Follow Up Sheet

כרטיס מעקב

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Physician's Prescribing Information

OXALIPLATIN HOSPIRA 5 MG/ML

Oxaliplatin 5 mg/ml Concentrate for Solution for Infusion

The format and contents of this leaflet were determined, checked and approved by the Israeli Ministry of Health in August 2016

1. NAME OF MEDICINAL PRODUCT:

OXALIPLATIN HOSPIRA 5 MG/ML

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

1 ml of concentrate for solution for infusion contains 5 mg oxaliplatin.
10 ml concentrate for solution for infusion contain 50 mg of oxaliplatin.
20 ml concentrate for solution for infusion contain100 mg of oxaliplatin.
40 ml concentrate for solution for infusion contain 200 mg of oxaliplatin.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

Concentrate for solution for infusion. Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications:

In combination with 5-fluorouracil and folinic acid (FA), oxaliplatin is indicated for:

- adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour
- the treatment of metastatic colorectal cancer
- Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil is indicated for the first-line treatment of patients with metastatic pancreatic adenocarcinoma (based on NCCN guidelines, version 2.2014).

4.2 Posology and method of administration:

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal product used, in conditions that guarantee the integrity of the medicinal product, the protection of the environment and in particular the protection of the personnel handling the medicinal products, in accordance with hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area (see section 6.6).

Posology:

FOR ADULTS ONLY.

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

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks until disease progression or unacceptable toxicity.

The recommended dose of oxaliplatin for the treatment of metastatic pancreatic adenocarcinoma is 85 mg/m² given as a 2-hour intravenous infusion, immediately followed by leucovorin (400 mg/m², 2-hour intravenous infusion) with the addition after 30 minutes of irinotecan (180 mg/m², 90-minute intravenous infusion through a Y-connector) and immediately followed by 5-fluorouracil (400 mg/m² intravenous bolus followed by 2,400 mg/m² continuous intravenous infusion for 46 hours), in 2-week cycles up to 6 months.

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

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of glucose 5% solution (50 mg/ml) to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin 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.

Oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil should only be administered to patients less than 76 years-old, with ECOG performance status (Eastern Cooperative Oncology Group) 0-1, who have no cardiac ischaemia, and normal or nearly normal level of bilirubin.

Special Populations:

- Renal impairment:
  Oxaliplatin must not be administered in patients with severe renal impairment (see sections 4.3, 4.4 and 5.2).
  In patients with mild to moderate renal impairment, the recommended dose of oxaliplatin is 85 mg/m² (see sections 4.3, 4.4 and 5.2).
- Hepatic impairment:
  In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepatobiliary disorders appeared to be related to progressive disease and impaired 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 agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.
- Paediatric Population:
  There is no relevant indication of Oxaliplatin in children. The effectiveness of oxaliplatin as single agent in the paediatric populations with solid tumors has not been established (see section 5.1).

Method of administration:

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted in 250 to 500 ml of glucose 5% solution (50 mg/ml) to give a concentration not less than 0.2 mg/ml must be infused either via a peripheral vein or central venous line over 2 to 6 hours. Oxaliplatin infusion must always precede that of 5-fluorouracil.

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

Instructions for use:

Oxaliplatin must be diluted before use. Only 5% glucose diluent is to be used to dilute the concentrate for solution for infusion product. (See section 6.6).

4.3 Contraindications:

Oxaliplatin is contraindicated in patients who

- have hypersensitivity to oxaliplatin or to the excipient.
- are breast feeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils <2x10^9/l and/or platelet count of <100x10^9/l.
- have a peripheral sensory neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use:

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

Renal impairment

Due to limited information on safety in patients with 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.

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).

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see section 4.8). Oxaliplatin 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 be not reversible with discontinuation of therapy and dialysis may be required.

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 to such patients is contraindicated. Cross reactions, sometimes fatal, have been reported with all platinum compounds.

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

Neurological Symptoms

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medicinal products 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 infusion should be administered over 6 hours.

Peripheral neuropathy

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage 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 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 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 should be discontinued.
- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

Patients should be informed of the possibilities of persistent symptoms of peripheral sensory neuropathy after the end of the treatment. Localised moderate parasthesias or parasthesias 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, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil.

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

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

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

If haematological toxicity occurs (neutrophils < 1.5x10^9/l or platelets < 50x10^9/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.

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 treatment should be discontinued.

Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with oxaliplatin treatment. If DIC is present, oxaliplatin treatment should be discontinued and appropriate treatment should be administered. (see section 4.8).

