOTRIX:

Sê altyd vir jou gesondheidsorgdeskundige indien jy enige ander medisyne neem (dit sluit aanvullende of tradisionele medisyne in).

Gebruik van **INOTRIX** saam met hierdie medisyne mag ongewenste interaksies veroorsaak.

Sê veral vir jou dokter indien jy medisyne gebruik wat die volgende aktiewe bestanddele bevat:

- Medisyne wat gebruik word om spierverlamming/anestesie tydens chirurgie te veroorsaak (neuromuskulêre blokkerende medisyne). Die effek van hierdie medisyne kan verleng word wanneer dit saam met **INOTRIX** toegedien word.
- Ander medisyne wat vir kankerterapie gebruik word (antineoplastiese medisyne). Wanneer dit gepaardgaande met **INOTRIX** toegedien word, kan hierdie medisyne die diarree en bloedversteurings wat ervaar mag word, vererger.
- 'n Kortisoonmedisyne bekend as deksametasoon, wat gebruik word om inflammasie en ook kanker te behandel. Wanneer dit saam met **INOTRIX** toegedien word, mag deksametasoon die kans vergroot om 'n afname in die aantal van 'n sekere soort witbloedselle te ervaar ('n bloedversteuring bekend as limfositopenie).
- Lakseermiddels, aangesien dit die insidensie of ernstigheidsgraad van diarree kan vererger.
- Medisyne wat urienlating verhoog (diuretika), aangesien dit saam met die braking en diarree wat met **INOTRIX** ervaar mag word, dehidrasie kan veroorsaak.
- Medisyne gebruik om epilepsie te behandel (d.i. antikonvulsante, bv. karbamasepien, fenobarbitoon of fenitoïen), wat die uitwerking van **INOTRIX** kan verminder.
- Medisyne gebruik om swaminfeksie te behandel, bekend as asool-antiswammiddels (bv. ketokonasool), aangesien dit die effek van **INOTRIX** mag laat toeneem.
- 'n MIV-medisyne genaamd atasanavir mag die effekte van **INOTRIX** laat toeneem.
- 'n Kankermedisyne genaamd bevakisumab mag die effekte van **INOTRIX** laat toeneem.
- Johanneskruid ('n kruiemedikasie wat gebruik word om depressie te behandel). Wanneer dit saam met **INOTRIX** toegedien word, word die effek van **INOTRIX** verminder.
- Siklosporien of takrolimus, wat immuunonderdrukkers is (gebruik om jou liggaam se immuunstelsel te demp).
- 'n Medisyne wat vitamien K teëwerk, aangesien dit jou risiko vir bloeding kan laat toeneem. Dit mag nodig wees dat jy meer gereeld toetse ondergaan.

Swangerskap, borsvoeding en vrugbaarheid

Indien jy swanger is of jou baba borsvoed, vermoed dat jy swanger mag wees of beplan om swanger te raak, raadpleeg asseblief jou dokter, apteker of ander gesondheidsorgverskaffer voordat jy **INOTRIX** neem.

INOTRIX behoort nie tydens swangerskap of indien jy jou baba borsvoed aan jou toegedien te word nie. Dit kan skadelik wees vir jou baba.

Vrouens wat nog kan swanger raak, sowel as mans wat **INOTRIX** ontvang het, moet voorbehoedmaatreëls gebruik tydens die tydperk van behandeling en vir ten minste 3 maande nadat die behandeling gestaak is.

Bestuur en die gebruik van masjiene

INOTRIX kan duiseligheid of dowwe visie veroorsaak. Moenie 'n voertuig bestuur of enige gereedskap of masjiene hanteer indien jy hierdie newe-effekte ondervind nie.

Dit is nie altyd moontlik om te voorspel tot watter mate **INOTRIX** mag inmeng met die pasiënt se daaglikse aktiwiteite nie. Pasiënte moet seker maak dat hulle nie bogenoemde aktiwiteite uitvoer nie, totdat hulle weet tot watter mate hulle deur **INOTRIX** beïnvloed word.

INOTRIX bevat sorbitol ('n suiker). Indien jou dokter jou ingelig het dat jy onverdraagsaam vir sekere suikers is, bespreek dit met jou dokter voordat jy **INOTRIX** ontvang.

