1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

(APPROVED COPY)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RECOTAXIN 50 mg/10 ml concentrate for solution for infusion

RECOTAXIN 100 mg/20 ml concentrate for solution for infusion

RECOTAXIN 200 mg/40 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of concentrate for solution for infusion contains 5 mg oxaliplatin.

RECOTAXIN 50 mg/10 ml: Each vial contains 10 ml of aqueous solution equivalent to 50 mg of oxaliplatin.

RECOTAXIN 100 mg/20 ml: Each vial contains 20 ml of aqueous solution equivalent to 100 mg of oxaliplatin.

RECOTAXIN 200 mg/40 ml: Each vial contains 40 ml of aqueous solution equivalent to 200 mg of oxaliplatin.

Sugar free.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

RECOTAXIN 50 mg/10 ml, 100 mg/20 ml & 200 mg/40 ml:

Concentrate for solution for infusion

A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

RECOTAXIN in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:

- Treatment of metastatic colorectal cancer.
- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour.

4.2. Posology and method of administration

The preparation of RECOTAXIN must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Posology

FOR ADULTS ONLY

Dosing regimen

Treatment of metastatic colorectal cancer

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks.

Adjuvant treatment of colon cancer

The recommended dose is 85 mg/m^2 intravenously repeated every 2 weeks for 12 cycles (6 months). The dosage given should be adjusted according to tolerability (See section 4.4 and 4.8).

RECOTAXIN should always be administered before fluoropyrimidines (5-FU).

RECOTAXIN is administered as a 2 to 6-hour intravenous infusion in 250 to 500 mL of 5 % glucose solution. It is mainly used in combination with continuous infusion 5-fluorouracil based

regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special populations:

Renal impairment:

In gastrointestinal cancer patients with varying degrees of renal impairment, treated with **RECOTAXIN** (2-hour IV infusion every two weeks for a maximum of 12 cycles) in combination with 5-FU/FA (FOLFOX4), oxaliplatin as in **RECOTAXIN** showed minimal clinical impact on renal function as assessed by mean creatinine clearance (see sections 4.3, 4.4 and 5.2).

The duration of exposure was shorter in patients with renal impairment. The median exposure was 4, 6 and 3 cycles for mild, moderate and severe renal impairment patients, respectively. In patients with normal renal function, the median exposure was 9 cycles. However, 7/13 with mild and 5/11 with moderate to severe renal impairment withdrew due to adverse effects.

In patients with normal renal function or mild to moderate renal impairment, the recommended dose of **RECOTAXIN** is 85 mg/m^2. In patients with severe renal impairment, **RECOTAXIN** should not be used.

Hepatic insufficiency:

RECOTAXIN has not been studied in patients with severe hepatic impairment. No increase in oxaliplatin acute toxicities was observed in the subset of patients with abnormal liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

A phase I study of oxaliplatin single agent, 2-hour IV infusion q3w, included adult cancer patients with different degrees of hepatic impairment (none to severe). The initial oxaliplatin dose was

based upon the degree of liver dysfunction and was then increased up to 130 mg/m^2 whatever the degree of liver impairment (none to severe). Overall the types of toxicities observed were toxicities expected with oxaliplatin (see section 4.8). The frequencies of adverse events were increased in patients with liver impairment.

Elderly patients:

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Method of administration

RECOTAXIN is administered by intravenous infusion. The administration of oxaliplatin does not require hyperhydration.

RECOTAXIN infusion should always precede that of 5-fluorouracil (5-FU).

RECOTAXIN diluted in 250 to 500 mL of 5 % glucose solution to give a concentration of not less than 0,2 mg/mL must be infused either via a peripheral vein or central venous line at the same time as folinic acid intravenous infusion in 5 % glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion. The two medicinal products should not be combined in the same infusion bag.

Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5 % glucose solution, and **NOT** in alkaline solutions or sodium chloride or chloride-containing solutions (see section 6.2 for incompatibilities).

Flush the line after **RECOTAXIN** administration.

In the event of extravasation, administration must be discontinued immediately.

Instructions for use:

RECOTAXIN must be further diluted before use. **DO NOT** administer undiluted. Only the recommended diluent (5 % glucose) should be used (see Method of administration above and section 6.2).

