PROFESSIONAL INFORMATION: CLEAN VERSION

SCHEDULING STATUS:

S4

PROPRIETARY NAME AND DOSAGE FORM:

OXALIWIN™ 50 mg/10 ml RTU Concentrate for infusion

OXALIWIN™ 100 mg/20 ml RTU Concentrate for infusion

COMPOSITION:

OXALIWIN™ 50 mg/10 ml RTU:

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

OXALIWIN™ 100 mg/20 ml RTU:

Each vial contains 20 ml of solution equivalent to 100 mg of oxaliplatin or 40 ml of solution equivalent to 200 mg of oxaliplatin.

Excipients: Water for injection.

Sugar free

CATEGORY AND CLASS:

A 26 Cytostatic agents

PHARMACOLOGICAL ACTION:

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*.

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								
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

Mean AUC_{0-48}, and C_{max} values were determined on cycle 3 (85 mg/m²). Mean AUC, V_{ss}, CL and CL_{R0-48} values were determined on cycle 1. C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis. $t_{1/2}\alpha$, $t_{1/2}\beta$, and $t_{1/2}\gamma$, were determined by compartmental analysis (cycles 1-3 combined).

At the end of a 2-hour infusion, 15 % of the administered platinum is present in the systemic circulation, the remaining 85 % being rapidly distributed into tissues or eliminated in the urine.

Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin.

No accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks 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 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.

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 patient).

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 DOSAGE AND DIRECTIONS FOR USE: Special Populations and WARNINGS AND SPECIAL PRECAUTIONS).

Clinical studies:

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/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid is reported in three clinical studies: The two randomised clinical trials, EFC2962 in front-line

therapy and EFC4584 in pre-treated 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.

Response Rate under FOLFOX4 versus LV5FU2

Response rate % (95 % CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	22 (16-27)	49 (42-46)	NA
	P value = 0,0001		
Pre-treated patients EFC4584 (refractory to CPT-11+5-FU/LV)	0,0 (0,0–2,5)	9,9 (5,6–15,8)	1,3 (0,1–4,6)
	P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	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) independent radiological review ITT analysis	**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		
Pre-treated patients EFC4584 (TTP) (refractory to CPT-11+5-FU/LV)	2,7 (1,8–3,0)	4,6 (4,2–6,1)	1,6 (1,4–2,7)
	Log-rank P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	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 (PFS)	14,7 (13,0–18,2)	16,2 (14,7–18,2)	NA
	Log-rank P value = 0,12		
Pre-treated patients EFC4584* (refractory to CPT-11+5-FU/LV)	8,8 (7,3–9,3)	9,9 (9,1–10,5)	8,1 (7,2–8,7)
	Log-rank P value = 0,0001		
Pre-treated patients EFC2964 (refractory to 5-FU/LV)	NA	10,8 (9,3–12,8)	NA

NA: Not Applicable

*Survival data with 90 % of the events (deaths) reported

In pre-treated patients who were symptomatic at baseline a higher proportion of those treated with oxaliplatin and 5-FU/FA experienced a significant improvement of their disease-related symptoms compared to those treated with 5FU/FA alone (32,6 % vs 11,9 %).

In non pre-treated patients no statistically significant difference was observed between the two treatment groups in terms of quality of life. However the quality of life scores were generally better in the control group with respect to global state of health and pain and worse in the oxaliplatin group with respect to nausea and vomiting.

In the adjuvant setting the MOSAIC comparative phase III study (EFC3313) randomised 2 246 patients (899 stage II/Duke's B2 and 1 347 stage III/Duke's C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N = 1 123, B2/C = 448/675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N = 1 123, B2/C = 451/672).

