PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

OXALIPLATIN 50 mg/10 ml FRESENIUS

OXALIPLATIN 100 mg/20 ml FRESENIUS

Concentrate for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

OXALIPLATIN 50 mg/10 ml FRESENIUS: Each vial contains 10 ml of concentrate

for solution for infusion equivalent to 50 mg oxaliplatin.

OXALIPLATIN 100 mg/20 ml FRESENIUS: Each vial contains 20 ml of concentrate

for solution for infusion equivalent to 100 mg oxaliplatin.

Sugar Free

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear, colourless solution, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Treatment of metastatic colorectal cancer
- Adjuvant treatment of colon cancer

4.2 Posology and method of administration

Posology

FOR ADULTS ONLY

Treatment of metastatic colorectal cancer:

The recommended dose is 85 mg/m² intravenously repeated every 2 weeks.

Adjuvant treatment of colon cancer:

The recommended dose is 85 mg/m² intravenously repeated every 2 weeks for 12 cycles (6 months).

Dosage given should be adjusted according to tolerability (see section 4.4)

OXALIPLATIN FRESENIUS was 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:

OXALIPLATIN FRESENIUS has not been studied in patients with severe renal impairment (see section 4.3).

In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose (see sections 4.4 and 4.8).

There is no need for dose adjustment in patients with mild renal dysfunction.

- Hepatic insufficiency:

OXALIPLATIN FRESENIUS 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.

- *Elderly patients:*

No increase in severe toxicities was observed when oxaliplatin was used as a single medicine 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:

OXALIPLATIN FRESENIUS is administered by intravenous infusion.

The administration of **OXALIPLATIN FRESENIUS** does not require hyperhydration.

OXALIPLATIN FRESENIUS 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 venous line over 2 to 6 hours.

OXALIPLATIN FRESENIUS infusion should always precede that of 5- fluorouracil.

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

4.3 Contraindications

OXALIPLATIN FRESENIUS is contraindicated in patients who:

- have a known hypersensitivity to oxaliplatin or to any of the excipients listed in section 6.1.
- are breastfeeding.
- have bone marrow failure.
- have myelosuppression prior to starting treatment.
- have peripheral sensory neuropathy with functional impairment before treatment.
- have severe renal impairment.

4.4 Special warnings and precautions for use

OXALIPLATIN FRESENIUS should only be used in specialised departments of oncology and should be administered under the supervision of an experienced oncologist**.**

Renal impairment

Patients with mild to moderate renal impairment should be closely monitored for adverse reactions and the dose adjusted according to toxicity (see section 5.2).

Hypersensitivity reactions

Special surveillance should be ensured for patients with a history of allergic manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion should be interrupted immediately and an appropriate symptomatic treatment started. Re-administration of **OXALIPLATIN FRESENIUS** to such patients is contraindicated.

Cross reactions, sometimes fatal, have been reported with all platinum compounds.

In case of **OXALIPLATIN FRESENIUS** extravasation, the infusion must be stopped immediately and usual local symptomatic treatment initiated.

Neurological Symptoms

Neurological toxicity of **OXALIPLATIN FRESENIUS** 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 FRESENIUS **infusion should be administered over 6 hours.**

Peripheral neuropathy

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

- If symptoms last longer than seven days and are troublesome, the subsequent **OXALIPLATIN FRESENIUS** 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 **OXALIPLATIN FRESENIUS** 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, **OXALIPLATIN FRESENIUS** should be discontinued.
- If these symptoms improve following discontinuation of **OXALIPLATIN FRESENIUS** 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 paresthesias or paresthesias that may interfere with functional activities can persist after up to 3 years following treatment cessation in the adjuvant setting.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS also known as PRES, Posterior Reversible Encephalopathy Syndrome) have been reported in patients receiving oxaliplatin in combination chemotherapy.

RPLS is a rare, reversible, rapidly evolving neurological condition, which can include seizure, hypertension, headache, confusion, blindness, and other visual and neurological disturbances (see section 4.8)

Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

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 caused by severe diarrhoea/emesis particularly when combining **OXALIPLATIN FRESENIUS** with 5-fluorouracil.