Precautions to be taken before manipulation or administering the product

Caution should be exercised when handling and preparing **RECOTAXIN** solutions, see section 6.6.

4.3. Contraindications

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin or any of the other ingredients (see Section 6.1).
- are breast feeding.
- have bone marrow failure.
- have myelosuppression prior to starting treatment
- have a peripheral sensory neuropathy with functional impairment prior to starting treatment
- have a severely impaired renal function (creatinine clearance less than 30 mL/min) (See section 5.2)

4.4. Special warnings and precautions for use

RECOTAXIN-should only be used in specialised departments of oncology and should be administered under the supervision of an experienced oncologist.

Renal impairment

Due to limited information on safety in patients with severely impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient. In this situation, renal function should be closely monitored and the recommended initial **RECOTAXIN** dose is 65 mg/m^2 (see section 4.2 and 5.2).

Hypersensitivity reactions

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. In case of an anaphylactic-like reaction to **RECOTAXIN**, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Re-administration of **RECOTAXIN** to such patients is contra-indicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.
In case of **RECOTAXIN** extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.

Neurological Symptoms

Sensory neurological toxicity of **RECOTAXIN** should be carefully monitored, especially if co-administered with other medicines with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see Section 4.8), during or within the hours following the 2-hour infusion, the next oxaliplatin, as in **RECOTAXIN,** infusion should be administered over 6 hours. To reduce such dysaesthesia, inform the patient to avoid exposure to cold and to avoid ingesting fresh/cold food and/or beverages during or within hours following **RECOTAXIN** administration.

Dysaesthesia/paraesthesia of extremities and peripheral neuropathy:

- The dose-limiting toxicity of **RECOTAXIN** is neurological. It involves a sensory peripheral neuropathy characterised by peripheral dysaesthesia and/or paraesthesia with or without cramps, often triggered by the cold. The symptoms occur in 95 % of patients treated.
- The duration of these symptoms, which usually recede between the cycles of treatment, increases with the number of treatment cycles. The onset of pain and/or a functional disorder and their duration are indications for dose adjustment, or even treatment discontinuation. This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of a functional disorder for cumulative dose of approximately 850 mg/m^2 (10 cycles) is 10 % and 20 % for a cumulative dose of 1020 mg/m^2 (12 cycles).
- In the majority of cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after recovery cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow-up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity or with paraesthesias that interfere with functional activities.

Acute neurosensory manifestations:

These symptoms usually develop at the end of the 2-hour **RECOTAXIN** infusion or within a few hours, abate spontaneously within the next hours or days, and frequently recur with further cycles. They may be precipitated or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypaesthesia.

An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 – 2 % of patients, and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

Other symptoms occasionally observed, particularly of cranial nerve dysfunction, may be either associated with above-mentioned events, or also occur isolated such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease of visual acuity, and visual field disorders. In addition, the following symptoms have been observed: jaw spasm/muscle spasms/involuntary muscle contractions/muscle twitching/myoclonus, coordination abnormal/abnormal gait/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

Peripheral neuropathy

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended **RECOTAXIN** dosage adjustment, based on the duration and severity of these symptoms, should be performed:

- If symptoms last longer than seven days and are troublesome, the subsequent **RECOTAXIN** dose should be reduced from 85 to 65 mg/m^2(metastatic setting) or 75 mg/m^2(adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent **RECOTAXIN** dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, **RECOTAXIN** administration should be discontinued.
- If these symptoms improve following discontinuation of **RECOTAXIN** therapy, resumption of therapy may be considered.

Patients should be informed of the possibility of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate paraesthesias or paraesthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation of adjuvant setting.

Nausea, vomiting, diarrhoea, dehydration, and haematological changes

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be associated with severe diarrhoea/emesis particularly when combining **RECOTAXIN** with 5-fluorouracil (5-FU).

Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin as in **RECOTAXIN** treatment. In case of intestinal ischaemia, **RECOTAXIN** treatment should be discontinued and appropriate measures initiated (see section 4.8).

If haematological toxicity occurs (neutrophils < 1,5 x 10^9/L or platelets < 50 x 10^9/L), after a course of therapy or if myelosuppression is present prior to the start (first course) of therapy (see section 4.3), administration of the next course or the first course of therapy should be postponed until the haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to the start of therapy and before each subsequent course.

Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin as in **RECOTAXIN**, including fatal outcomes (see section 4.8). If any of these events occurs, **RECOTAXIN** should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after **RECOTAXIN**/5-fluorouracil administration in order to contact their treating doctor urgently for appropriate management.
If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/ stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1,5 x 10^9/L.

For **RECOTAXIN** combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If severe/life-threatening diarrhoea, severe neutropenia (neutrophils < 1,0 x 10^9/L), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection

with an absolute neutrophil count < 1,0 x 10^9/L , a single temperature of > 38,3 °C or a sustained temperature of > 38 °C for more than one hour), or severe thrombocytopenia(platelets < 50 x 10^9/L) occurs, **RECOTAXIN** must be discontinued until improvement or resolution, and the dose of **RECOTAXIN** should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting) at subsequent cycles, in addition to any 5-fluorouracil dose reductions required.

Pulmonary

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, **RECOTAXIN** should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8).

Blood disorders

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see section 4.8). **RECOTAXIN** should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may not be reversible with discontinuation of therapy and dialysis may be required.
Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin as in **RECOTAXIN** treatment. If DIC is present, **RECOTAXIN** treatment should be discontinued and appropriate treatment should be administered (see section 4.8).

Hepatic

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, cases of drug-induced hepatic vascular disorders should be considered.

Reversible posterior leukoencephalopathy syndrome (RPLS)

Signs and symptoms of reversible posterior leukoencephalopathy syndrome (RPLS, also known as PRES, posterior reversible encephalopathy syndrome), could be induced headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated with or without hypertension (see section 4.8). Diagnosis of RPLS/PRES is based upon confirmation by brain imaging.

QT prolongation

QT prolongation may lead to an increased risk for ventricular dysrhythmias including Torsade de Pointes, which can be fatal. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicines known to prolong QT interval and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, **RECOTAXIN** treatment should be discontinued (see sections 4.5 and 4.8).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with oxaliplatin as in **RECOTAXIN**, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, **RECOTAXIN** treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicines associated with rhabdomyolysis are administered concomitantly with **RECOTAXIN** (see sections 4.5 and 4.8).

Gastrointestinal ulcer, gastrointestinal ulcer haemorrhage and perforation

RECOTAXIN treatment can cause duodenal ulcer (DU) and potential complications, such as duodenal ulcer haemorrhage and perforation, which can be fatal. In case of duodenal ulcer, **RECOTAXIN** treatment should be discontinued and appropriate measures taken (see section 4.8).

Do not use intraperitoneal route of administration

Do not use **RECOTAXIN** intraperitoneally. Peritoneal haemorrhage may occur when **RECOTAXIN** is administered by intraperitoneal route (off-label route of administration).

Fertility

Male patients treated with **RECOTAXIN** are advised not to father a child during and up to 6 months after treatment, and to seek advice on conservation of sperm prior to treatment because **RECOTAXIN** may have an anti-fertility effect which could be irreversible.

Pregnancy

Women should not become pregnant during and up to 4 months after treatment with **RECOTAXIN** and should use an effective method of contraception (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed.

In vitro, no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following medicines: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when **RECOTAXIN** treatment is co-administered with other medicines known to cause QT interval prolongation (such asquinidine, disopyramide, amiodarone, sotalol, dofetilide and ibutilide). In case of combination with such medicines, the QT interval should be closely monitored (see section 4.4).

Caution is advised when **RECOTAXIN** treatment is administered concomitantly with other medicines known to be associated with rhabdomyolysis (such as statins, antipsychotics, zidovudine, colchicine, selective serotonin reuptake inhibitors, and lithium) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with **RECOTAXIN**. Further, barrier contraceptive measures must be taken during and after cessation of therapy (4 months for women and 6 months for men) (see section 4.4).

Pregnancy

To date there is no available information on the safety of use in pregnant women. Based on pre-clinical findings, **RECOTAXIN** is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic doses, and is consequently not recommended during pregnancy and should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Breastfeeding

Excretion in breast milk has not been studied. **RECOTAXIN** is contraindicated during breastfeeding; therefore, if treatment with this medicine is required, breastfeeding must be discontinued (see section 4.3).