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)	72,9 (70,2-75,7)	78,2 (75,6–80,7)
Hazard ratio (95 % CI)	0,77 (0,65–0,91)	
Stratified log rank test	P = 0,002	

* Median (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 (80,6-87,9)	87,0 (83,6-90,3)	65,3 (61,6-69,1)	72,2 (68,6-75,8)
Hazard ratio (95 % CI)	0,8 (0,56-1,15)		0,76 (0,62-0,92)	

Log-rank test	P = 0,151	P = 0,002

* Median (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, 87,7 % of the patients were still alive in the FOLFOX4 arm versus 86,6 % in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10 % in favour of FOLFOX4 not reaching statistical significance (hazard ratio = 0,90).

The figures were 93,2 % versus 93,6 % in the stage II (Duke's B2) sub-population (hazard ratio = 1,06) and 84,4 % versus 81,9 % in the stage III (Duke's C) sub-population (hazard ratio = 0,86), for FOLFOX4 and LV5FU2, respectively.

INDICATIONS:

OXALIWIN 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.

CONTRAINDICATIONS:

- History of allergy to OXALIWIN.
- Breastfeeding.
- Bone marrow failure.
- Myelosuppression prior to starting treatment.
- Peripheral sensory neuropathy with functional impairment before treatment.
- Severe renal impairment (Clcr < 30 ml/min).

WARNINGS AND SPECIAL PRECAUTIONS:

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

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 OXALIWIN dose is 65 mg/m^2 (see DOSAGE AND DIRECTIONS FOR USE: Special populations).

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 OXALIWIN, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. OXALIWIN re-challenge is contraindicated. In case of OXALIWIN extravasation, the infusion must be stopped immediately and the usual local symptomatic treatment initiated.

Sensory peripheral neurotoxicity of OXALIWIN should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter.

For patients who develop acute laryngopharyngeal dysaesthesia (see SIDE EFFECTS, during or within the hours following the 2-hour infusion, the next OXALIWIN 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 OXALIWIN administration.

Dysaesthesia/paraesthesia of extremities and peripheral neuropathy:

- The dose limiting toxicity of OXALIWIN is neurological. 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 OXALIWIN 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, visual field disorders. In addition, the following symptoms have been observed: jaw spasm/ muscle spasms/muscle contractions-involuntary/muscle twitching/ myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended OXALIWIN 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 OXALIWIN 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 OXALIWIN 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, OXALIWIN administration should be discontinued.
- If these symptoms improve following discontinuation of OXALIWIN 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.

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

Cases of intestinal ischaemia, including fatal outcomes, have been reported with OXALIWIN treatment. In case of intestinal ischaemia, OXALIWIN treatment should be discontinued and appropriate measures initiated (See SIDE EFFECTS).

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, 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.

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after OXALIWIN/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. For OXALIWIN combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If severe/life-threatening diarrhoea, severe neutropenia (neutrophils < 1,0 x 10^9/l), febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection with an absolute neutrophil count < 1,0 x 10^9/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) occur, OXALIWIN must be discontinued until improvement or resolution, and the dose of OXALIWIN 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.

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

Disseminated intravascular coagulation (DIC), including fatal outcomes, has been reported in association with OXALIWIN treatment. If DIC is present, OXALIWIN

treatment should be discontinued and appropriate treatment should be administered (see SIDE EFFECTS).

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, OXALIWIN should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see SIDE EFFECTS).

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see SIDE EFFECTS). OXALIWIN 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.

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

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 SIDE EFFECTS). Diagnosis of RPLS/PRES is based upon confirmation by brain imaging.

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 hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, OXALIWIN treatment should be discontinued (see INTERACTIONS and SIDE EFFECTS).

Rhabdomyolysis has been reported in patients treated with OXALIWIN, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, OXALIWIN 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 OXALIWIN (see INTERACTIONS and SIDE EFFECTS).

OXALIWIN 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, OXALIWIN treatment should be discontinued and appropriate measures taken (see SIDE EFFECTS).

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

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

Women should not become pregnant during and up to 4 months after treatment with OXALIWIN and should use an effective method of contraception (see HUMAN REPRODUCTION).

