1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

OXALIPLATIN KEY 50 (powder for injection)

OXALIPLATIN KEY 100 (powder for injection)

2 QUALITIVE AND QUANTITIVE COMPOSITION

OXALIPLATIN KEY 50: Each vial contains 50 mg oxaliplatin.

OXALIPLATIN KEY 100: Each vial contains 100 mg oxaliplatin.

Contains sugar:

OXALIPLATIN KEY 50 contains sugar: Mannitol 200 mg/vial

OXALIPLATIN KEY 100 contains sugar: Mannitol 400 mg/vial

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Well-formed white cake free from foreign particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

1.3.1.1 Professional Information for medicines for human use

- 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.

***A*djuvant 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 4.8).

OXALIPLATIN KEY should always be administered before fluoropyrimidines.

OXALIPLATIN KEY is administered as a 2- to 6- hour intravenous infusion in 250 to 500 ml of 5 % glucose solution.

OXALIPLATIN KEY 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 KEY has not been studied in patients with severe renal impairment (see 4.3). In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose (see section 4.8). There is no need for dose adjustment in patients with mild renal dysfunction.

Hepatic insufficiency:

OXALIPLATIN KEY has not been studied in patients with severe hepatic impairment. No specific dose adjustment is required for patients with abnormal liver function tests.

Elderly patients:

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

Method of administration

OXALIPLATIN KEY is administered by intravenous infusion.

The administration of OXALIPLATIN KEY does not require hyperhydration.

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

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

Instruction for use/handling:

OXALIPLATIN KEY must be reconstituted and further diluted before use. Only the recommended diluents should be used to reconstitute and then dilute the freeze-dried product.

Caution should be exercised when handling and preparing OXALIPLATIN KEY solutions.

The preparation of injectable solutions of cytotoxic agents 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 medicine. 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. See section below “Disposal”.

Disposal:

If OXALIPLATIN KEY concentrate, reconstituted solution or infusion solution should come into contact with skin, wash immediately and thoroughly with water.

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

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

Incompatibilities:

- DO NOT use in association with alkaline medicines or solutions (in particular 5-fluorouracil, basic solutions, trometamol and folinic acid products containing trometamol as an excipient).

  OXALIPLATIN KEY can be co-administered with folinic acid infusion using a Y-line placed immediately before the site of injection. The medicines should not be combined in the same infusion bag. Folinic acid must be diluted using isotonic infusion solutions such as 5 % glucose solution but NOT sodium chloride solutions or alkaline solutions. Flush the line after OXALIPLATIN KEY administration.
- DO NOT reconstitute or dilute for infusion with saline solution.
- DO NOT mix with other medicines in the same infusion bag or infusion line (see section 4.2).
- DO NOT use injection equipment containing aluminium.

4.3 Contraindications

- History of hypersensitivity to oxaliplatin and excipients of OXALIPLATIN KEY or other platinum compounds.
- Pregnancy and breastfeeding.
- Bone marrow failure.
- Myelosuppression prior to starting treatment.
- Peripheral sensory neuropathy with functional impairment before treatment.
- Severe renal impairment (creatinine clearance less than 30 ml/min).
- Pulmonary toxicity.

4.4 Special warnings and precautions for use

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

Fertility

OXALIPLATIN KEY may have an antifertility effect, which could be irreversible. Male patients are therefore 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 (see section 4.6).

Renal impairment

Due to limited information on safety in patients with moderately 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 dose adjusted according to toxicity (see section 4.2 and 4.3).

Hypersensitivity reactions

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to OXALIPLATIN KEY**,** the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. OXALIPLATIN KEY re-challenge is contraindicated.

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

Allergy/allergic reactions, occurring mainly during perfusion, sometimes fatal (frequent allergic reactions such as skin rash, in particularly urticaria, conjunctivitis, rhinitis and frequent anaphylactic reactions, including bronchospasm, angioedema, low blood pressure and

anaphylactic shock) has been reported. Delayed hypersensitivity has also been reported with oxaliplatin hours or even days after the infusion.

There have been frequent reports of fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

In case of OXALIPLATIN KEY extravasations, the infusion must be stopped immediately and usual local symptomatic treatment initiated. 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 KEY is infused through a peripheral vein.

