SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE:

OXALIPLATIN PCH 50 Concentrate for solution for infusion

OXALIPLATIN PCH 100 Concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

Each 10 ml vial of OXALIPLATIN PCH 50 contains oxaliplatin 50 mg (5 mg/ml).

Each 20 ml vial of OXALIPLATIN PCH 100 contains oxaliplatin 100 mg (5 mg/ml).

Contains sugar (lactose monohydrate 45 mg/ml).

For full list of excipients, see **section 6.1**.

3. PHARMACEUTICAL FORM:

Concentrate for solution for infusion

Clear and colourless to almost colourless solution that is free from visible particles.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

OXALIPLATIN PCH 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/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). Dosage given should be adjusted according to tolerability (see **section 4.4**)

OXALIPLATIN PCH should always be administered before fluoropyrimidines.

OXALIPLATIN PCH is administered as a 2 to 6 hour intravenous infusion in 250 to 500 ml of glucose solution. OXALIPLATIN PCH was mainly used in combination with continuous infusion of 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 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:

No specific dose adjustment for a patient with abnormal liver function tests is recommended.

Elderly patient:

No specific dose adaptation is required for elderly patients.

Method of administration:

OXALIPLATIN PCH is administered by intravenous infusion. The administration of OXALIPLATIN PCH does not require hyperhydration.

OXALIPLATIN PCH 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 PCH should always precede that of 5-fluorouracil.

Instruction for use:

OXALIPLATIN PCH must be diluted before use. Only the recommended diluents should be used. For instructions on dilution of the medicine before administration, see **section 6.6.**

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

4.3 Contraindications:

OXALIPLATIN PCH is contraindicated during:

- Hypersensitivity to oxaliplatin or to any of the ingredients of OXALIPLATIN PCH listed in **section 6.1.**
- Pregnancy and breastfeeding
- Severe renal function impairment (creatinine clearance less than 30 ml/min)
- Bone marrow failure
- Myelosuppression prior to starting treatment
- Peripheral sensory neuropathy with functional impairment before treatment
- Pulmonary toxicity

4.4 Special warnings and precautions for use:

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

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 PCH, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. OXALIPLATIN PCH 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.

The infusion must be stopped immediately, and usual local symptomatic treatment initiated, in case of OXALIPLATIN PCH extravasations. 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 PCH is infused through a peripheral vein.

Renal impairment:

The primary route of OXALIPLATIN PCH elimination is renal, and clearance of OXALIPLATIN PCH is decreased in patients with renal impairment. Administration of OXALIPLATIN PCH should only be considered after suitable appraisal of the benefit/risk for the patient with moderately impaired renal function. In this situation, renal function should be closely monitored and dose adjusted according to toxicity (see **section 4.2, Special populations**).

***Neurological symptoms**:*

Neurological toxicity of OXALIPLATIN PCH 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 laryngo-pharyngeal dysaesthesia (see **section 4.8**), during or within the hours following the 2-hour infusion, the next OXALIPLATIN PCH 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 PCH administration.

Peripheral neuropathy:

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended OXALIPLATIN PCH 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 PCH 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 PCH 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 PCH should be discontinued.
- Continuation of therapy may be considered if these symptoms improve following discontinuation of OXALIPLATIN PCH therapy.

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 for 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**). Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis, and renal impairment may be caused by severe diarrhoea/emesis particularly when combining OXALIPLATIN PCH with 5-fluorouracil.

Cases of intestinal ischemia, including fatal outcomes, have been reported with OXALIPLATIN PCH treatment. In case of intestinal ischemia, OXALIPLATIN PCH 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 the start of therapy and before each subsequent course. Myelosuppressive effects may be additive to those of concomitant 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 PCH including fatal outcomes (see **section 4.8**). If any of these events occurs, OXALIPLATIN PCH should be discontinued.

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after OXALIPLATIN PCH/5-fluorouracil administration in order to urgently contact their treating medical practitioner for appropriate treatment. The next treatment should be delayed if mucositis/stomatitis occurs with or without neutropenia, until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1,5 \times 10^9/l$.

For OXALIPLATIN PCH 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 $< 1,0 \times 10^9/l$), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count $< 1,0 \times 10^9/L$, a single temperature of > 38,3 °C or a sustained temperature of > 38 °C for more than one hour), or grade 3-4 thrombocytopenia (platelets $< 50 \times 10^9/l$) occur, the dose of OXALIPLATIN PCH should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

Pulmonary:

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

Blood disorders:

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

Cardiac disorders:

Post-marketing reports with OXALIPLATIN PCH use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with OXALIPLATIN PCH may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **section 4.8**).

Post-marketing reports with oxaliplatin include cardiac dysrhythmias (including bradydysrhythmia, tachycardia and atrial fibrillation). In case of cardiac dysrhythmias, treatment with OXALIPLATIN PCH may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **section 4.8**).