Effects on ability to drive and use machines:

No studies on the effects on the ability to drive and use machines have been performed. However, OXALIWIN treatment is associated with increased risk of dizziness, nausea and vomiting, and other neurologic 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.

INTERACTIONS:

In patients who have received a single dose of 85 mg/m^2 of OXALIWIN, 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 OXALIWIN treatment is co-administered with other medicinal products known to cause QT interval prolongation (such as quinidine, disopyramide, amiodarone, sotalol, dofetilide and ibutilide). In case of combination with such medicinal products, the QT interval should be closely monitored (see WARNINGS AND SPECIAL PRECAUTIONS).

Caution is advised when OXALIWIN 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 WARNINGS AND SPECIAL PRECAUTIONS).

HUMAN REPRODUCTION:

Pregnancy:

To date there is no available information on the safety of use in pregnant women. Based on pre-clinical findings, OXALIWIN is likely to be lethal and/or teratogenic to the human foetus 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 foetus and with the patient's consent.

Women of Childbearing Potential:

Effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with OXALIWIN. Further, barrier contraceptive measures must be taken during and after cessation of therapy (4 months for women and 6 months for men) (See WARNINGS AND SPECIAL PRECAUTIONS).

Fertility:

OXALIWIN 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 WARNINGS AND SPECIAL PRECAUTIONS).

Lactation:

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

DOSAGE AND DIRECTIONS FOR USE:

Dosage:

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 SIDE EFFECTS and WARNINGS AND SPECIAL PRECAUTIONS.

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

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

OXALIWIN 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 OXALIWIN (2-hour IV infusion every two weeks for a maximum of 12 cycles) in combination with 5FU/FA (FOLFOX4), OXALIWIN showed minimal clinical impact on renal function as assessed by mean creatinine clearance (see PHARMACOLOGICAL ACTION: Pharmacokinetic Properties).

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 severe renal impairment withdrew due to adverse effects.

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

- *Hepatic impairment:*

OXALIWIN has not been studied in patients with severe hepatic impairment. No increase in OXALIWIN 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 OXALIWIN single agent, 2-hour IV infusion q3w, included adult cancer patients with different degrees of hepatic impairment (none to severe). The initial OXALIWIN 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 OXALIWIN (see SIDE EFFECTS). The frequencies of adverse events were increased in patients with liver impairment.

- *Elderly patients:*

No increase in severe toxicities was observed when OXALIWIN was used as a single agent 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 and preparation of infusion solution:

OXALIWIN is administered by intravenous infusion.

The administration of OXALIWIN does not require hyperhydration.

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

OXALIWIN 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 medicinal 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 5 % glucose solution, and NOT in alkaline solutions or sodium chloride or chloride containing solutions (See Incompatibilities).

Flush the line after OXALIWIN administration.

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

Instructions for use or handling:

OXALIWIN 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 OXALIWIN solutions.

The preparation of OXALIWIN 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 OXALIWIN concentrate or infusion solution, should come into contact with skin, wash immediately and thoroughly with water.

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

Disposal:

Remnants of OXALIWIN 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.

Incompatibilities:

- DO NOT use in association with alkaline medicines or solutions (in particular 5-fluorouracil, basic solutions, trometamol and folinic acid products containing trometamol as an excipient).
- OXALIWIN can be co-administered with folinic acid infusion using a Y-line placed immediately before the site of infusion. These two medicinal products 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 OXALIWIN 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.

SIDE EFFECTS:

Adverse reactions have been ranked under heading of system-organ class and frequency, using the following convention:

- very common: ≥ 1/10
- common : ≥ 1/100; < 1/10
- uncommon : ≥ 1/1 000; < 1/100
- rare : ≥ 1/10 000; < 1/1 000
- very rare : < 1/10 000, including isolated reports.