Patients must be adequately informed of the risk of diarrhoea/emesis, mucositis/stomatitis and neutropenia after oxaliplatin 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 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 < 1.0x10^9/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1.0x10^9/l, a single temperature of > 38.3°C or a sustained temperature of > 38°C for more than one hour), grade 3-4 thrombocytopenia (platelets < 50x10^9/l) occur, oxaliplatin must be discontinued until improvement or resolution, and the dose of oxaliplatin 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 should be discontinued until further pulmonary investigations exclude an interstitial lung disease or pulmonary fibrosis (see section 4.8).

Hepatic

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

Cardiac

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

Musculoskeletal and connective tissue

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 treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin. (see sections 4.5 and 4.8).

Combined therapy of oxaliplatin with leucovorin, irinotecan and 5-fluorouracil (FOLFIRINOX)

Risk of neutropenia: Patients treated with FOLFIRINOX may receive prophylactic G-CSF, as per American Society of Clinical Oncology (ASCO) guidelines and/or current institutional guidelines, to reduce the risk or manage neutropenia complications (febrile neutropenia, prolonged neutropenia or neutropenic infection). Primary prophylaxis with G-CSF should be considered in patients with high-risk clinical features (e.g., age>65 years, poor nutritional status, or other serious comorbidities) that predispose them to increased complications from prolonged neutropenia. The use of G-CSF has been shown to limit the incidence and severity of neutropenia.

When using oxaliplatin in combination with leucovorin, irinotecan and 5-fluorouracil, beyond the information contained in the leaflet of oxaliplatin, the information in the leaflets of each of the other drugs as part of combination therapy should also be checked.

Pregnancy

For use in pregnant women see section 4.6.

Fertility

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

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

4.5 Interaction with other medicinal products and other forms of interaction:

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

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

Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored (see section 4.4).

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis (see section 4.4)

4.6 Pregnancy and lactation:

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 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 and 6 months for men.

Excretion in breast milk has not been studied. Breast-feeding is contra-indicated during oxaliplatin therapy.

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

4.7 Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machinery have been performed. However, oxaliplatin treatment resulting in an increased risk of dizziness, nausea and 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 patients' ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects:

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.

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: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), rare (≥ 1/10000 to < 1/1000), very rare (< 1/10000) not known (cannot be estimated from the available data).

Further details are given after the table.

MedDRA Organ System Class	Very common	Common	Uncommon	Rare
Infections and infestations*	- Infection	- Rhinitis - Upper respiratory tract infection - Neutropenic sepsis, including fatal outcomes	- Sepsis - including fatal outcomes	
Blood and lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocytopenia - Leukopenia - Lymphopenia	- Febrile neutropenia		- Autoimmune thrombocytopenia - Haemolytic anaemia
Immune system disorders*	- Allergy/allergic reaction+			
Metabolism and nutrition disorders	- Anorexia - Glycaemia alterations - Hypokalaemia - Natremia alterations	- Dehydration	- Metabolic acidosis	
Psychiatric disorders		- Depression - Insomnia	- Nervousness	
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria - Reversible Posterior Leukoencephalopathy syndrome (RPLC, or PRES)** (see section 4.4)
Eye disorders		- Conjunctivitis - Visual disturbances	Transient vision loss (reversible following therapy discontinuation)	- Visual acuity reduced transiently - Visual field disturbance - Optic neuritis
Ear and labyrinth disorders			- Ototoxicity	- Deafness
Vascular disorders	- Epistaxis	- Haemorrhage - Flushing - Deep vein thrombosis - Pulmonary embolism		Disseminated intravascular coagulation (DIC) including fatal outcomes (see section 4.4)
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Coughing	- Hiccups		- Interstitial lung disease - Pulmonary fibrosis**
Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis / mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastroesophageal reflux - Rectal haemorrhage - Gastrointestinal hemorrhage	- Ileus - Intestinal obstruction	- Colitis including *Clostridium difficile* diarrhoea - Pancreatitis
Hepato-biliary disorders	- Hepatic enzyme increase - Blood bilirubin increase			
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfolation (i.e. Hand and Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder		
Musculo-skeletal, connective tissue disorders	- Back pain	- Arthralgia - Bone pain		
Renal and urinary disorders		- Dysuria - Micturition frequency abnormal - Haematuria - Blood Creatinine increase		
General disorders and administration site conditions	- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++ - Rigors			
Investigations	- Blood alkaline phosphatase increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting)	- Weight decrease (metastatic setting)		

* See detailed section below

** See section 4.4

+ Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis. Common anaphylactic reactions, including bronchospasm, sensation of chest pain, angioedema, hypotension and anaphylactic shock.