Cases of intestinal ischaemia, including fatal outcomes, have been reported with oxaliplatin treatment. In case of intestinal ischaemia, **OXALIPLATIN FRESENIUS** 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), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood

count with white cell differential should be performed prior to start of therapy and before each subsequent course. Myelosuppressive effects may be additive to those of concomitant chemotherapy. Patient with severe and persistent myelosuppression are at high risk of infectious complications. Sepsis, neutropenic sepsis and septic shock have been reported in patients treated with oxaliplatin including fatal outcomes (see section 4.8). If any of these events occurs, **OXALIPLATIN FRESENIUS** should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after **OXALIPLATIN FRESENIUS** and 5-fluorouracil administration so that they can urgently contact their treating physician 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 **OXALIPLATIN FRESENIUS** combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils <1,0 x 10^9/L), febrile neutropenia (temperature of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1,0 x 10^9/L, temperature > 38,3 °C or a sustained temperature > 38 °C for more than one hour), or grade 3-4 thrombocytopenia (platelets < 50 x 10^9/L) occur, the dose of **OXALIPLATIN FRESENIUS** should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m^2 (adjuvant setting), 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, **OXALIPLATIN FRESENIUS** 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 (frequency not known). **OXALIPLATIN FRESENIUS** 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, 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 treatment. If DIC is present, **OXALIPLATIN FRESENIUS** treatment should be discontinued and appropriate treatment should be administered. (see section 4.8).

QT prolongation

QT prolongation may lead to an increased risk for ventricular dysrhythmias including Torsade de Pointes, which can be fatal (see section 4.8). The QT interval should be closely monitored on a regular basis before and after administration of **OXALIPLATIN FRESENIUS**.

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, **OXALIPLATIN FRESENIUS** treatment should be discontinued (see sections 4.5 and 4.8).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with oxaliplatin including fatal outcomes.

In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, **OXALIPLATIN FRESENIUS** 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 **OXALIPLATIN FRESENIUS** (see sections 4.5 and 4.8).

Gastrointestinal ulcer/ Gastrointestinal ulcer haemorrhage and perforation

OXALIPLATIN FRESENIUS treatment can cause gastrointestinal ulcer and potential complications, such as

duodenal ulcer ***haemorrhage*** and perforation, which can be fatal.

In case of gastrointestinal ulcer, **OXALIPLATIN FRESENIUS** treatment should be discontinued and appropriate measures taken (see section 4.8).

Hepatic

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

Fertility

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore, male patients treated with **OXALIPLATIN FRESENIUS** 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 **OXALIPLATIN FRESENIUS** may have an anti-fertility effect which could be irreversible. Women should not become pregnant during treatment with **OXALIPLATIN FRESENIUS** and should use an effective method of contraception (see section 4.6).

4.5 Interaction with other medicines and other forms of interaction

It is reported that 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.

As per reported in *vitro studies,* no significant displacement of oxaliplatin binding to plasma proteins has been observed with the following agents: erythromycin, salicylates, granisetron, paclitaxel, and sodium valproate.

Caution is advised when **OXALIPLATIN FRESENIUS** treatment is co-administered with other medicines known to cause QT interval prolongation. In case of combination with such medicines, the QT interval should be closely monitored (see section 4.4). Caution is advised when **OXALIPLATIN FRESENIUS** treatment is administered concomitantly with other medicines known to be associated with rhabdomyolysis. (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently,oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures.

The use of **OXALIPLATIN FRESENIUS** should only be considered after suitably appraising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women.

Breastfeeding

Excretion in breast milk has not been studied. Breastfeeding is contraindicated during **OXALIPLATIN FRESENIUS** therapy.

Fertility

OXALIPLATIN FRESENIUS may have an anti-fertility effect (see section 4.4).

Due to the potential genotoxic effects of **OXALIPLATIN FRESENIUS**, appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

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, **OXALIPLATIN FRESENIUS** treatment resulting in an increase risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient’s 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

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

Tabulated list of adverse reactions

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5-FU/FA treatment arms) and from post marketing experience.

Frequencies in this table are defined using the following convention:

frequent, less frequent.

Further details are given after the table.

MedDRA Organ system classes	**Frequent**	**Less Frequent**
Infections and infestations *	- Infection - Rhinitis - Upper respiratory tract infection -Neutropenic sepsis	Sepsis^{+}
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia - Febrile neutropenia^{+}	- Immuno-allergic Thrombocyte-penia - Haemolytic anaemia
Immune system disorders*	- Allergy/ allergic reaction^{++}	
Metabolism and nutrition disorders	- Anorexia - Hypokalaemia - Hyperglycaemia -Hypernatraemia - Dehydration -Hypocalcaemia	- Metabolic acidosis
Psychiatric disorders	- Depression - Insomnia	- Nervousness
Nervous system disorders*	- Peripheral sensory neuropathy - Sensorydisturbance	- Dysarthria - Reversible Posterior