COMBINATION THERAPY OF OXALIWIN WITH 5-FU/FA (FOLFOX):

Infections and infestations:

Very common: infection.

Common: neutropenic sepsis, including fatal outcomes.

Uncommon: sepsis, including fatal outcomes.

Blood and lymphatic system disorders:

Very common: anaemia, neutropenia, thrombocytopenia.

- The frequency increases when OXALIWIN is administered (85 mg/m^2 every 2 weeks) in combination with 5-FU +/- folinic acid, as compared to a single agent administration (130 mg/m^2 every 3 weeks) e.g. anaemia (80 % vs 60 % of patients), neutropenia (70 % vs 15 %), thrombocytopenia (80 % vs 40 %).

- Severe anaemia (Haemoglobin < 8,0 g/dl) or thrombocytopenia (platelets < 50 x 10^9/l) occurs with a similar frequency (< 5 % of patients) when OXALIWIN is administered as a single agent or in combination with 5-FU.
- Severe neutropenia (neutrophils < 1,0 x 10^9/l) occurs with a greater frequency when OXALIWIN is administered in combination with 5-FU than as a single agent (40 % vs < 3 % of patients).

Common: febrile neutropenia.

Rare: immuno-allergic haemolytic anaemia and thrombocytopenia, disseminated intravascular coagulation (DIC), including fatal outcomes (see WARNINGS AND SPECIAL PRECAUTIONS

Immune system disorders:

Very common: allergic reactions such as: skin rash (particularly urticaria), conjunctivitis, rhinitis.

Common: anaphylactic reactions including bronchospasm, angioedema, hypotension, sensation of chest pain and anaphylactic shock.

Metabolism and nutrition disorders:

Very common: anorexia, glycaemia abnormalities, hypokalaemia, natraemia abnormalities.

Common: dehydration, hypocalcaemia.

Uncommon: metabolic acidosis.

Psychiatric disorders:

Common: depression and insomnia.

Uncommon: nervousness.

Nervous system disorders:

Very common: dysaesthesia/paraesthesia of extremities and peripheral neuropathy, headache, acute neuro-sensory manifestations (see WARNINGS AND SPECIAL PRECAUTIONS) and dysgeusia.

Common: dizziness, neuritis motor, flushing and meningism.

Rare: dysarthria, loss of deep tendon reflexes, Lhermitte's sign, Reversible Posterior Leucoencephalopathy Syndrome (RPLS, also known as PRES) (see WARNINGS AND SPECIAL PRECAUTION).

Eye disorders:

Common: conjunctivitis and abnormal vision.

Rare: visual acuity reduced transiently, visual field disturbances and optic neuritis. Transient vision loss, reversible following therapy discontinuation.

Ear and labyrinth disorders:

Uncommon: ototoxicity.

Rare: deafness.

Vascular disorders:

Very common: epistaxis.

Common: haemorrhage nose, haematuria, thrombophlebitis deep, embolism pulmonary, haemorrhage rectum, deep vein thrombosis, thromboembolic events and hypertension.

Respiratory, thoracic and mediastinal disorders:

Very common: dyspnoea and cough.

Common: rhinitis, hiccups and upper respiratory infection.

Rare: acute interstitial lung diseases, which may be fatal and pulmonary fibrosis (See WARNINGS AND SPECIAL PRECAUTIONS).

Gastrointestinal disorders:

Very common: nausea, vomiting and diarrhoea; stomatitis/mucositis; abdominal pain and constipation.

Dehydration, hypokalaemia, metabolic acidosis, ileus, intestinal obstruction, renal disorders may be associated with severe diarrhoea/vomiting, particularly when OXALIWIN is combined with 5-FU (see WARNINGS AND SPECIAL PRECAUTIONS).

Common: dyspepsia, gastro-oesophageal reflux and gastrointestinal haemorrhage.

Rare: colitis (including *Clostridium difficile)* diarrhoea. Pancreatitis.