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

+++ Injection site reaction including local pain, redness, swelling and thrombosis have been reported. Extravasation may 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 4.4).

Post-marketing experience with frequency unknown

Infections and infestations

Septic shock, including fatal outcomes.

Blood and lymphatic system 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
Anaemia	82.2	3	<1	75.6	0.7	0.1
Neutropenia	71.4	28	14	78.9	28.8	12.3
Thrombocytopenia	71.6	4	<1	77.4	1.5	0.2
Febrile neutropenia	5.0	3.6	1.4	0.7	0.7	0.0
Neutropenic sepsis	1.1	0.7	0.4	1.1	0.6	0.4

Post-marketing experience with frequency unknown

Hemolytic uremic syndrome

Immune system disorders:
Incidence of allergic reactions 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
Allergic reactions / Allergy	9.1	1	<1	10.3	2.3	0.6

Nervous system:

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dysaesthesia and/or parasthesia 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 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 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 localised paraesthesias of moderate intensity (2.3%) or with paraesthesias 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 paresthesia, 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 spasm/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort /pain. In addition, cranial nerve dysfunction 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. Isolated cases of optic neuritis have been reported.

Post-marketing experience with frequency unknown

Convulsion

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 agents is indicated.

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

Post-marketing experience with frequency unknown

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

Hepatobiliary disorders:

Very rare (≤1/10,000): Liver sinusoidal obstruction syndrome, also known as veno-occlusive liver disease or pathological manifestations related to such liver disorders, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or elevation of transaminases.

Renal and urinary disorders:

Very rare (≤1/10000): Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Cardiac disorders

Post-marketing experience with frequency unknown

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 unknown

Laryngospasm

Musculoskeletal and connective tissue disorders

Post-marketing experience with frequency unknown

Rhabdomyolysis, including fatal outcomes. (see section 4.4).

Combined therapy of oxaliplatin with leucovorin, irinotecan and 5-fluorouracil (FOLFIRINOX) - Grade 3 and 4 adverse reactions:

Blood and lymph system disorders
Very common
Neutropenia (45.7%)
Common
Thrombocytopenia (9.1%)
Anemia (7.8%)
Febrile neutropenia (5.4%)

Vascular disorders
Common
Thromboembolism (6.6%)

Metabolic and nutritional disorders
Very common
Fatigue (23.6%)

Gastrointestinal disorders
Very common
Vomiting (14.5%)
Diarrhea (12.7%)

Nervous system disorders
Common
Sensory neuropathy (9%)

Hepatobiliary disorders
Common
Increased ALAT (7.3%)

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il).

4.9 Overdose:

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties:

Pharmacotherapeutic group: Other antineoplastic agents, platinum compounds. ATC code: L01XA 03

Oxaliplatin is an antineoplastic drug 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, the Cis-[oxalato (trans-1-1,2- DACH) 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.*

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 antitumour effects.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m² repeated every two weeks) combined with 5-fluorouracil/folinic acid is reported in three clinical studies:

- In front-line treatment, the 2-arm comparative phase III EFC2962 study randomized patients either to 5-fluorouracil/folinic acid alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-fluorouracil/folinic (FOLFOX4, N=210)
- In pretreated patients the comparative 3-arm EFC4584 study randomized patients refractory to an irinotecan (CPT-11) + 5-fluorouracil/folinic combination either to 5-fluorouracil/folinic acid alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-fluorouracil/folinic (FOLFOX4, N=271)
- Finally, the uncontrolled phase II EFC2964 study included patients refractory to 5-fluorouracil/folinic acid alone, that were treated with the oxaliplatin and 5-fluorouracil/folinic acid combination (FOLFOX4, N=57)

The two randomized clinical trials, EFC2962 in front-line therapy and EFC4584 in pretreated patients, demonstrated a significantly higher response rate and a prolonged progression-free survival (PFS)/time to progression (TTP) as compared to treatment with 5-fluorouracil/folinic acid alone. IN EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Response rate under FOLFOX4 versus LV5FU2