MedDRA Organ system classes	Frequent	Less Frequent
	- Dysgeusia - Headache - Dizziness - Motor neuritis - Meningism	Leukoencephalopathy syndrome (RPLS, or PRES) (see section 4.4)
Eye disorders	- Conjunctivitis - Visual disturbance	- Visual acuity reduced transiently - Visual field disturbances - Optic neuritis - Transient vision loss, reversible following therapy discontinuation
Ear and labyrinth disorders		- Ototoxicity - Deafness
Vascular disorders	- Haemorrhage - Flushing - Deep vein thrombosis - Hypertension	
Respiratory, thoracic and Mediastinal disorders	- Dyspnoea - Cough - Epistaxis - Hiccups - Pulmonary embolism	- Interstitial lung disease, sometimes fatal - Pulmonary fibrosis**
Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis /Mucositis - Abdominal pain - Constipation - Dyspepsia - Gastro-esophageal reflux - Rectal haemorrhage -Gastrointestinal haemorrhage	- Ileus - Intestinal obstruction - Colitis including *Clostridium difficile* diarrhoea - Pancreatitis
Skin and subcutaneous Tissue disorders	- Skin disorder - Alopecia - Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder	
Musculo-skeletal and connective tissue disorders	- Back pain - Arthralgia - Bone pain	
Renal and urinary disorders	- Haematuria - Dysuria - Micturition frequency abnormal	
General disorders and administration site conditions	- Fatigue - Fever^{+++} - Asthenia - Pain - Injection site reaction^{++++}	

MedDRA Organ system classes	Frequent	Less Frequent
Investigations	- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting) - Blood creatinine increase - Weight decrease (metastatic setting)	

* See detailed section below

** See section 4.4.

[+] Frequent neutropenic sepsis, including fatal outcomes.

[++] Frequent allergies/allergic reactions, occurring mainly during infusion, sometimes fatal.

Frequent allergic reactions include skin rash, particularly urticaria, conjunctivitis, and rhinitis.

Frequent 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).

Postmarketing experience with frequency not known:

Haemolytic uremic syndrome

Autoimmune pancytopenia

Pancytopenia

Secondary leukaemia

Infections and infestations

Incidence by patient (%)

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
	All grades			**All grades**		
Sepsis *(including sepsis and neutropenic sepsis)*	1,5			1,7		

Postmarketing experience with frequency not known

Septic shock, including fatal outcomes.

Immune system disorders

Incidence of allergic reactions by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m²	**Metastatic Setting**			**Adjuvant Setting**		
every 2 weeks	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Allergic reactions/Allergy	9,1	1	< 1	10,3	2,3	0,6

Nervous system disorders

The dose limiting toxicity of **OXALIPLATIN FRESENIUS** is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. These Symptoms are reported to occur in up to 95 % of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10 % and 20 % for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of the reported cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment 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 localized paraesthesia of moderate intensity (2,3 %) or with paraesthesia that may interfere with functional activities (0,5 %).

Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paraesthesia, dysesthesia and hypoesthesia.
An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1 % - 2 % of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective 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 (see section 4.4). Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ ataxia/ balance disorders, throat or chest tightness/ pressure/ discomfort/pain. In addition, cranial nerve dysfunctions may be associated with above mentioned events, or also occur as an isolated event 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 in visual acuity, visual field disorders.

Other neurological symptoms such as dysarthria, loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Post-marketing experience with frequency not known:

Convulsion

Ischemic or haemorrhagic cerebrovascular disorder

Cardiac disorders

Post-marketing experience with frequency not known:

QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see section 4.4).

Respiratory, thoracic and mediastinal disorders

Post-marketing experience with frequency not known:

Laryngospasm

Pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders:

Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m² every 2 weeks	***Metastatic Setting***			**Adjuvant Setting**		
	All grades	Gr 3	Gr 4	All grades	Gr 3	Gr 4
Nausea	69,9	8	< 1	73,7	4,8	0,3
Diarrhoea	60,8	9	2	56,3	8,3	2,5
Vomiting	49,0	6	1	47,2	5,3	0,5
Mucositis/Stomatitis	39,9	4	<1	42,1	2,8	0,1

Prophylaxis and/or treatment with potent antiemetic medicines is indicated.

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining **OXALIPLATIN FRESENIUS** with 5-fluorouracil (5-FU) (see section 4.4).

Post marketing experience with frequency not known

Intestinal ischemia, including fatal outcomes (see section 4.4).

Gastrointestinal ulcer and perforation, which can be fatal. (see section 4.4).

Hepato-biliary disorders

Less frequent

Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Musculoskeletal and connective tissue disorders

Post-marketing experience with frequency not known

Rhabdomyolysis, including fatal outcomes (see section 4.4).