Neurological symptoms

Neurological toxicity of OXALIPLATIN KEY should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngo-pharyngeal dysaesthesia (see section 4.8 ~~Side-effects~~), during or within the hours following the 2-hour infusion, the next OXALIPLATIN KEY 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 OXALIPLATIN KEY administration.

1.3.1.1 Professional Information for medicines for human use

Peripheral neuropathy (see section 4.3)

- If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended OXALIPLATIN KEY dosage adjustment based on the duration and severity of the symptoms should be performed:
- If symptoms last longer than seven days and are troublesome, the subsequent OXALIPLATIN KEY dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia without functional impairment persists until the next cycle, the subsequent OXALIPLATIN KEY dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).
- If paraesthesia with functional impairment persists until the next cycle, OXALIPLATIN KEY should be discontinued.
- If these symptoms improve following discontinuation of OXALIPLATIN KEY 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 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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Reversible Posterior Leukoencephalopathy Syndrome (RPLS) 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~~h~~). Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis, and renal impairment may be caused by severe diarrhoea/emesis particularly when combining OXALIPLATIN KEY with 5-fluorouracil.

Intestinal ischemia, including fatal outcomes, have been reported with OXALIPLATIN KEY treatment. In case of intestinal ischemia, OXALIPLATIN KEY 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 the 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. See section 4.3 before starting with chemotherapy. Patients 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 KEY including fatal outcomes (see section 4.8). If any of these events occurs, OXALIPLATIN KEY should be discontinued.

If diarrhoea/emesis 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 KEY 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 10^2/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) occur, the dose of OXALIPLATIN KEY should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (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 KEY should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.3 & 4.8).
In case of abnormal liver function tests or portal hypertension which does not obviously results from liver metastases, rare cases of medicine-induced hepatic vascular disorders should be considered.

Blood disorders

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (frequency not known). OXALIPLATIN KEY 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 KEY treatment. If DIC is present, OXALIPLATIN KEY 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 KEY. 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 KEY treatment should be discontinued (see sections 4.5 and 4.8).

Cardiac disorders

Post-marketing side effects with OXALIPLATIN KEY use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with OXALIPLATIN KEY may need to be interrupted (see section 4.8).

Post-marketing side effects with oxaliplatin include cardiac dysrhythmias (including bradydysrhythmia, tachycardia and atrial fibrillation). In case of cardiac dysrhythmias, treatment with OXALIPLATIN KEY may need to be interrupted (see section 4.8).

Rhabdomyolysis

Rhabdomyolysis has been reported in patients treated with OXALIPLATIN KEY, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin 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 KEY (see sections 4.5 and 4.8).

Gastrointestinal ulcer/ Gastrointestinal haemorrhage and perforation

OXALIPLATIN KEY treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal ulcer, OXALIPLATIN KEY treatment should be discontinued (see section 4.8).

Hepatic

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

There have been reports of 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 and peri-sinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Immunosuppressant effects/increased susceptibility to infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic medicines, may results in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving OXALIPLATIN KEY. Killed or inactivated vaccines may be administered. However, the response to such vaccines may be diminished.

Do not use intraperitoneal route of administration.

Peritoneal haemorrhage may occur when OXALIPLATIN KEY is administered by intraperitoneal route (off-label route of administration).

Mannitol Warning

OXALIPLATIN KEY contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of Interaction

OXALIPLATIN KEY may have interactions with the following medicines:

- Bone marrow depressants.
- Anticoagulants (prolongation of prothrombin time and of INR in patients with concomitant use).
- Nephrotoxic medicine.
- Ototoxic medicine.
- Vaccination with live or live attenuated vaccines should be avoided in patients receiving OXALIPLATIN KEY (see section 4.4).

In patients who have received a single dose of 85 mg/m² of OXALIPLATIN KEY, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-flourouracil has been observed.

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

Additive bone marrow depression and gastrointestinal adverse events may occur when two or more bone marrow depressants, including radiation, are used concomitantly or consecutively. For bone marrow failure see section 4.3.

Vaccine immunisation of patients treated with OXALIPLATIN KEY should be undertaken with extreme caution, because normal defense mechanisms may be suppressed by treatment with OXALIPLATIN KEY and concurrent use with a live virus vaccine may potentiate the replication of the vaccine virus and/or may decrease the patient's antibody response to the immunisation. The interval between discontinuation of OXALIPLATIN KEY and restoration of the patient's ability to respond to the vaccine, depends on the intensity and type of immunosuppression-causing medicine used, the underlying disease, and other factors; estimates vary from 3 months to 1 year.