Response rate % (95% CI) **Independent radiological review ITT analysis**	**LV5FU2**	**FOLFOX4**	**Oxaliplatin** **Single agent**
Front-line treatment EFC2962 (Response assessment every 8 weeks)	22 (16-27)	49 (42-46)	NA*
	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA) Response assessment every 6 weeks	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
	P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5-FU/FA) Response assessment every 12 weeks	NA*	23 (13-36)	NA*

NA: Not Applicable

Median Progression-Free Survival (PFS) / Median Time to Progression (TTP) FOLFOX4 versus LV5FU2

Median PFS/TTP, **Months (95% CI)** **ITT analysis with independent radiological examination**	**LV5FU2**	**FOLFOX4**	**Oxaliplatin** **Single agent**
Front-line treatment EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (TTP) (refractory to CPT-11 + 5-FU/FA)	2.6 (1.8-2.9)	5.3 (4.7-6.1)	2.1 (1.6-2.7)
	Log-rank P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	5.1 (3.1-5.7)	NA*

NA: Not Applicable

Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, **Months (95% CI)** **ITT analysis**	**LV5FU2**	**FOLFOX4**	**Oxaliplatin** **Single agent**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	8.8 (7.3-9.3)	9.9 (9.1-10.5)	8.1 (7.2-8.7)
	Log-rank P value = 0.09		
Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

NA: Not Applicable

In pretreated patients (EFC4584), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin/5-fluorouracil/folinic acid experienced a significant improvement of their disease-related symptoms compared to those treated with 5-fluorouracil/folinic acid alone (27.7% vs 14.6% p = 0.0033).

In non pretreated patients (EFC2962), no statistical difference between the two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting.

In the adjuvant setting, the MOSAIC comparative phase III study (EFC3313) randomised 2246 patients (899 stage II/Duke's B2 and 1347 stage III/Duke's C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4).

EFC 3313 3-year disease free survival (ITT analysis)* for the overall population

Treatment arm	**LV5FU2**	**FOLFOX4**
Percent 3-year disease free survival (95% CI)	73.3 (70.6-75.9)	78.7 (76.2-81.1)
Hazard ratio (95% CI)	0.76 (0.64-0.89)	
Stratified log rank test	P = 0.0008	

* median follow-up 44.2 months (all patients followed for at least 3 years)

The study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5-FU/FA combination (FOLFOX4) over 5-FU/FA alone (LV5FU2).

EFC 3313 3-year disease free survival (ITT analysis)* according to stage of disease

Patient stage	**Stage II** **(Duke's B2)**		**Stage III** **Duke's C**	
Treatment arm	LV5FU2	FOLFOX4	LV5FU2	FOLFOX4
Percent 3-year disease free survival (95% CI)	84.3 (80.9-87.7)	87.4 (84.3-90.5)	65.8 (62.2-69.5)	72.8 (69.4-76.2)
Hazard ratio (95% CI)	0.79 (0.57-1.09)		0.75 (0.62-0.90)	
Log-rank test	P = 0.151		P = 0.002	

* median follow-up 44.2 months (all patients followed for at least 3 years)

Overall Survival (ITT analysis):

At time of the analysis of the 3-year disease free survival, which was the primary endpoint of the MOSAIC trial, 85.1% of the patients were still alive in the FOLFOX4 arm versus 83.8% in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10% in favour of the FOLFOX4 not reaching statistical significance (hazard ratio = 0.90). The figures were 92.2% versus 92.4% in the stage II (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4% versus 78.1% in the stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

Oxaliplatin single agent has been evaluated in paediatric population in 2 Phase I (69 patients) and 2 Phase II (166 patients) studies. A total of 235 paediatric patients (7 months-22 years of age) with solid tumors have been treated. The effectiveness of oxaliplatin single agent in the paediatric populations treated has not been established.

Accrual in both Phase II studies was stopped for lack of tumor response.

Treatment regimen with FOLFIRINOX (oxaliplatin, leucovorin, irinotecan and 5-fluorouracil)

In patients with metastatic pancreatic adenocarcinoma not previously treated with chemotherapy, oxaliplatin was evaluated in PRODIGE 4/ACCORD 11 study (N=342). The intent-to-treat population included 171 patients groups and the safety population (all patients who received treatment) included 167 patients in the FOLFIRINOX group and 169 patients in the Gemcitabine group.