3. Hoe INOTRIX aan jou toegedien sal word

Daar sal nie van u verwag word om **INOTRIX** self toe te dien nie. Dit sal deur 'n persoon wat gekwalifiseerd is om dit te doen, gedoen word.

Jou dokter sal die presiese dosering vir jou bereken gegrond op jou liggaamsmassa en lengte.

Wanneer **INOTRIX** alleen toegedien word, is die gebruiklike dosis 350 mg/m^2 gegee as 'n intraveneuse infusie oor 30 tot 90 minute elke drie weke.

Wanneer **INOTRIX** saam met 5-fluoorurasiel en foliniensuur gebruik gaan word, is die gebruiklike dosis 80 mg/m^2 gegee as 'n intraveneuse infusie oor 30 tot 90 minute, gevolg deur 'n infusie van foliniensuur en 5-fluoorurasiel, oor ses weke. Na hierdie tydperk sal daar 'n rusperiode van een week wees.

Die gebruiklike dosis sal aangepas of uitgestel word indien jy neutropenie (baie lae bloedtelling van 'n soort witbloedsel), hewige diarree of braking het, of indien jy 'n bejaarde pasiënt is.

Jou dokter sal vir jou sê hoe lank jou behandeling met **INOTRIX** gaan duur. Moenie enige behandeling staak nie, behalwe as jou dokter sê jy moet.

Indien jy die indruk kry dat die uitwerking van **INOTRIX** te sterk of te swak is, bespreek dit met jou dokter.

Indien jy meer INOTRIX ontvang as wat jy moet

Aangesien 'n gesondheidsorgverskaffer **INOTRIX** sal toedien, sal hy/sy die dosis kontroleer. In geval van 'n oordosering sal jou dokter die oordosis behandel.

Indien jy vergeet om INOTRIX te gebruik

Jou dokter sal **INOTRIX** toedien, dus behoort dit nie te gebeur nie. In die geval dat 'n dosis oorgeslaan word, sal jou dokter nie vir jou 'n dubbele dosis gee om op te maak vir die dosis wat oorgeslaan is nie.

Indien jy ophou om INOTRIX te neem

Jou dokter sal vir jou sê wanneer die behandeling gestaak gaan word.

4. Moontlike newe-effekte

INOTRIX kan newe-effekte hê.

Nie al die newe-effekte wat vir **INOTRIX** gerapporteer is, word in hierdie inligtingsblad ingesluit nie. Indien jou algemene gesondheid verswak of indien jy enige ongunstige effekte ervaar terwyl jy **INOTRIX** ontvang, raadpleeg asseblief jou dokter, apteker of gesondheidsorgverskaffer.

Indien enige van die volgende gebeur, sê onmiddellik vir jou dokter of gaan na die ongevalle-afdeling by jou naaste hospitaal:

- Swelling rondom die oë of gesig of tong (wat in seldsame gevalle 'n ernstige allergiese reaksie mag wees)
- Swelling van die enkels, gewrigte, arms en bene
- Sukkel om asem te haal
- Hewige naarheid, braking
- Koors
- Hewige diarree.

Hierdie is alles baie ernstige newe-effekte. Indien jy dit het, mag jy 'n ernstige reaksie op **INOTRIX** gehad het. Jy mag dringend mediese bystand of hospitalisasie benodig.

'n Newe-effek wat dikwels met **INOTRIX** voorkom, is diarree. Neem asseblief kennis van die volgende belangrike inligting:

Diarree

INOTRIX mag veroorsaak dat jy diarree kry. Daar is twee tipes diarree, wat onderskei kan word deur wanneer dit begin. "Vroeë" diarree begin minder as 24 uur na die infusie en "vertraagde" diarree begin meer as 24 uur na die infusie.

Indien jy ENIGE DIARREE ondervind is dit BELANGRIK dat jy onmiddellik vir jou dokter of gesondheidsorgdeskundige daarvan sê.

Pasiënte met 'n verhoogde risiko vir diarree is daardie wat voorheen radioterapie van die buik/bekken ondergaan het en wat aanvanklik 'n verhoogde witbloedseltelling gehad het.

Vroeë diarree (Dikwels)

- indien diarree minder as 24 uur na die infusie begin ("vroeë diarree") moet jy ONMIDDELLIK jou dokter kontak.

