SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE:

ZALITIN 50 (concentrate for solution for infusion)

ZALITIN 100 (concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

ZALITIN 50

Each vial contains 10 ml of solution equivalent to 50 mg of oxaliplatin.

ZALITIN 100

Each vial contains 20 ml of solution equivalent to 100 mg of oxaliplatin

Sugar Free

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

3. PHARMACEUTICAL FORM:

ZALITIN 50 and ZALITIN 100 concentrate for solution for infusion is clear and colourless.

4. CLINICAL PARTICULARS:

4.1 Therapeutic Indications

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

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

4.2 Posology and method of administration

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

Posology:

FOR ADULTS ONLY:

Treatment of metastatic colorectal cancer:

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

Adjuvant treatment of colon cancer:

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

Dosage given should be adjusted according to tolerability (see section 4.4 and 4.8)

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

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

ZALITIN 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:

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

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

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

Hepatic impairment:

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

A phase I study of oxaliplatin as in **ZALITIN** single agent, 2-hour IV infusion q3w, included adult cancer patients with different degrees of hepatic impairment (none to severe). The initial oxaliplatin as in **ZALITIN** dose was based upon the degree of liver dysfunction and was then increased up to 130 mg/m^2 whatever the degree of

liver impairment (none to severe). Overall, the types of toxicities observed were toxicities expected with oxaliplatin as in **ZALITIN** (see section 4.8). The frequencies of adverse events were increased in patients with liver impairment.

Elderly patients:

No increase in severe toxicities was observed when **ZALITIN** was used as a single medicine or in combination with 5-fluorouracil (5-FU) in patients over the age of 65. In consequence, no specific dose adaptation is required for elderly patients.

Method of administration

ZALITIN is administered by intravenous infusion.

The administration of **ZALITIN** does not require hyperhydration.

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

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

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

Flush the line after **ZALITIN** administration.

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

Instructions for use

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

Precautions to be taken before manipulation or administering the product

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

4.3 Contraindications

- Hypersensitivity to oxaliplatin or to any of the ingredients of **ZALITIN** listed in section 6.1.
- Breastfeeding.
- Bone marrow failure.
- Myelosuppression prior to starting treatment.
- Peripheral sensory neuropathy with functional impairment before treatment.
- Severe renal impairment (Clcr < 30 mL/min).

4.4 Special warnings and precautions for use

General

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

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

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

Renal impairment

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

Hypersensitivity reactions

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. In case of an anaphylactic-like reaction to **ZALITIN**, the infusion should be immediately discontinued, and appropriate symptomatic treatment initiated. **ZALITIN** re-challenge is contraindicated.

Neurological symptoms

Sensory peripheral neurotoxicity of **ZALITIN** 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.

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

• If symptoms last longer than seven days and are troublesome, the subsequent **ZALITIN** 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 **ZALITIN** 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, **ZALITIN** administration should be discontinued.

If these symptoms improve following discontinuation of **ZALITIN** therapy, resumption of therapy may be considered.

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

For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next **ZALITIN** 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 **ZALITIN** administration.

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

Gastrointestinal toxicity

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8). Dehydration, paralytic ileus, intestinal obstruction, hypokalaemia, metabolic acidosis and renal impairment may be associated with severe diarrhoea/emesis particularly when combining **ZALITIN** with 5-fluorouracil (5-FU).

Intestinal ischaemia

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

Haematological toxicity

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

If severe/life-threatening diarrhoea, severe neutropenia (neutrophils < 1,0 x 10^9/L), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1,0 x 10^9/L, a single temperature of > 38,3 °C or a sustained temperature of > 38 °C for more than one hour), or severe thrombocytopenia (platelets < 50 x 10^9/L) occurs, **ZALITIN** must be discontinued until improvement or resolution, and the dose of **ZALITIN** should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting) at subsequent cycles, in addition to any 5-fluorouracil dose reductions required.

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after **ZALITIN**/5-fluorouracil administration in order to contact their treating doctor urgently for appropriate management.

If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is ≥ 1,5 x 10^9/L.

Infection

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

Pulmonary toxicity

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, **ZALITIN** should be

discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8).

Haemolytic-uraemic syndrome (HUS)

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see section 4.8). **ZALITIN** 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)

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

Hepatic toxicity

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

QT prolongation

QT prolongation may lead to an increased risk for ventricular dysrhythmias including Torsade de Pointes, which can be fatal. Caution should be exercised in patients with a history or a predisposition for prolongation of QT, those who are taking medicines

known to prolong QT interval and those with electrolyte disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, **ZALITIN** treatment should be discontinued (see sections 4.5 and 4.8).

Cardiac disorders

Post-marketing reports with **ZALITIN** use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with **ZALITIN** 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 bradyarrhythmia, tachycardia and atrial fibrillation). In case of cardiac dysrhythmias, treatment with **ZALITIN** 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 **ZALITIN**, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, **ZALITIN** 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 **ZALITIN** (see sections 4.5 and 4.8).