Renal and urinary disorders

Less frequent

Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Skin and Subcutaneous tissue disorders

Post-marketing experience with frequency not known

Hypersensitivity vasculitis

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 Drug Reactions Reporting Form”,

found online under SAHPRA’s publications:

http://www.sahpra.org.za

Healthcare providers should also report adverse reactions to the Holder of

Certificate of Registration, **Fresenius Kabi South Africa (Pty) Limited.**

The contact details for our national reporting system are:

Email: safety.fksa@fresenius-kabi.com

Tel: +27 11 545 0000

Emergency: 0860 203 900

4.9 Overdose

Symptoms

There is no known antidote to oxaliplatin. In cases of overdose, exacerbation of adverse events can be expected.

Management

Monitoring of haematological parameters should be initiated and symptomatic treatment given.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Class of medicine: A 26 Cytostatic agents

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds.

ATC code: L01XA03

Mechanism of Action

Oxaliplatin is an antineoplastic active substance belonging to a new 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, (*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-k*N*, k*N'*] [ethanedioato(2-)-kO^1, kO^2] platinum.

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour 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*.

Reported studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter

and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumor effects.

5.2 Pharmacokinetic properties

Absorption and distribution

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 two-hour infusion of oxaliplatin at 130 mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 g/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 or at 130 mg/m² Every Three Weeks

Dose	**C_{max}**	**AUC_{0-48}**	**AUC**	**$t_{1/2\alpha}$**	**$t_{1/2\beta}$**	**$t_{1/2\gamma}$**	**V_{ss}**	**CL**
	µg /mL	**µg.h /mL**	**µg.h /mL**	**h**	**h**	**h**	**L**	**L/h**
85 mg/m²								
Mean	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
130 mg/m²								
Mean	1,21	8,20	11,9	0,28	16,3	273	582	10,1
SD	0,10	2,40	4,60	0,06	2,90	19,0	261	3,07

Mean AUC_{0-48}, and C_{max} values were determined on Cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²).

Mean AUC, V_{ss}, and CL values were determined on Cycle 1.

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

$t_{1/2\alpha}$, $t_{1/2\beta}$, and $t_{1/2\gamma}$, were determined by compartmental analysis (Cycles 1-3 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 ultrafiltrate following 85 mg/m^2 every two weeks or 130 mg/m^2 every three 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 drug was detectable in plasma ultrafiltrate at the end of a 2h-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.

Special Populations

Renal Impairment

The effect of renal impairment on the disposition of oxaliplatin was studied in patients with varying degrees of renal function. Oxaliplatin was administered at a dose of 85 mg/m^2 in the control group with a normal renal function (CLcr > 80 ml/min, n=12) and in patients with mild (CLcr = 50 to 80 ml/min, n=13) and moderate (CLcr = 30 to 49 ml/min, n=11) renal impairment, and at a dose of 65mg/m^2 in patients with severe renal impairment (CLcr < 30 ml/min, n=5).

Median exposure was 9, 4, 6, and 3 cycles, respectively, and PK data at cycle 1 were obtained in 11, 13, 10, and 4 patients respectively. There was an increase in plasma ultrafiltrate (PUF) platinum AUC, AUC/dose and a decrease in total and renal CL and Vss with increasing renal impairment especially in the (small) group of patients with severe renal impairment: point estimate (90 % CI) of estimated mean ratios by renal status versus normal renal function for AUC/dose were 1.36 (1,08, 1,71), 2.34 (1,82, 3,01) and 4,81 (3,49,

6,64) for patients with mild and moderate and in severe renal failure respectively.

Elimination of oxaliplatin is significantly correlated with the creatinine clearance. Total PUF platinum CL was respectively 0,74 (0,59, 0,92), 0,43 (0,33, 0,55) and 0,21 (0,15, 0,29) and for Vss respectively 0,52 (0,41, 0,65), 0,73 (0,59, 0,91) and 0,27 (0,20, 0,36) for patients with mild, moderate and severe renal failure respectively. Total body clearance of PUF platinum was therefore reduced by respectively 26 % in mild, 57 % in moderate, and 79 % in severe renal impairment compared to patients with normal function. Renal clearance of PUF platinum was reduced in patients with impaired renal function by 30 % in mild, 65 % in moderate, and 84 % in severe renal impairment compared to patients with normal function. There was an increase in beta half-life of PUF platinum with increasing degree of renal impairment mainly in the severe group. Despite the small number of patients with severe renal dysfunction, these data are of concern in patients in severe renal failure and should be taken into account when prescribing oxaliplatin in patients with renal impairment (see sections 4.2, 4.3 and 4.4)

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

6.2 Incompatibilities

The diluted medicine should not be mixed with other medicines in the same infusion bag or infusion line. Under instructions for use described in section 6.6 **OXALIPLATIN FRESENIUS** can be co-administered with folinic acid (FA) via a Y-line.