Hierdie "vroeë diarree" mag met 'n groep ander simptome gepaardgaan, soos wat hier onder gelys word. Dit is bekend as akute cholinergiese sindroom, wat voorkom gedurende of binne die eerste 24 uur na infusie van INOTRIX. Die simptome kan wees:

Dikwels:

- buikpyn/buikkrampe

Minder dikwels:

- kouekoors
- traansekresie (waterige oë)
- rinitis (irritasie en inflammasie in die neus, wat 'n toe neus, loopneus en/of postnasale drup mag veroorsaak)
- duiseligheid
- hipotensie (lae bloeddruk)
- malaise (algemene gevoel van ongesteldheid)
- verhoogde speekselafskeiding (mond water)
- miose (sametrekking/vernouing van die oog se pupil)

Frekwensie onbekend:

- sweting
- visuele steurings
- konjunktivitis (inflammasie van die oog)
- vasodilatasie (verwyding van bloedvate)

Vertraagde diarree (Dikwels)

- indien diarree meer as 24 uur na die infusie begin ("vertraagde diarree") moet jy ONMIDDELLIK jou dokter kontak.

Jy moet vir jou dokter sê indien:

- jy naarheid en braking sowel as diarree ervaar
- jy enige koors saam met die diarree het
- jy 48 uur nadat behandeling vir diarree begin is nog steeds diarree het

Moenie enige behandeling gebruik vir die diarree buiten dit wat jou dokter vir jou gee nie.

Afname in witbloedselle (Dikwels)

INOTRIX mag 'n afname in die getal van sommige van jou witbloedselle veroorsaak, wat 'n belangrike rol speel om infeksies te beveg. Dit word neutropenie genoem.

Indien jy enigsins koors het, mag dit 'n aanduiding van infeksie gepaardgaande met die neutropenie wees.

Kontak onmiddellik jou dokter of gesondheidsorgverskaffer.

Naarheid en braking (Dikwels)

Indien jy enige koors het, en veral indien jy ook diarree en/of naarheid en/of braking ondervind, kontak ONMIDDELLIK jou dokter of gesondheidsorgverskaffer.

Sê ONMIDDELLIK vir jou dokter indien jy enige van die volgende opmerk:

Newe-effekte wat dikwels voorkom:

- sukkel om asem te haal
- dehidrasie
- verandering in resultate van nierfunksietoetse
- oormatige bilirubien (afbraakproduk van rooibloedselle) in die bloed
- lae bloedvolume, wat lei tot duiseligheid of floute
- inflammasie en ulserasie van die membrane wat die spysverteringskanaal uitvoer
- infeksie
- anemie, wat 'n verlaagde aantal rooibloedselle is, wat tot 'n gevoel van swakheid, moegheid en swak konsentrasie mag lei
- leukopenie, wat te min witbloedselle is, wat 'n groter risiko vir infeksie veroorsaak
- trombositopenie, wat te min plaatjies in die bloed is, en bloeding in die vel, kneusing of verlengde bloeding na 'n besering mag veroorsaak
- blokkasie van bloedvate, wat erge pyn in die bors, beroerte, inflammasie van 'n aar met vorming van 'n klont, hartaanval, hartstilstand of skielike sterfte kan veroorsaak.

Ander newe-effekte wat ook met INOTRIX gerapporteer is

Dikwels:

- haarverlies
- gebrek aan eetlus
- hardlywigheid
- inflammasie van die mond
- gewigsverlies
- pyn
- gebrek aan energie.

Indien jy enige newe-effekte opmerk wat nie in hierdie inligtingsblad genoem word nie, lig asseblief jou dokter of apteker in.

Rapportering van newe-effekte

Indien jy newe-effekte ondervind, bespreek dit met jou dokter, apteker of verpleegster. Dit sluit enige moontlike newe-effekte in wat nie hierdie inligtingsblad gelys word nie. Jy kan ook newe-effekte rapporteer via https://www.sahpra.org.za/Publications/Index/8. Deur newe-effekte te rapporteer, kan jy help om meer inligting rakende die veiligheid van **INOTRIX** te verskaf.

5. Hoe om INOTRIX te bewaar

BEWAAR ALLE MEDISYNE BUITE BEREIK VAN KINDERS.

INOTRIX sal in die apteek bewaar word.

