Applicant: Aurogen SA (Pty) Ltd
Product Name: TRINAXID 40 mg/2 mL, 100 mg/5 mL, 300 mg/15 mL
Dosage form and strength: Concentrate for solution for infusion, each mL contains 20 mg of irinotecan hydrochloride trihydrate

MODULE 1
1.3.1.1
Date: ~~11 May 2020~~
~~6 November 2020~~
~~02 December 2021~~
18 May 2022

1.3.1.1 Professional Information for Medicines for Human Use – CLEAN

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

TRINAXID 40 mg/2 mL concentrate for solution for infusion

TRINAXID 100 mg/5 mL concentrate for solution for infusion

TRINAXID 300 mg/15 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TRINAXID 40 mg/2 mL concentrate for solution for infusion contains 40 mg irinotecan hydrochloride trihydrate.

Contains 90,0 mg sorbitol.

TRINAXID 100 mg/5 mL concentrate for solution for infusion contains 100 mg irinotecan hydrochloride trihydrate.

Contains 225,0 mg sorbitol.

TRINAXID 300 mg/15 mL concentrate for solution for infusion contains 300 mg irinotecan hydrochloride trihydrate.

Contains 675,0 mg sorbitol.

Each mL of solution contains 20 mg irinotecan hydrochloride trihydrate

TRINAXID 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

TRINAXID 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 TRINAXID 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 TRINAXID in combination with 5-fluorouracil (5FU) and folinic acid (FA) have been assessed with either of the following schedules:

1) TRINAXID plus 5FU/FA in weekly schedule:

The recommended dose of TRINAXID 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:

TRINAXID 80 mg/m^2 as a 30-to-90-minute infusion on Day 1 and then weekly for 6 weeks.

Folinic acid 500 mg/m^2 intravenous infusion as a 2-hour infusion, followed by 5-fluorouracil 2 000 mg/m^2 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) TRINAXID plus 5FU/FA in every 2 weeks schedule:

The recommended dose of TRINAXID 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:

TRINAXID 180 mg/m^2 intravenous infusion as a 30 - to 90 - minute infusion on Day 1 only.

Folinic acid 200 mg/m^2 intravenous infusion as a 2-hour infusion, followed by 5-fluorouracil 400 mg/m^2 intravenous infusion bolus, followed by 5-fluorouracil 600 mg/m^2 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:

TRINAXID should not be administered until the neutrophil count remains above 1 500 cells/mm^3. In patients who experienced severe neutropenia or severe gastrointestinal adverse events such as diarrhoea, nausea and vomiting, dosing of TRINAXID should be delayed until there has been a full recovery of these effects, especially diarrhoea.

TRINAXID 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 TRINAXID, 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 TRINAXID 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 TRINAXID should be continued until there is an objective progression of the disease or an unacceptable toxicity.

Method of administration

TRINAXID infusion solution should be infused into a peripheral or central vein.

TRINAXID 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 TRINAXID see section 6.6.

4.3. Contraindications

Contraindications of TRINAXID:

- History of severe hypersensitivity reactions to irinotecan hydrochloride trihydrate or to one of the excipients of TRINAXID (see section 6.1).
- Chronic inflammatory bowel disease, and/or bowel obstruction or ileus. Patients should not be treated with TRINAXID until resolution of the ileus.
- Pregnancy and lactation. Women of childbearing age receiving TRINAXID 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 TRINAXID 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

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

The use of TRINAXID 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 TRINAXID be administered only in healthcare institutions with adequately equipped facilities, including an intensive care unit.

In all instances where the use of TRINAXID 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 TRINAXID, patients should be aware of the high risk of delayed diarrhoea occurring more than 24 hours after the administration of

TRINAXID 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 TRINAXID. 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 TRINAXID 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 TRINAXID 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/mm^3).

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 TRINAXID treatment.

Patients should be aware of the risk of infection and the significance of a fever. Febrile neutropenia (temperature ≥ 38 ºC and neutrophil count ≤ 1 000 cells/mm^3) should be urgently treated in the hospital with broad spectrum intravenous antibiotics.

TRINAXID administration should be delayed until the neutrophil count is ≥ 1 500 cells/mm^3.

In patients who experienced severe asymptomatic neutropenia (< 500 cells/mm^3), fever or infections associated with neutropenia, the dose of TRINAXID 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.