Rhabdomyolysis:

Rhabdomyolysis has been reported in patients treated with OXALIPLATIN PCH, 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 PCH (see **sections 4.5 and 4.8**).

Gastrointestinal ulcer/ Gastrointestinal haemorrhage and perforation:

OXALIPLATIN PCH treatment can cause gastrointestinal ulcer and potential complications, such as gastrointestinal haemorrhage and perforation, which can be fatal. In case of gastrointestinal ulcer, OXALIPLATIN PCH 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, OXALIPLATIN PCH-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.

***Pregnancy*:**

For use in pregnant women (see **section 4.6**).

Women should not become pregnant during treatment with OXALIPLATIN PCH and should use an effective method of contraception (see **section 4.6**).

***Fertility*:**

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with OXALIPLATIN PCH 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 PCH may have an anti-fertility effect, which could be irreversible.

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 PCH. 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 PCH is administered by intraperitoneal route (off-label route of administration).

4.5 Interaction with other medicines and other forms of interaction:

OXALIPLATIN PCH 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 PCH (see **section 4.4**).

The interval between discontinuation of OXALIPLATIN PCH 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.

In patients who have received a single dose of 85 mg/m^2 of OXALIPLATIN PCH, 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 OXALIPLATIN PCH 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 PCH 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:

Women of childbearing potential should be advised not to become pregnant. OXALIPLATIN PCH is considered teratogenic (see **section 4.4**).

Due to the genotoxic potential of oxaliplatin (see **section 4.4**), women of childbearing potential should use effective contraceptive measures while being treated with OXALIPLATIN PCH and for 9 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving OXALIPLATIN PCH and for 6 months following completion of treatment (see **section 4.4**).

Pregnancy:

OXALIPLATIN PCH is contraindicated during pregnancy.

Breastfeeding:

OXALIPLATIN PCH is contraindicated during lactation.

It is not known if OXALIPLATIN PCH or its derivatives is excreted in breastmilk. Because of the potential for serious adverse reactions in infants, breastfeeding should be discontinued before starting treatment with OXALIPLATIN PCH.

Fertility:

OXALIPLATIN PCH may have anti-fertility effects (see **section 4.4**).

4.7 Effects on ability to drive and use machines:

OXALIPLATIN PCH may cause dizziness, nausea and vomiting, vision abnormalities such as a transient loss of vision (reversible following therapy discontinuation), and other neurologic symptoms that affect gait and balance which can affect the 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 PCH 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 PCH and 5-FU/FA combination than with 5-FU/FA alone.

Tabulated list of adverse reactions:

MedDRA system organ classes	*Frequent*	*Less Frequent*	*Frequency unknown*
Infections and	Infection, rhinitis,	Sepsis+	Septic shock*+

infestations	upper respiratory tract infection, neutropenic sepsis+		
Blood and lymphatic system disorders	Anaemia, neutropenia, thrombocytopenia, leukopenia, lymphopenia, febrile neutropenia	Immuno-allergic thrombocytopenia, haemolytic anaemia, Disseminated intravascular coagulation (DIC)+	Haemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia*
Immune system disorders	Allergy/allergic reaction ++		
Metabolism and nutrition disorders	Anorexia, hyperglycaemia, hypokalaemia, hyponatraemia, dehydration, hypocalcaemia	Metabolic acidosis	
Psychiatric disorders	Depression, insomnia	Nervousness	
Nervous system disorders	Peripheral sensory neuropathy, sensory disturbance, dysgeusia,	Dysarthria, loss of deep tendon reflexes, Lhermitte's sign, reversible	Cranial nerve palsies, fasciculations, convulsion, ischemic or haemorrhagic cerebrovascular disorder*

	headache, dizziness, motor neuritis, meningism	posterior leuko-encephalopathy syndrome (RPLS, or PRES)	
Eye disorders	Abnormal lacrimation, 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	
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	Haemorrhage,		

disorders	flushing, deep vein thrombosis, hypertension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, epistaxis, hiccups, pulmonary embolism	Interstitial lung disease, sometimes fatal, pulmonary fibrosis	Laryngospasm, pneumonia and broncho-pneumonia*+
Gastrointestinal disorders	Nausea, diarrhoea, vomiting, stomatitis/ mucositis, abdominal pain, constipation, dyspepsia, gastroesophageal reflux, gastrointestinal haemorrhage, rectal haemorrhage, flatulence	Ileus, intestinal obstruction, colitis including *clostridium difficile* diarrhoea, pancreatitis	Severe diarrhoea, oesophagitis, intestinal ischaemia+, gastrointestinal ulcer and perforation+
Hepato-biliary disorders		Hepatic veno-occlusive disease, portal hypertension, ascites, hepatic	Focal nodular hyperplasia