Bewaar by of benede 25 °C.

Na verdunning in of 0,9 % natriumchloried óf 5 % dekstrose, is die verdunde oplossing stabiel vir 24 uur teen 'n temperatuur by of onder 25 °C, vir 4 dae in die yskas (tussen 2 en 8 °C). Gooi daarna enige ongebruikte oplossing weg. Moenie vries nie.

Hou die flessie in die buitenste karton om teen lig te beskerm.

Moenie gebruik na die vervaldatum wat op die flessie en karton voorkom nie.

Neem enige ongebruikte medisyne terug na jou apteker.

Moenie ongebruikte medisyne in dreine of rioolstelsels (bv. toilette) wegdoen nie.

6. Inhoud van die pak en ander inligting

Wat INOTRIX bevat

Die aktiewe bestanddeel is irinotekaanhidrochloriedtrihidraat.

Elke mL oplossing bevat 20 mg irinotekaanhidrochloriedtrihidraat.

INOTRIX 40 mg/2 mL konsentraat vir oplossing vir infusie bevat 40 mg irinotekaanhidrochloriedtrihidraat.

Bevat 90,0 mg sorbitol.

INOTRIX 100 mg/5 mL konsentraat vir oplossing vir infusie bevat 100 mg irinotekaanhidrochloriedtrihidraat.

Bevat 225,0 mg sorbitol.

INOTRIX 300 mg/15 mL konsentraat vir oplossing vir infusie bevat 300 mg irinotekaanhidrochloriedtrihidraat.

Bevat 675,0 mg sorbitol.

Die ander bestanddele van **INOTRIX** is Sorbitol, Melksuur, Natriumhidroksied, Soutsuur, Water vir inspuiting.

Hoe INOTRIX lyk en inhoud van die verpakking

INOTRIX konsentraat vir oplossing vir infusie is 'n deurskynende, kleurlose tot effens geel oplossing, essensieel sonder enige sigbare deeltjies.

INOTRIX 40 mg/2 mL konsentraat vir oplossing vir infusie word bemark in Tipe – I, 2 R amberkleurige BB tubulêre glasflessie met 'n 13 mm nek, toegemaak met 13 mm Omniflex plus bedekte donkergrys broombutiel-rubberprop en verseël met 'n helder lakbedekte aluminiumseël met Taxim blou (Donkerblou) Kleur PP-skyfie. 'n Enkele flessie word dan in 'n voorafgedrukte karton saam met 'n voubiljet verpak.

INOTRIX 100 mg/5 mL konsentraat vir oplossing vir infusie word bemark in Tipe – I, 6 R amberkleurige BB tubulêre glasflessie met 'n 20 mm nek, toegemaak met 20 mm Omniflex plus bedekte donkergrys broombutiel-rubberprop en verseël met 'n helder lakbedekte aluminiumseël met Donkergroen Kleur PP-skyfie. 'n Enkele flessie word dan in 'n voorafgedrukte karton saam met 'n voubiljet verpak.

INOTRIX 300 mg/15 mL konsentraat vir oplossing vir infusie word bemark in Tipe – I, 20 R amberkleurige BB tubulêre glasflessie met 'n 20 mm nek, toegemaak met 20 mm Omniflex plus bedekte donkergrys broombutiel-rubberprop en verseël met 'n helder lakbedekte aluminiumseël met Donkergroen Kleur PP-skyfie. 'n Enkele flessie word dan in 'n voorafgedrukte karton saam met 'n voubiljet verpak.

Nie al die verpakkingsgroottes word noodwendig bemark nie.

NAAM, BESIGHEIDSADRES EN TELEFOONNOMMER VAN DIE HOUER VAN DIE REGISTRASIESERTIFIKAAT

AUROGEN SA (EDMS.) BPK.
Woodhill Office Park, Gebou 1, Eerste Vloer
Phillip Engelbrechtlaan 53
Meyersdal, Uitbr. 12
1448 Johannesburg
Suid-Afrika

Hierdie inligtingsblad is laas hersien

31 Mei 2022

REGISTRASIENOMMER

INOTRIX 40 mg/2 ml 55/26/0362
INOTRIX 100 mg/5 ml 55/26/0363
INOTRIX 300 mg/15 ml 55/26/0364

P1532219