TRINAXID 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/m^2 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 TRINAXID.

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 TRINAXID.

Immunosuppressant effects/increased susceptibility to infections:

Administration of live or live-attenuated vaccines in patients immunocompromised by TRINAXID, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving TRINAXID. 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 TRINAXID should be cautious in this population.

Respiratory disorders:

Interstitial lung disease presenting as lung infiltration is uncommon during TRINAXID 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 TRINAXID 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 TRINAXID 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 TRINAXID. 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 TRINAXID). Dosing adjustment may apply to this population.

Cardiac disorders:

Myocardial ischaemic events have been observed following TRINAXID 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:

TRINAXID 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 TRINAXID with a strong inhibitor (e.g. ketoconazole) or inducer (e.g. rifampicin, carbamazepine, phenobarbitone, phenytoin) of CYP3A4 may alter the metabolism of TRINAXID and should be avoided (see section 4.5).

Since TRINAXID contains sorbitol, patients with rare hereditary problems of fructose intolerance should not be given TRINAXID.

Paediatric population

The safety and efficacy of TRINAXID 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 TRINAXID combined with 5-fluorouracil-folinic acid are comparable to those observed in monotherapy

Neuromuscular blocking medicines:

Interaction between TRINAXID 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 TRINAXID, 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 TRINAXID, 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 TRINAXID. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycaemia in some patients.

Laxatives:

Laxative use during therapy with TRINAXID is expected to worsen the incidence or severity of diarrhoea.

Diuretics:

Dehydration secondary to vomiting and/or diarrhoea may be induced by TRINAXID. The medical practitioner may wish to withhold diuretics during dosing with TRINAXID 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 TRINAXID therapy in patients requiring anticonvulsant treatment.

Azole antifungals:

TRINAXID 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 TRINAXID therapy and should not be administered during TRINAXID therapy (see section 4.3).

St. John's Wort (Hypericum perforatum):

Exposure to the active metabolite of TRINAXID 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 TRINAXID and should not be administered during TRINAXID 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 TRINAXID.
Atazanavir should not be used with TRINAXID.

Bevacizumab:

In one study, TRINAXID plasma concentrations were similar in patients receiving TRINAXID/5-FU/FA alone and in combination with bevacizumab. Concentrations of SN-38, the active metabolite of TRINAXID, were analysed in a subset of patients. Concentrations of SN-38 were on average 33 % higher in patients receiving TRINAXID/5-FU/FA in combination

with bevacizumab compared with TRINAXID/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 TRINAXID were reported for patients receiving
TRINAXID/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 TRINAXID 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 TRINAXID. Women of childbearing potential and men have to use effective contraception during and up to 3 months after treatment.

Pregnancy

TRINAXID 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 TRINAXID in pregnant women. If TRINAXID is used during pregnancy, or if the patient becomes pregnant, while receiving TRINAXID, 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 TRINAXID is excreted in human milk. Consequently, because of the potential for adverse reactions in nursing infants, breastfeeding should be discontinued for the duration of TRINAXID therapy (see section 4.3)

Fertility

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

4.7. Effects on ability to drive and use machines

TRINAXID 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 TRINAXID 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 TRINAXID 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 TRINAXID have been reported from patients at the recommended dose of 350 mg/m^2 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
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.

TRINAXID 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 TRINAXID have been reported from patients treated by INTOTRIX 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)
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 TRINAXID. 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/m² irinotecan dose leads to plasma irinotecan exposure comparable to that observed at

350 mg/m² 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

TRINAXID 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

TRINAXID 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 red colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

TRINAXID 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 sky blue colour PP disc. A single vial is further packed in a pre-printed carton with a package leaflet.

TRINAXID 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 TRINAXID 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.

TRINAXID 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.
- TRINAXID is an antineoplastic agent and, as with other potentially toxic compounds, caution should be exercised when handling it and preparing TRINAXID solutions.
- The work surface should be covered with disposable plastic-backed absorbent paper.
- Adequate protective gloves and clothing should be worn.
- If TRINAXID solution or infusion solution should come into contact with the skin, wash immediately and thoroughly with soap and water.
- If TRINAXID 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

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8. REGISTRATION NUMBER

9. DATE OF FIRST AUTHORISATION

10. DATE OF REVISION OF TEXT