Caution is advised when OXALIPLATIN KEY treatment is co-administered with other medicines known to cause QT interval prolongation (such as quinidine, 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 OXALIPLATIN KEY 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/ Contraception in males and females

Effective contraceptive measures must be taken in potentially fertile patients prior to initiating chemotherapy with OXALIPLATIN KEY and after cessation of treatment, for a period of 4 months in women and 6 months in men.

Pregnancy

There is no available information on safety of use in pregnant women. Based on pre-clinical findings, OXALIPLATIN KEY is likely to be lethal and/or teratogenic to the human foetus at the recommended therapeutic dose and is consequently not recommended during pregnancy.

Breastfeeding

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

Fertility

Male patients who are treated with OXALIPLATIN KEY are advised not to conceive a child during and until 6 months after the end of oxaliplatin therapy.

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 KEY treatment resulting in an increase of dizziness, nausea, vomiting and other neurological 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 and use machines or engage in dangerous activities.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse events of OXALIPLATIN KEY 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 KEY and 5-FU/FA combination than with 5-FU/FA alone.

Tabulated list of adverse reactions

Body System	Undesirable effect		
	Frequent	**Less frequent**	**Frequency not known**

Infections and Infestations:	Infection, neutropenic sepsis [+], upper respiratory infection, rhinitis	Sepsis[+]	Septic shock[*+]
Blood and the lymphatic system disorders:	Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphocytopenia, febrile neutropenia, thrombophlebitis	Immuno-allergic thrombocytopenia, haemolytic anaemia. Disseminated intravascular coagulation (DIC)[+]	Haemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia*
Immune system disorders:	Isolated fever from immunological mechanism, anaphylactic or anaphylactoid reactions, including bronchospasm, angioedema,		

	hypotension, sensation or chest pain and anaphylactic shock.		
Metabolism and nutrition disorders:	Anorexia, hyperglycaemia, hypokalaemia, hyponatraemia, dehydration, hypocalcaemia	Metabolic acidosis	
Psychiatric disorders:	Depression and insomnia	Nervousness	
Nervous system disorders:	Dysaethesia/paraesthesia, peripheral sensory neuropathy, headache, fasciculations, acute sensory disturbances, dizziness, motor	Dysarthria, loss of deep tendon reflexes, Lhermitte's sign. Reversible posterior leuko-encephalopathy syndrome	Cranial nerve palsies, fasciculations, convulsion, ischemic or haemorrhagic cerebrovascular disorder*

	neuritis, meningism, cranial nerve palsies, taste perversion	(RPLS, or PRES)	
Eye disorders:	Conjunctivitis, abnormal vision, abnormal lachrymation.	Visual acuity reduced transiently, visual field disturbances, optic neuritis, transient vision loss (reversible following therapy discontinuation)	
Ear and labyrinth disorders:		Deafness, ototoxicity	
Cardiac disorders:	Chest pain		Acute coronary syndrome, including myocardial infarction and coronary

			arteriospasm and angina pectoris in patients treated with oxaliplatin in combination with 5-FU and bevacizumab; QT prolongation which may lead to ventricular dysrhythmias including Torsade de Pointes*+
Vascular disorders:	Flushing, hypertension, thromboembolism.		
Respiratory, thoracic and mediastinal disorders:	Epistaxis, bronchospasm, bronchoconstriction, chest pain,	Interstitial lung diseases and pulmonary fibrosis.	Laryngospasm, pneumonia and broncho-pneumonia*+

	dyspnoea and coughing, pharyngitis, pulmonary embolism, pulmonary fibrosis		
Gastrointestinal disorders:	Haemorrhage (rectum), anorexia, nausea, vomiting and diarrhoea, stomatitis/mucositis, abdominal pain and constipation, dehydration, metabolic acidosis, intestinal obstruction, dyspepsia, gastroesophage	Colitis including *Clostridium difficile* pancreatitis, ileus	Severe diarrhoea, oesophagitis, intestinal ischaemia+, gastrointestinal ulcer and perforation+

	al reflux, hiccup, flatulence, abdominal pain, gastroesophageal reflux, gastrointestinal haemorrhage		
Hepato-biliary disorders:		Clinical manifestations may be portal hypertension and/or increased transaminases. Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of the liver or pathological manifestations	Focal nodular hyperplasia

		related to such liver disorder, including peliosis hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis, ascites, hepatic lesions	
Skin and subcutaneous tissue disorders:	Alopecia, skin exfoliation (hand and foot syndrome), skin rash, urticaria, erythematous rash, increased sweating and nail disorder.		Hypersensitivity vasculitis*