Fertility

RECOTAXIN may have an anti-fertility effect which could be irreversible, and patients are advised to seek advice on conservation of sperm prior to treatment (see section 4.4).

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, **RECOTAXIN** treatment resulting in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to an impaired ability to drive and use machines.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhoea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

b) Tabulated list of adverse drug reactions

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Infections and infestations	Infection, neutropenic sepsis[+]	Frequent
	Sepsis [+]	Less frequent
Blood and lymphatic Disorders[$]	Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, febrile neutropenia	Frequent
	Immuno-allergic thrombocytopenia, haemolytic anaemia, disseminated intravascular coagulation (DIC)	Less frequent
Immune system disorders	Allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis [++], anaphylactic reactions including bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock	Frequent
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hypokalaemia, natraemia abnormalities, dehydration, hypocalcaemia	Frequent
	Metabolic acidosis	Less frequent
Psychiatric disorders	Depression, insomnia	Frequent
	Nervousness	Less frequent

Nervous system disorders	Dysaesthesia/paraesthesia of extremities and peripheral neuropathy, headache, acute neuro-sensory manifestations**, dysgeusia, dizziness, motor neuritis, flushing, meningism	Frequent
	Dysarthria, loss of deep tendon reflexes, Lhermitte's sign, reversible posterior leukoencephalopathy syndrome (RPLS or PRES)**	Less frequent
Eye disorders	Conjunctivitis, abnormal vision	Frequent
	Visual acuity reduced transiently, visual field disturbances, optic neuritis, transient vision loss (reversible following therapy discontinuation)	Less frequent
Ear and labyrinth disorders	Ototoxicity, deafness	Less frequent
Vascular disorders	Epistaxis, haemorrhage of the nose, haematuria, deep thrombophlebitis, pulmonary embolism, haemorrhage of the rectum, deep vein thrombosis, thromboembolic events, hypertension	Frequent

Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, rhinitis, hiccups, pulmonary embolism, upper respiratory infection	Frequent
	Acute interstitial lung diseases, which may be fatal and pulmonary fibrosis**	Less frequent
Gastrointestinal disorders*	Nausea, vomiting and diarrhoea, stomatitis/mucositis, abdominal pain, constipation, dehydration, ileus, intestinal obstruction, renal disorders may be associated with severe diarrhoea/vomiting, particularly when combined with 5-FU**, dyspepsia, gastro-oesophageal reflux and gastrointestinal haemorrhage	Frequent
	Colitis including *clostridium difficile,* diarrhoea, pancreatitis	Less frequent
Hepato-biliary disorders	liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of the liver, or pathological manifestations related to such liver disorder, including peliosis hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	Less frequent

Skin and subcutaneous tissue disorders	Skin disorder, alopecia, skin exfoliation (i.e. Hand & Foot syndrome), erythematous rash, rash, hyperhidrosis, nail disorder	Frequent
Musculoskeletal and connective tissue disorders	Back pain[***], arthralgia, skeletal pain	Frequent
Renal and urinary disorders	Dysuria, abnormal micturition frequency	Frequent
	Acute tubular necrosis, acute interstitial nephritis and acute renal failure	Less frequent
General disorders and administration site conditions	Fatigue, fever[+++], asthenia, pain, weight increase, injection site reaction[++++]	Frequent
Investigations	Mild to moderate hepatic enzymes (ALT/AST) increase, and alkaline phosphatase, bilirubin increase, LDH increase, blood creatinine increase, weight decrease (metastatic setting)	Frequent
Injury, poisoning, and procedural complications	Fall	Frequent

[$] The frequency increases when **RECOTAXIN** is administered (85 mg/m^2 every 2 weeks) in combination with 5-FU+/-folinic acid, as compared to a single medicine administration (130 mg/m^2 every 3 weeks), e.g. anaemia (80 % vs 60 % of patients), neutropenia (70 % vs 15 %),

thrombocytopenia (80 % vs 40 %). Severe anaemia (haemoglobin <8,0 g/dL) or thrombocytopenia (platelets < 50 x 10^9/L) occurs with a similar frequency (<5 % of patients) when **RECOTAXIN** is administered as a single medicine or in combination with 5-FU. Severe neutropenia (neutrophils < 1,0 x 10^9/L) occurs with a greater frequency when **RECOTAXIN** is administered in combination with 5-FU than as a single medicine (40 % vs < 3 % of patients).

