

DATA SHEET

OXALICCORD

Oxaliplatin 5 mg/mL Concentrate for Solution for Infusion, 10 mL and 20 mL

NAME OF THE DRUG

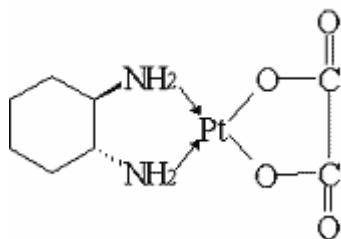
Oxaliplatin 5 mg/mL Concentrate for Solution for Infusion, 10 mL and 20 mL

DESCRIPTION

Oxaliplatin is designated chemically as $[SP-4-2]-(1R,2R)$ -(cyclohexane-1,2-diamine- k^2N,N' (oxalato(2-)- k^2O^1,O^2)]platinum (II)

The empirical formula of oxaliplatin is $C_8H_{14}N_2O_4Pt$ and its molecular weight is 397.3.

Oxaliplatin has the following chemical structure:



CAS Number: 61 825-94-3

Oxaliplatin is a white to off-white crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol.

Oxallicord Concentrate for Solution for Infusion contains oxaliplatin and lactose.

PHARMACOLOGY

Pharmacodynamics

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-1,2-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 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.

Pharmacokinetics

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} µg/mL	AUC ₀₋₄₈ µg.h/mL	AUC µg.h/mL	t _{1/2α} h	t _{1/2β} h	t _{1/2γ} 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
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 AUC₀₋₄₈ and C_{max} values were determined on Cycle 3 (85 mg/m²) or Cycle 5 (130 mg/m²).

Mean AUC, V_{ss}, and CL values were determined on Cycle 1. C_{max}, AUC, AUC₀₋₄₈, V_{ss} and CL values were determined by non-compartmental analysis. t_{1/2 α}, t_{1/2 β} and t_{1/2 γ} 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 diamminocyclohexane (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 of ultrafilterable platinum from 17.6 ± 2.18 L/h to 9.95 ± 1.91 L/h in renal impairment (creatinine clearance 12 ± 57 mL/min) was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 L. The effect of severe renal impairment on platinum clearance has not been evaluated.

CLINICAL TRIALS

Adjuvant treatment of Stage III (Duke's C) colon cancer

Use in Combination with fluorouracil and folinic acid (FU/FA)

EFC3313 (MOSAIC)

EFC3313 (MOSAIC) was an international, multicentre, open-label, randomised phase III study comparing two treatment regimens (FOLFOX4 versus FU/FA) as adjuvant treatment of Duke's stage B2/C colon cancer. FOLFOX4 - Day 1; Oxaliplatin $85\text{mg}/\text{m}^2$ as 2 hour infusion, folinic acid $200\text{ mg}/\text{m}^2$ over 2 hours, followed by a FU bolus of $400\text{ mg}/\text{m}^2$, then a FU infusion of $600\text{ mg}/\text{m}^2$ over 22 hours. Folinic acid and FU repeated on Day 2. FU/FA - the same regimen without oxaliplatin. Both were repeated every two weeks. A total of 1108 patients were treated in the FOLFOX4 arm and 1111 in the FU/FA arm. The median number of cycles received in both arms was 12.

In the ITT population, after a median of 4 years follow-up, patients treated with FOLFOX4 had significantly increased disease-free survival, the primary endpoint, compared to patients treated with FU/FA (Table 1). In the sub-group analysis by disease stage, only patients with Stage III disease had significantly increased disease-free survival. The trial was not powered to show such a benefit with Stage II disease, but the trend indicated a small benefit is likely. This benefit is not as great as in Stage III patients. The trial was not powered to show significant benefit in overall survival.

Table 1: Disease Free Survival and Overall Survival - ITT population

	Disease Stage	FOLFOX4	FU/FA	Hazard Ratio [95% CI]
Disease-free Survival - 4 year probability (%) of Surviving disease-free [95% CI]	all	75.9 [73.4, 78.5] (n=1123)	69.1 [66.3, 71.9] (n=1123)	0.76 [0.65, 0.90]
	II	85.1 [81.7, 88.6] (n=451)	81.3 [77.6, 85.1] (n=448)	0.80 [0.58, 1.11]
	III	69.7 [66.2, 73.3] (n=672)	61.0 [57.1, 64.8] (n=675)	0.75 [0.62, 0.90]
Overall Survival* - 4 year probability (%) of	all	84.0 [81.7, 86.3]	82.4 [80.0, 84.8]	0.89 [0.72, 1.09]

Surviving [95% CI]		(n=1123)	(n=1123)	
	II	91.0 [88.1, 93.9] (n=451)	91.1 [88.3, 93.9] (n=448)	0.98 [0.63, 1.53]
	III	79.2 [76.0, 82.5] (n=672)	76.6 [73.2, 80.0] (n=675)	0.86 [0.68, 1.08]

* The trial was not powered to show significant benefit in overall survival.

Treatment of Advanced Colorectal Cancer

Use in Combination with fluorouracil and folinic acid (FU/FA)

A total of 1312 patients have been enrolled in 3 pivotal trials, for untreated (EFC7462/N9741, EFC 2962) and pretreated patients (EFC 2964). These studies evaluated the efficacy of oxaliplatin at the same dose intensity (85 mg/m²/2 weeks) when added to different FU/FA doses and regimens, in terms of overall survival, progression free survival and tumour response.