Duodenal ulcer

ZALITIN 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, **ZALITIN** treatment should be discontinued and appropriate measures taken (see section 4.8).

Do not use intraperitoneal route of administration

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

Fertility

Male patients treated with **ZALITIN** 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 **ZALITIN** may have an anti-fertility effect which could be irreversible.

Pregnancy

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

4.5 Interaction with other medicines and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 of **ZALITIN**, 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 **ZALITIN** 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 **ZALITIN** treatment is administered concomitantly with other medicines known to be associated with rhabdomyolysis (such as statins, antipsychotics, zidovudine, colchicine, selective serotonin reuptake inhibitors, and lithium) (see section 4.4).

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

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

Pregnancy

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

Breastfeeding

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

Fertility

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

4.7 Effects on the ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, **ZALITIN** treatment is associated with increased risk of dizziness, nausea and vomiting, and other neurological symptoms that affect gait and balance, which may lead to an impaired ability to drive and use machines. Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect the patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

MeDRA system organ classification	**Frequent**	**Less Frequent**	**Frequency Unknown**
Infections and infestations	infection, neutropenic sepsis, including fatal outcomes	sepsis, including fatal outcomes	
Blood and lymphatic system disorders	anaemia, neutropenia, thrombocytopenia, leucopoenia and lymphopenia, febrile neutropenia	immuno-allergic thrombocytopenia and haemolytic anaemia, disseminated intravascular coagulation (DIC), including fatal outcomes (see section 4.4)	haemolytic uraemic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia
Immune system disorders	allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis, anaphylactic reactions including bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock		delayed hypersensitivity
Metabolism and nutrition disorders	anorexia, hyperglycaemia, hypokalaemia, natraemia abnormalities,	Metabolic acidosis	

	dehydration, hypocalcaemia		
Psychiatric disorders	Depression, Insomnia	Nervousness	
Nervous system disorders	dysaesthesia/paraesthesia of extremities and peripheral neuropathy, headache, acute neuro-sensory manifestations (see section 4.4) and dysgeusia, dizziness, motor neuritis, flushing and meningism	dysarthria, loss of deep tendon reflexes, Lhermitte's sign, reversible posterior leucoencephalopathy syndrome (RPLS, also known as PRES) (see section 4.4)	convulsion, ischaemic and haemorrhagic cerebrovascular disorder
Eye disorders	conjunctivitis and abnormal vision	visual acuity reduced transiently, visual field disturbances and optic neuritis. Transient vision loss, reversible following therapy discontinuation.	
Ear and labyrinth disorders		ototoxicity, deafness	
Cardiac Disorders			QT prolongation, which may lead to ventricular dysrhythmias including Torsade de Pointes, which may be fatal (see sections 4.4 and 4.5), acute coronary syndrome

			including myocardial infarction and coronary arteriospasm and cardiac arrest; cardiac dysrhythmias including bradyarrhythmia, tachycardia and atrial fibrillation.
Vascular disorders	epistaxis, haematuria, deep thrombophlebitis, rectum haemorrhage, deep vein thrombosis, thromboembolic events (including pulmonary embolism), and hypertension		
Respiratory, thoracic and mediastinal disorders	Dyspnoea, cough, rhinitis, hiccups and upper respiratory infection	acute interstitial lung diseases, which may be fatal and pulmonary fibrosis (see section 4.4)	laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes
Gastrointestinal disorders	Nausea, vomiting and diarrhoea, stomatitis/mucositis, abdominal pain and constipation. Dehydration, hypokalaemia, metabolic	colitis (including Clostridium difficile diarrhoea), pancreatitis	intestinal ischaemia, including fatal outcomes, duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be

	acidosis, ileus, intestinal obstruction, renal disorders may be associated with severe diarrhoea/vomiting, particularly when ZALITIN is combined with 5-FU (see section 4.4). dyspepsia, gastro-oesophageal reflux and gastrointestinal haemorrhage		fatal (see section 4.4), oesophagitis
Hepato-biliary disorders		liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of the liver, or pathological manifestations related to such liver disorder, including peliosis hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or	

		increased transaminases.	
Skin and subcutaneous tissue disorders	skin disorder and alopecia, skin exfoliation (hand and foot syndrome), erythematous rash, rash, increased sweating and nail disorder		hypersensitivity vasculitis
Musculo-skeletal and connective tissue disorders	back pain. In case of such adverse reaction, haemolysis which has been rarely reported should be investigated, arthralgia and skeletal pain		rhabdomyolysis, including fatal outcomes (see sections 4.4 and 4.5). Injury, poisoning, and procedural complications: fall and fall-related injuries
Renal and urinary disorders	dysuria and abnormal micturition frequency Less Frequent: Acute tubular necrosis, acute interstitial nephritis, acute renal failure		
General disorders and administration site conditions	fatigue, fever, rigors (tremors) either from infection (with or without febrile neutropenia) or		

	possibly from immunological mechanism; asthenia, pain, weight increase (adjuvant setting). Injection site reactions 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 ZALITIN is infused through a peripheral vein.		
Investigations	mild to moderate elevation of hepatic enzymes (ALT/AST) and alkaline phosphatase, increased bilirubin, increased LDH, increased creatinine,		

	decreased weight (metastatic setting)		
Injury, poisoning and procedural complication	Fall		

Description of selected adverse reactions

Nervous system disorders

Dysaesthesia/paraesthesia of extremities and peripheral neuropathy:

The dose-limiting toxicity of **ZALITIN** is neurological (see section 4.4). It involves a sensory peripheral neuropathy characterised by peripheral dysaesthesia and/or paraesthesia with or without cramps, often triggered by the cold. The symptoms occur in 95 % of patients treated. The duration of these symptoms, which usually recede between the cycles of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder and their duration are indications for dose adjustment, or even treatment discontinuation.