- DO NOT mix with alkaline medicines or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of others medicine affect the stability of oxaliplatin (see section 6.6).

- DO NOT dilute **OXALIPLATIN FRESENIUS** with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- DO NOT mix with other medicines 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, chemical and physical in-use stability has been demonstrated for24 hours at room temperature (15 °C - 25 °C) and at refrigerated condition (2 °C - 8 °C). From a microbiological point of view, the solution for infusion should be used immediately.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze.

Keep the vial in the outer carton.

For storage conditions after dilution of this medicine, see section 6.3

KEEP OUT OF REACH OF CHILDREN

6.5 Nature and contents of container

OXALIPLATIN 50 mg/10 ml FRESENIUS: 10 ml concentrate in a vial (Type I clear tubular glass) with Flurotec elastomeric stopper and green aluminium flip-off overseal.

OXALIPLATIN 100 mg/20 ml FRESENIUS: 20 ml concentrate in a vial (Type I clear tubular glass) with Flurotec elastomeric stopper and blue aluminium flip-off overseal.

6.6 Special precautions for disposal and other handling

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

Instructions for Handling

The handling of this cytotoxic medicine by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.
The preparation of injectable solutions of cytotoxic medicines must be carried out
by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the integrity of the product, the protection of the environment and in particular the protection of the personnel handling the medicines, in accordance with the hospital policy. 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 medicines.
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 below section “Disposal”. If **OXALIPLATIN FRESENIUS** concentrate or solution for infusion, should come into contact with skin, wash immediately and thoroughly with water.

If **OXALIPLATIN FRESENIUS** concentrate or solution for infusion, should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection equipment containing aluminium.
- DO NOT administer undiluted.
- Only 5 % glucose infusion solution is to be used as a diluent. DO NOT dilute for infusion with sodium chloride or chloride containing solutions
- DO NOT mix with any other medicines in the same infusion bag or administer simultaneously by the same infusion line.

- DO NOT mix with alkaline medicines 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.

Instruction for use with folinic acid (FA) (as calcium folinate or disodium folinate)

OXALIPLATIN FRESENIUS 85 mg/m² IV infusion in 250 ml to 500 ml of 5 % glucose solution is given 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.

These two medicines 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, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil

OXALIPLATIN FRESENIUS should always be administered before fluoropyrimidines - i.e. 5- fluorouracil.

After **OXALIPLATIN FRESENIUS** administration, flush the line and then administer 5- fluorouracil.

For additional information on medicines combined with oxaliplatin, see the corresponding manufacturer's prescribing information.

Concentrate for solution for infusion

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

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

Dilution for intravenous infusion

Withdraw the required amount of concentrate from the vial(s) and then dilute with 250 ml to 500 ml of a 5 % glucose solution to give an oxaliplatin concentration between 0,20 mg/ml and 0,70 mg/ml; the concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.

Administer by IV infusion.

Inspect visually prior to use. Only clear solutions without particles should be used.
The medicine is for single use only. Any unused infusion solution should be discarded (see chapter "disposal" below).

NEVER use sodium chloride or chloride containing solutions for dilution.

The compatibility of oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets

Infusion

The administration of **OXALIPLATIN FRESENIUS** does not require prehydration.

OXALIPLATIN FRESENIUS diluted in 250 ml to 500 ml of a 5 % glucose solution to give a concentration not less than 0,2 mg/ml must be infused either by peripheral vein or central venous line over 2 to 6 hours. When **OXALIPLATIN FRESENIUS** is administered with 5-fluorouracil, the **OXALIPLATIN FRESENIUS** infusion must precede the administration of 5-fluorouracil.

Disposal

Remnants of the medicine as well as all materials that have been used for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic medicines in accordance with local requirements related to the disposal of hazardous waste.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Limited

Stand 7, Growthpoint Business Park

162 Tonetti Street

Midrand, 1685

8 REGISTRATION NUMBERS

OXALIPLATIN FRESENIUS 50 mg/10 ml FRESENIUS: 46/26/0897

OXALIPLATIN 100 mg/20 ml FRESENIUS: 46/26/0898

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04 May 2021

10 DATE OF REVISION OF THE TEXT