		lesions	
Skin and subcutaneous tissue disorders	Skin disorders, alopecia, skin exfoliation (i.e. hand & foot syndrome), rash, erythematous rash, hyperhidrosis, nail disorder		Hypersensitivity vasculitis*
Musculo-skeletal and connective tissue disorders	Back pain, arthralgia, bone pain		Rhabdomyolysis*+
Renal and urinary disorders	Haematuria, dysuria, abnormal micturition frequency	Acute tubular necrosis, acute interstitial nephritis and acute renal failure	
General disorders and administration site conditions	Fatigue, fever+++, asthenia, pain, injection site reaction++++		
Investigations	Increase hepatic enzyme, increased blood alkaline phosphatase, increased blood		

	bilirubin, increased blood lactate dehydrogenase (LDH), increased weight (adjuvant setting), increased blood creatinine, decreased weight (metastatic setting)		
Injury, poisoning and procedural complications	Fall		

***** post-marketing experience

+ 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 PCH 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:

Dysaesthesia/ paraesthesia of extremities and peripheral neuropathy:

The dose limiting toxicity of OXALIPLATIN PCH is neurological (see **section 4.4**). 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 occur in up to 95 % of patients treated. The duration of these symptoms, which usually regress between courses of OXALIPLATIN PCH 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 OXALIPLATIN PCH treatment discontinuation.

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 1 020 mg/m² (12 cycles).

In the majority of the cases, the neurological signs and symptoms improve or totally recover when OXALIPLATIN PCH 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 localised paraesthesias of moderate intensity (2,3 %) or with paraesthesias that may interfere with functional activities (0,5 %).

Acute neurosensory manifestations:

Acute neurosensory manifestations have been reported. They start within hours of administration and often occur on exposure to cold. They 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, co-ordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain. In addition, cranial nerve dysfunctions may be associated, 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 PCH. Isolated cases of optic neuritis have been reported.

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:

There is no known specific antidote for OXALIPLATIN PCH. The management of overdosage is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 26 Cytostatic agent

Pharmacotherapeutic group: other antineoplastic medicines, platinum compounds

ATC code: L01XA 03

Oxaliplatin is an antineoplastic medicine that undergoes non-enzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Both inter- and intra-strand Pt-DNA cross-links are formed.

Cross-links are formed between the *N7* positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These cross-links inhibit DNA replication and transcription. Cytotoxicity is cell-cycle non-specific.

5.2 Pharmacokinetic properties:

After intravenous doses, oxaliplatin is widely distributed throughout the body. Protein binding is 90 %, irreversible plasma protein binding, primarily to albumin and gamma globulins and accumulates in erythrocytes. The mean terminal half-life varies and has been stated to be 273 hours and 391 hours. Oxaliplatin is extensively metabolised to both inactive and active compounds and is predominantly excreted in the urine.

6. PHARMACEUTICAL PARTICULARS:

6.1 List of excipients:

Lactose monohydrate

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:

2 years

OXALIPLATIN PCH 5 mg/ml is chemically and physically stable at final concentrations of 0,2 to 2,0 mg/ml in 5 % glucose solution for infusion for 24 hours at 2 to 8 °C when stored in the dark and for 6 hours when stored in ambient light at 15 to 25 °C. However, 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.

Do not freeze the vial or solution for infusion.

For storage conditions after dilution of the medicine, see **section 6.3**.

6.5 Nature and contents of container:

OXALIPLATIN PCH 50 is filled in a clear, colourless Type I glass vial (10R) with dark grey bromobutyl rubber stopper and aluminium seal with a coloured polypropylene cover.

OXALIPLATIN PCH 100 is filled in a clear, colourless Type I glass vial (20R) with dark grey bromobutyl rubber stopper and aluminium seal with a coloured polypropylene cover.

6.6 Special precautions for disposal and other handling:

Instructions for handling:

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

The preparation of injectable solution of cytotoxic medicines 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 medicines. Any broken container must be treated with the same precaution and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. (See below section on ***Disposal***).

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

Special precautions for administration:

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

  OXALIPLATIN PCH 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 solution such as 5 % glucose solution but NOT sodium chloride solutions or alkaline solutions. Flush the line after OXALIPLATIN PCH administration.
- DO NOT dilute for infusion with saline solution.
- DO NOT mix with other medicines in the same infusion line (refer to the instructions concerning simultaneous administration with folinic acid).
- DO NOT use needles or intravenous administration sets containing aluminium.

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 solution should be discarded.

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 with due regard to current laws related to the disposal of hazardous waste.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

Teva Pharmaceuticals (Pty) Ltd

Maxwell Office Park

Magwa Crescent West

Waterfall City, Midrand

2090

South Africa

8. REGISTRATION NUMBER(S):

OXALIPLATIN PCH 50: 43/26/0102

OXALIPLATIN PCH 100: 43/26/0103

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of Registration: 27 July 2012

10. DATE OF REVISION OF THE TEXT:

20 June 2024