Patients were randomized in a 1:1 ratio with stratification by site, performance status (0 vs. 1) and primary tumor location (head vs. body or tail of the pancreas), to receive FOLFIRINOX (oxaliplatin 85 mg/m², leucovorin 400 mg/m², irinotecan 180 mg/m², 5-fluorouracil 400 mg/m² IV bolus followed by 2,400 mg/m² continuous IV infusion for 46 hours every 14 days) or gemcitabine (1,000 mg/m² IV over 30 minutes, weekly for 7 weeks followed by 1-week rest, then weekly for 3 weeks in subsequent 4-week cycles). Each cycle was defined as being a period of 2 weeks for both regimens. Six months of chemotherapy were recommended for patients who had a response.

The median number of treatment cycles administered was 10 (range 1-47) in FOLFIRINOX arm and 6 (range 1-26) in Gemcitabine arm (p <0.001). The median duration of follow-up of patients was 26.6 months (95% CI: 20.5 to 44.9). The median relative dose intensities of fluorouracil, irinotecan, oxaliplatin and gemcitabine were 82%, 81%, 78% and 100%, respectively. More patients in Gemcitabine group had disease progression prior to complete 12 cycles (6 months) of treatment (79.9% vs. 54.6% in FOLFIRINOX group, p <0.001).

The median overall survival was significantly higher in FOLFIRINOX arm compared to Gemcitabine arm (11.1 months vs. 6.8 months, HR = 0.57, 95% CI: 0.45 to 0.73, p <0.001). The overall survival rates after 6, 12 and 18 months were higher for all patients treated with FOLFIRINOX (75.9%, 48.4% and 18.6% respectively) compared with 57.6%, 20.6% and 6.0%, respectively for those treated with gemcitabine.

The median progression-free survival was significantly higher in FOLFIRINOX arm compared to Gemcitabine arm (6.4 months vs. 3.3 months, HR = 0.47, 95% CI: 0.37 to 0.59, p <0.001). The objective response rate was 31.6% in FOLFIRINOX group versus 9.4% in Gemcitabine group (p <0.001). The beneficial effect of FOLFIRINOX was similar in all subgroups of patients. This data are summarized in the following table.

Summary of Efficacy results of FOLFIRINOX versus Gemcitabine

	FOLFIRINOX **(N=171)**	**Gemcitabine** **(N=171)**	**Hazard** **Ratio**	**p-Value**
Complete Response (CR) Partial Response (PR) Objective Response rate (CR + PR) 95% CI Stable Disease (SD) Disease Control (CR + PR + SD) 95% CI	1 (0.6%) 53 (31%) 54 (31.6%) 24.7-39.1 66 (38.6%) 120 (70.2%) 62.7-76.9	0 (0%) 16 (9.4%) 16 (9.4%) 5.4-14.7 71 (41.5%) 87 (50.9%) 43.1-58.6		 < 0.001 < 0.001
Median Overall Survival (months) 95% CI 1-year Survival 18-month Survival	11.1 9.0-13.1 48.4% 18.6%	6.8 5.5-7.6 20.6% 6%	0.57 0.45-0.73	< 0.001
Median Progression-free Survival (months) 95% CI	6.4 5.5-7.2	3.3 2.2-3.6	0.47 0.37-0.59	< 0.001

Safety results

Patients who received FOLFIRINOX had significantly higher rates of grade 3 and 4 neutropenia (45.7% vs. 21%), febrile neutropenia (5.4% vs. 1.2%), thrombocytopenia (9.1% vs. 3 6%), diarrhea (12.7% vs. 1.8%), and sensory neuropathy (9% vs. 0%). Cholangitis was not observed in either group.

Filgrastim was administered in 42.5% of patients receiving FOLFIRINOX and 5.3% of patients who received gemcitabine.

Quality of Life

Despite the high incidence of adverse events associated with FOLFIRINOX regimen, there was a significant increase in time to definitive Quality of Life deterioration in FOLFIRINOX group compared to gemcitabine group.

At 6 months, 31% of patients in the FOLFIRINOX group had a definitive decrease in their scores on the Global Health Status and Quality of Life scale compared to 66% in the Gemcitabine group (HR = 0.47, 95% CI: 0.30-0.70, p <0.001). In the FOLFIRINOX group, the time to definitive deterioration in the quality of life was significantly increased in all items of the EORTC QLQ-C30 questionnaire, except the time to a definitive decrease in the scores associated with insomnia, diarrhea, and financial difficulties caused by a physical condition or medical treatment, which did not differ significantly between regimens.