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of a functional disorder for a cumulative dose of approximately 850 mg/m^2 (10 cycles) is 10 % and 20 % for a cumulative dose of 1 020 mg/m^2 (12 cycles).

In the majority of cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6

months after recovery cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow-up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity (2,3 %) or with paraesthesias that interfere with functional activities (0,5 %).

Acute neurosensory manifestations:

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

An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 - 2 % of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing).

Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

Other symptoms occasionally observed, particularly of cranial nerve dysfunction may be either associated with above-mentioned events, or also occur isolated such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease of visual acuity and

visual field disorders. In addition, the following symptoms have been observed: jaw spasm/muscle spasms/involuntary muscle contractions/muscle twitching/myoclonus, abnormal coordination/abnormal gait/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

Reporting side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

There is no known antidote to **ZALITIN**. 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

Oxaliplatin belongs to the medicine class A 26 Cytostatic agents.

Pharmacotherapeutic group: other antineoplastic agents, platinum compounds, ATC code: L01XA03.

5.1 Pharmacodynamic properties

Oxaliplatin is an antineoplastic medicine 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-λ-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*.

5.2 Pharmacokinetic properties

The pharmacokinetics of individual active compounds have not been determined.

The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a 2-hour infusion of oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

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

Dose	**C_{max}** µg/mL	**AUC_{0-48}** µg.h/mL	**AUC** µg.h/mL	**$t_{½\alpha}$** h	**$t_{½\beta}$** h	**$t_{½\gamma}$** h	**V_{ss}** L	**CL** L/h
85 mg/m²	0,814	4,19	4,68	0,43	16,8	391	440	17,4
Mean	0,193	0,647	1,40	0,35	5,74	406	199	6,35
SD								

Mean AUC_{0-48}, and C_{max} values were determined on cycle 3 (85 mg/m^2). Mean AUC, Vss, CL and CLR_{0-48} 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/m^2 every two weeks and steady state was attained by cycle 1 in this matrix.

Inter- and intrasubject 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 2-hour-infusion. Several cytotoxic biotransformation medicines 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.

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 fully evaluated (see Special populations: Renal impairment patients).

Special populations:

Renal impairment patients:

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

6. Pharmaceutical particulars

6.1 List of excipients

Water for injection.

6.2 Incompatibilities

- DO NOT use in association with alkaline medicines or solutions (in particular 5-fluorouracil, basic solutions, trometamol and folinic acid medicines containing trometamol as an excipient).
- **ZALITIN** can be co-administered with folinic acid infusion using a Y-line placed immediately before the site of infusion. These two medicines should not be combined in the same infusion bag. Folinic acid must be diluted using isotonic infusion solutions such as 5 % glucose solution but NOT sodium chloride solutions, chloride containing solutions or alkaline solutions. Flush the line after **ZALITIN** administration.
- DO NOT dilute for infusion with saline solution.
- DO NOT mix with other medicines in the same infusion bag or infusion line. Refer to the instructions concerning the simultaneous administration with folinic acid.
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

36 months

6.4 Special precautions for storage

After dilution in 5% dextrose is 12 hours at ≤ 25℃ and 24 hours at 2-8℃.

Do not freeze.

Protect from light (keep in outer carton until use).

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.

6.5 Nature and contents of container

ZALITIN 50 and ZALITIN 100 concentrate for infusion is packed in a 20H, borosilicate, colourless, type I glass vial with a 20mm, Teflon-coated chlorobutyl rubber stopper and a 20mm, aluminium seal with a plastic flip-off cap, packed in an outer carton with a package insert.

6.6 Special precautions for disposal and other handling

ZALITIN must be further diluted before use. DO NOT administer undiluted. Only the recommended diluents should be used (See Method of administration and preparation of infusion solution and Incompatibilities).

Caution should be exercised when handling and preparing **ZALITIN** solutions.

The preparation of **ZALITIN** must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area. Personnel must be provided with appropriate handling materials, notably long-sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

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

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

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

Disposal:

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

7. Holder of certificate of registration

Innovata Pharmaceuticals

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Johannesburg

2091

South Africa

8. Registration numbers

ZALITIN 50: 56/26/0891

ZALITIN 100: 56/26/0892

9. Date of first authorization/Renewal of the authorization

15 July 2025

10. Date of revision of the text

TBI