**See section 4.4.

*** In case of such adverse reaction, haemolysis which has been rarely reported should be investigated

+ including fatal outcomes.

++ Frequent allergies/allergic reactions, occurring mainly during infusion, sometimes fatal. Allergic reactions include skin rash, particularly urticaria, conjunctivitis, and rhinitis. Anaphylactic or anaphylactoid reactions include bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.

+++ Frequent fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

++++ Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation may also result in local pain and inflammation which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein (see section 4.4).

Post-marketing experience with frequency unknown

Infections and infestations: septic shock, including fatal outcomes

Immune system disorders: delayed hypersensitivity.

Blood and lymphatic system disorders: haemolytic uraemic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia.

Nervous system disorders: convulsion, ischaemic and haemorrhagic cerebrovascular disorder.

Cardiac disorders: QT prolongation, which may lead to ventricular dysrhythmias including Torsade de Pointes, which may be fatal (see sections 4.4 and 4.5), acute coronary syndrome including myocardial infarction and coronary arteriospasm.

Respiratory, thoracic and mediastinal disorders: laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes.

Gastrointestinal disorders: intestinal ischaemia, including fatal outcomes, duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see section 4.4), oesophagitis.

Skin and subcutaneous tissue disorders: hypersensitivity vasculitis

Musculoskeletal, connective tissue and bone disorders: rhabdomyolysis, including fatal outcomes (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Medicine Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

There is no known antidote to **RECOTAXIN.** In cases of overdose, exacerbation of adverse events can be expected. Monitoring of haematological parameters should be initiated and symptomatic treatment given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacological classification: A. 26 Cytostatic Agents

Pharmacotherapeutic group: ATC Code: L01XA03

Mechanism of action

Oxaliplatin is an antineoplastic medicine belonging to a class of platinum-based compounds in which the platinum atom is complexed with 1, 2-diaminocyclohexane ("DACH") and an oxalate group. Oxaliplatin is a single enantiomer, the Cis-[oxalato (trans-λ-1,2-DACH) platinum].

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* anti-tumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and in vivo activity in various cisplatin-resistant models.

A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a 2-hour infusion of oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin at 85 mg/m² every two weeks

Dose	**C_{max} µg/mL**	**AUC_{0-48} µg.h/mL**	**AUC µg.h/mL**	**t½α h**	**t½ß h**	**t½γ h**	**V_{ss} L**	**CL L/h**
85 mg/m²	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35

Mean AUC_{0-48}, and C_{max} values were determined on cycle 3 (85 mg/m^2).

Mean AUC, V_{ss}, CL and CL_{R0-48} values were determined on cycle 1.

C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.

t½α, t½β and t½γ were determined by compartmental analysis (cycles 1 to 3 combined).

At the end of a 2-hour infusion, 15 % of the administered platinum is present in the systemic circulation, the remaining 85 % being rapidly distributed into tissues or eliminated in the urine.

Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin.

No accumulation was observed in plasma ultra-filtrate following 85 mg/m^2 every two weeks and steady state was attained by cycle one in this matrix.

Inter-and intra-subject variability is generally low.

Biotransformation

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact oxaliplatin was detectable in plasma ultrafiltrate at the end of a 2-hour infusion. Several cytotoxic biotransformation products including the monochloro-, dichloro-and diaquo-DACH platinum species have been identified in the systemic circulation, together with a number of inactive conjugates at later time points.

Elimination

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours, following administration. By day 5, approximately 54 % of the total dose was recovered in the urine and < 3 % in the faeces.

A significant decrease in clearance from 17,6 ± 2,18l/h to 9,95 ± 1,91 l/h in renal impairment was observed, together with a statistically significant decrease in distribution volume from 330 ± 40,9 to 241 ± 36,1 l. The effect of severe renal impairment on platinum clearance has not been evaluated (see section 4.2. Special populations: Renal impairment patients).