Hepato-biliary disorders:

Very rare: liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of 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:

Very common: skin disorder and alopecia.

Common: skin exfoliation (hand and foot syndrome), rash erythematous, rash, sweating increased and nail disorder.

Musculoskeletal, connective tissue and bone disorders:

Very common: back pain. In case of such adverse reaction, haemolysis which has been rarely reported should be investigated.

Common: arthralgia and skeletal pain.

Renal and urinary disorders:

Common: dysuria and abnormal micturition frequency.

Very rare: acute tubular necrosis, acute interstitial nephritis and acute renal failure.

General disorders and administration site conditions:

Very common: 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 OXALIWIN is infused through a peripheral vein.

Rare: immunoallergic, thrombocytopenia and haemolytic anaemia.

Investigations:

Very common: mild to moderate elevation of transaminases and alkaline phosphatase.

Common: weight decrease (metastatic setting).

Laboratory abnormalities:

Very common:

- **Haematological:** anaemia, neutropenia, thrombocytopenia, leucopenia and lymphopenia.
- **Biochemical:** alkaline phosphatase increase, bilirubin increase, LDH increase, hepatic enzymes (ALT/AST) increase.

Common:

- **Haematological:** febrile neutropenia, neutropenic sepsis (i.e. severe neutropenia and documented infections).
- **Biochemical:** creatinine increase.

Post-marketing experience with frequency unknown:

Infections and infestations: septic shock, including fatal outcomes.

Blood and lymphatic system disorders: haemolytic uraemic syndrome

Nervous system disorders: convulsion

Cardiac disorders: QT prolongation, which may lead to ventricular dysrhythmias including Torsade de Pointes, which may be fatal (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

Respiratory, thoracic and mediastinal disorders: laryngospasm.

Gastrointestinal disorders: intestinal ischaemia, including fatal outcomes, duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal. (see WARNINGS AND SPECIAL PRECAUTIONS).

Musculoskeletal, connective tissue and bone disorders: rhabdomyolysis, including fatal outcomes (see WARNINGS AND SPECIAL PRECAUTIONS and INTERACTIONS).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

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

IDENTIFICATION:

OXALIWIN 50 mg/10 ml RTU: A clear, colourless solution contained in a 15 ml clear glass vial with a dark grey rubber stopper and aluminium seal fitted with a green flip-off® cover.

OXALIWIN 100 mg/20 ml RTU:

20 ml: A clear, colourless solution contained in a 20 ml clear glass vial with a dark grey rubber stopper and aluminium seal fitted with a mauve/blue flip-off® cover.

40 ml: A clear, colourless solution contained in a 40 ml clear glass vial with a dark grey rubber stopper and aluminium seal fitted with an orange flip-off® cover.

PRESENTATION:

OXALIWIN 50 mg/10 ml RTU: A clear glass vial, containing 50 mg of oxaliplatin, closed with a grey chlorobutyl rubber stopper and a silver aluminium seal fitted with a green flip-off® cover.

OXALIWIN 100 mg/20 ml RTU:

20 ml: A clear glass vial, containing 100 mg of oxaliplatin, closed with a grey chlorobutyl rubber stopper and a silver aluminium seal fitted with a mauve/blue flip-off® cover.

40 ml: A clear glass vial, containing 200 mg of oxaliplatin, closed with a grey chlorobutyl rubber stopper and a silver aluminium seal fitted with an orange flip-off® cover.

STORAGE INSTRUCTIONS:

Store at room temperature at or below 25 °C.

Do not freeze.

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

Infusion preparation:

If not used immediately, should be stored at 2 °C to 8 °C for not longer than 24 hours.

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

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

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBERS:

OXALIWIN 50 mg/10 ml RTU: A39/26/0521

OXALIWIN 100 mg/20 ml RTU: A39/26/0522

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:

Zentiva South Africa (Pty) Ltd

2 Bond Street

Midrand, 1685

South Africa

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