Musculoskeletal, connective tissue and bone disorders:	Back pain, arthralgia, skeletal pain; myelosuppression.		Rhabdomyolysis*+
Renal and urinary disorders:	Dysuria, abnormal micturition frequency. Renal disorders may be associated with severe diarrhoea/ vomiting. Haematuria	Acute tubular necrosis, acute interstitial nephritis and acute renal failure.	
General disorders and administrative site conditions:	Fever +++, rigors (tremors), oedema, chest pain, asthenia, fatigue, injection site reaction. Extravasation		

	may result in local pain and inflammation and thrombosis, which may be severe and lead to complications including necrosis, especially when OXALIPLATIN KEY is infused through a peripheral vein.		
Investigations:	Increased alkaline phosphatase, increased bilirubin, increased LDH, increased hepatic enzymes (SGPT/ALT/SG		

	OT/AST), increased creatinine, weight decrease (metastatic setting), increased weight (adjuvant setting)		
Injury and poisoning:	Fall		

+ including fatal outcomes.

++ Very 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 KEY hours or even days after the infusion.

+++ Very 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).

Description of selected adverse reactions

Dysaethesia/paraesthesia of extremities and peripheral sensory neuropathy:

The dose limiting toxicity of OXALIPLATIN KEY is neurological. It involves a sensory peripheral neuropathy characterised by peripheral dysaethesia 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 regress between courses of treatment, increases with the number of treatment cycles.

The duration of these symptoms, which usually regress between courses of treatment, increases with the number of 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 a cumulative dose of approximately 850 mg/m² (10 cycles) is 10 % and 20 % for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of case, 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 (2,3 %) or with paraesthesias that interfere with functional activities (0,5 %).

Acute neuro-sensory manifestations:

Symptoms start within hours of administration and often occur in exposure to cold. This usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 to 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.

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.

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:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

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

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

Treatment should be symptomatic and supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 Cytostatic agents

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds

ATC code: L01XA 03

Oxaliplatin is an antineoplastic agent 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 –[oxalate(trans-l-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.*

1.3.1.1 Professional Information for medicines for human use

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 anti-tumour effects.

5.2 Pharmacokinetic properties

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultra filterable platinum levels following oxaliplatin administration is triphasic, characterised by two relatively short distribution phases (t ½ α; 0,43 hours and t ½ β; 16,8 hours) and a long terminal elimination phase (t ½ γ; 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of oxaliplatin at a dose of 85 mg/m^2 expressed as ultra filterable platinum were C_{max} of 0,814 µg/mL and volume of distribution of 440 l. Interpatient and intrapatient variability in ultra filterable platinum exposure (AUC_{0-48}) assessed over 3 cycles was moderate to low (23 % to 6 %, respectively).

Distribution: Approximately 15 % of platinum is present in the systemic circulation. The remaining 85 % is rapidly distributed into tissues or eliminated in the urine.

Protein binding: Very high (> 90 %), irreversible plasma protein binding, primarily to albumin and gamma-globulins. Binding is irreversible and accumulates (approximately 2-fold) in erythrocytes.

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 2hr -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 daily dose was recovered in the urine and < 3 % in the faeces.

A significant decrease in clearance from 17,6 + 2,18 l/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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol and water for injection.

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

OXALIPLATIN KEY 50 & OXALIPLATIN KEY 100:

36 months

1.3.1.1 Professional Information for medicines for human use

From a microbiological point of view the solution for infusion should be used immediately after preparation.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

The freeze-dried product is packed in a Type I transparent glass vial, with a grey bromobutyl stopper and a red flip-off cap.

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

Any unused product or waste material should be disposed of in accordance with local requirements.

7 HOLDER OF THE CERTIFICATE OF REGISTRATION

Key Oncologics (Pty) Ltd

39 – 11th avenue

Houghton Estate

Johannesburg

South Africa

8 REGISTRATION NUMBER(S)

OXALIPLATIN KEY 50: 45/26/0330

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 November 2015

10 DATE OF REVISION OF TEXT

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