5.2 Pharmacokinetic properties:

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two-hour infusion of oxaliplatin at 130 mg /m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of Oxaliplatin at 85 mg/m² Every Two Weeks or at 130 mg/m² Every Three Weeks

Dose	C_{max}	AUC_{0-48}	AUC	$t_{1/2\alpha}$	$t_{1/2\beta}$	$t_{1/2\gamma}$	Vss	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, Vss, CL, and CL_{R0-48} values were determined on Cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, Vss 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/m² every two weeks or 130 mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

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.

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.

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/m² 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 65 mg/m² 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).

5.3 Preclinical safety data:

The target organs identified in preclinical species (mice, rats, dogs, and/or monkeys) in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing drugs and DNA-damaging, cytotoxic drugs used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation. Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m²) were well-tolerated by humans. Preclinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to Oxaliplatin may involve an interaction with voltage-gated Na^+ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipient(s):

Water for Injections, Tartaric acid, Sodium Hydroxide (for pH adjustment).

6.2 Incompatibilities:

This medicinal product should not be mixed with other medicinal products except for those mentioned in section 6.6. Oxaliplatin can be co-administered with folinic acid via a Y-line.

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

6.3 Shelf-life:

Medicinal product as packaged for sale: 18 months.

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

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C to +8°C and for 6 hours at +25°C.

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

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

6.4 Special precautions for storage:

Store below 25°C.

Medicinal product as packaged for sale: Keep the vial in the outer carton in order to protect from light. Do not freeze.

For storage conditions of the diluted medicinal product see section 6.3.

6.5 Nature and contents of container:

- 1 vial with 10 ml concentrate (Type I clear glass vial with or without Onco-Tain sleeve) with elastomeric stopper and flip-off cap.
- 1 vial with 20 ml concentrate (Type I clear glass vial with or without Onco-Tain sleeve) with elastomeric stopper and flip-off cap.
- 1 vial with 40 ml concentrate (Type I clear glass vial with or without Onco-Tain sleeve) with elastomeric stopper and flip-off cap.

Pack size: 1 vial per box. Not all pack sizes may be marketed.

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 agent by healthcare personnel requires every precaution to guarantee the protection of the handler and his surroundings.

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 integrity of the medicinal 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 agents.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See below chapter "Disposal".

If oxaliplatin concentrate or solution for infusion should come into contact with skin, wash immediately and thoroughly with water.

If oxaliplatin 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 material containing aluminium.
- DO NOT administer undiluted.
- Only glucose 5% 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 medicinal products in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipients and trometamol salts of other drugs. Alkaline drugs or solutions will adversely effect the stability of oxaliplatin.

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

Oxaliplatin 85 mg/m² intravenous infusion in 250 to 500 ml of glucose 5% solution is given at the same time as folinic acid (FA) intravenous infusion in glucose 5% solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.

These two medical products should **not** be combined in the same infusion bag. Folinic acid must not contain trometamol as an excipient and must only be diluted using isotonic glucose 5% solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instructions for use with 5-fluorouracil:

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil. After oxaliplatin administration, flush the line and then administer 5-fluorouracil.

For additional information on drugs combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

Instructions for use in combined therapy of oxaliplatin with leucovorin, irinotecan and 5-fluorouracil (FOLFIRINOX)

Oxaliplatin 85 mg/m² given as a 2-hour intravenous infusion, immediately followed by leucovorin (400 mg/m², 2-hour intravenous infusion) with the addition after 30 minutes of irinotecan (180 mg/m², 90-minute intravenous infusion through a Y-connector) and immediately followed by 5-fluorouracil (400 mg/m² intravenous bolus followed by 2,400 mg/m² continuous intravenous infusion for 46 hours), in 2-week cycles up to 6 months.

For additional information on drugs combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

Concentrate for solution for infusion:

Inspect visually prior to use. Only clear solutions without particles should be used. The medicinal product 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 glucose 5% solution to give an oxaliplatin concentration between 0.2 mg/ml and 0.7 mg/ml. The concentration range over which the physico-chemical stability of oxaliplatin has been demonstrated is 0.2 mg/ml to 1.3 mg/ml.

Administer by intravenous infusion.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C to +8°C and for 6 hours at 25°C.

From a microbiological point of view, this infusion preparation should be used immediately.

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

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

The medicinal product is for single-use only. Any unused infusion solution should be discarded.

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 does not require prehydration.

Oxaliplatin diluted in 250 to 500 ml of a glucose 5% 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 is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Disposal:

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

Registration Number:
148-20-33431

Manufacturer:
Hospira UK Limited, Honey Lane, Hurley, Maidenhead, SL6 6RJ, United Kingdom

License Holder:
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