Special populations

Renal impairment

The disposition of oxaliplatin was studied in patients with varying degrees of renal function. Elimination of oxaliplatin was found to be significantly correlated with the creatinine clearance (Cl_{cr}). Total body clearance of plasma ultrafiltrate (PUF) platinum was reduced in patients with impaired renal function by 34 % in mild (Cl_{cr}= 50 to 80 mL/min), 57 % in moderate (Cl_{cr} = 30 to 49 mL/min), and 79 % in severe (Cl_{cr} <30 mL/min) renal impairment compared to patients with normal function (Cl_{cr} >80 mL/min). There was a trend of increased beta and gamma half-lives of PUF platinum with increasing degree of renal impairment and mainly in the severe group. However, the results were not conclusive due to the large inter-patient variability and the small number (4) of patients with severe renal impairment. Urinary excretion of platinum and renal clearance of PUF platinum also decreased with impaired renal function (see sections 4.2 and 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The active substance is oxaliplatin. The other ingredients of RECOTAXIN are:

- Water for injection

6.2 Incompatibilities

The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Under instructions for use described in section 6.6, oxaliplatin can be co-administered with folinic acid via a Y-line.

- **DO NOT** mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others medicines. Alkaline medicines or solutions will adversely affect the stability of oxaliplatin (see section 6.6).
- **DO NOT** dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- **DO NOT** mix with other medicinal products in the same infusion bag or infusion line (see section 6.6 for instructions concerning simultaneous administration with folinic acid).
- **DO NOT** use injection equipment containing aluminium.

6.3 Shelf life

2 years

After dilution in 5 % glucose, chemical and physical in-use stability has been demonstrated for 48 hours at +2 °C to +8 °C and for 24 hours at +25 °C.

Infusion preparation:

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

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

Inspect visually prior to use. Only clear solutions without particles should be used. The medicinal product is for single use only. Any unused solution should be discarded.

For storage conditions of the infusion preparation, see section 6.3.

6.5 Nature and contents of container

RECOTAXIN 50 mg/10 ml:

10 mL concentrate for solution for infusion in a 20 mL clear glass vial, containing 50 mg of oxaliplatin, stoppered with a gray rubber stopper and sealed with an aluminium seal having a sky blue colour PP disk. The vial shall be packed in pre-printed carton with a packaging leaflet.

Pack size: 1 vial.

RECOTAXIN 100 mg/20 ml:

20 mL concentrate for solution for infusion in a 20 mL clear glass vial, containing 100 mg of oxaliplatin, stoppered with a gray rubber stopper and sealed with an aluminium seal having a sky blue colour PP disk. The vial shall be packed in pre-printed carton with a packaging leaflet.

Pack size: 1 vial.

RECOTAXIN 200 mg/40 ml:

40 mL concentrate for solution for infusion in a 50 mL clear glass vial, containing 50 mg of oxaliplatin, stoppered with a gray rubber stopper and sealed with an aluminium seal having a sky blue colour PP disk. The vial shall be packed in pre-printed carton with a packaging leaflet.

Pack size: 1 vial.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

As with other potentially toxic compounds, caution should be exercised when handling and preparing **RECOTAXIN** solutions.

Recommendations for safe handling

The preparation of **RECOTAXIN** must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose.
It is forbidden to smoke, eat or drink in this area. Personnel must be provided with appropriate handling materials, notably long-sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.
Excreta and vomit must be handled with care.
Pregnant women must be warned to avoid handling cytotoxic agents.
Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers (see Disposal).
If **RECOTAXIN** concentrate or infusion solution, should come into contact with skin, wash immediately and thoroughly with water.
If **RECOTAXIN** concentrate, premix solution or infusion solution, should come into contact with mucous membranes, wash immediately and thoroughly with water.

Concentrate for solution for infusion and dilution for intravenous infusion

Inspect visually prior to use. Only clear solutions without particles should be used.

RECOTAXIN is for single use only. Any unused concentrate should be discarded.

Disposal:

Remnants of **RECOTAXIN** as well as all materials that have been used for reconstitution, dilution or administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws relating to the disposal of hazardous waste.

7 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(S)

RECOTAXIN 50 MG/10 ML: 56/26/0776.773

RECOTAXIN 100 MG/20 ML: 56/26/0777.774

RECOTAXIN 200 MG/40 ML: 56/26/0778.775

9 DATE OF FIRST AUTHORISATION

06 DECEMBER 2022