EFC 7462/N9741 was a multicentre open-label randomised, 3-arm phase III study of irinotecan and FU/LV (IFL), or oxaliplatin and irinotecan (IROX), or oxaliplatin and FU/LV (FOLFOX4) as initial treatment of patients with advanced colorectal cancer. Therapy consisted of 2-week FOLFOX4, 6-week IFL, or 3-week IROX treatment cycles.

A total of 795 patients were enrolled and 773 treated from May 1999 in 301 centres in the United States and Canada.

Treatment arms - FOLFOX4 Day 1: oxaliplatin 85 mg/m² over 2 hours, folinic acid 200 mg/m² over 2 hours, followed by a FU bolus of 400 mg/m², then a FU infusion of 600 mg/m² over 22 hours. Folinic acid and FU repeated on Day 2. Cycle repeated every 2 weeks.

IFL Day 1: irinotecan 125 mg/m² over 90 minutes, folinic acid 20 mg/m² over 15 minutes or IV push, FU bolus of 500 mg/m² weekly x 4. Cycle repeated every 6 weeks.

IROX Day 1: oxaliplatin 85 mg/m² over 2 hours, irinotecan 200 mg/m² over 30 minutes. Cycle repeated every 3 weeks.

This study has demonstrated a statistically significant longer TTP (time to progression) and OS (overall survival), and a significantly higher overall RR (response rate) for oxaliplatin in combination with bolus/infusional FU/LV (FOLFOX4) compared with the IFL control arm. The IROX arm has a significantly longer OS compared with the IFL arm, while TTP and RR on the IROX arm were not significantly different from the IFL arm. Median durations of treatment for each group were 24, 24 and 21 weeks for IFL, FOLFOX4 and IROX (respectively)

Table 2: Summary of time to progression - ITT population

EFC7462/N9741 Time to Progression	IFL N = 264	FOLFOX4 N = 267	IROX N = 264
Number of progressors n (%)	216 (81.8)	221 (82.8)	236 (89.4)
Median TTP (months)	6.9	8.7	6.5
95% confidence interval	(6.0-7.5)	(7.8-9.8)	(5.8-7.6)

P-value (Log-Rank Test)

Hazard Ratio (95% confidence interval)

FOLFOX4 vs. IFL: P=0.0014

FOLFOX4 vs. IFL: 0.74 (0.61-0.89)

IROX vs. IFL: P=0.8295

IROX vs. IFL: 1.02 (0.85-1.23)

Table 3: Summary of overall survival - ITT population

EFC7462/N9741 Overall Survival	IFL N = 264	FOLFOX4 N = 267	IROX N = 264
Number of deaths n (%)	192 (72.7)	155 (58.1)	175 (66.3)
Median survival (months)	14.6	19.4	17.6
95% confidence interval	(12.4-16.7)	(17.9-21.0)	(15.8-19.6)

P-value (Log-Rank Test)

Hazard Ratio (95% confidence interval)

FOLFOX4 vs. IFL: P< 0.0001

FOLFOX4 vs. IFL: 0.65 (0.53-0.80)

IROX vs. IFL: P=0.0252

IROX vs. IFL: 0.79 (0.65-0.97)

Table 4: Summary of confirmed overall response - Patients (N, %) with measurable disease

EFC7462/N9741 Overall Response	IFL N = 212	FOLFOX4 N = 210	IROX N = 215
Complete and partial response	69 (32.5)	95 (45.2)	74 (34.4)
95% confidence interval	(26.2-38.9)	(38.5-52.0)	(28.1-40.8)
Complete response	5 (2.4)	13 (6.2)	7 (3.3)
Partial response	64 (30.2)	82 (39.0)	67 (31.2)
Regression ^a	0	3 (1.4)	1 (0.5)
Stable disease	94 (44.3)	75 (35.7)	86 (40.0)

P-value (Chi-Squared Test)

FOLFOX4 vs. IFL: P< =0.0075

IROX vs. IFL: P=0.6820

^a Patients with measurable disease at randomisation that became too small to measure during the study were classified as regression and not partial response in this study

Table 5: Number of deaths - Treated patients N (%)

EFC7462/N9741	IFL N = 256	FOLFOX4 N = 259	IROX N = 258
Number of deaths within 30 days of last dose	12 (4.7)	8 (3.1)	8 (3.1)
Number of deaths within 60 days of first dose	13 (5.1)	6 (2.3)	8 (3.1)
Number of deaths during the entire study	189 (73.8)	149 (57.5)	170 (65.9)

EFC 2962 was a multinational multicentre randomised phase III study in previously untreated patients, comparing two-weekly fluorouracil bolus plus infusion and high dose folinic acid (FU/FA regimen: Day 1; folinic acid 200 mg/m² over 2 hours, followed by a FU bolus of 400 mg/m², then a FU infusion of 600 mg/m² over 22 hours. Repeated on Day 2.) to the same regimen combined with oxaliplatin at the dosage of 85 mg/m² every two weeks. A total of 420 patients were enrolled and 417 treated from August 1995 to July 1997 in 35 centres from 9 countries. The median number of treatment cycles was 12 in the FU/FA plus oxaliplatin group and 11 in the FU/FA group. Confirmed responses after independent radiological review (intent to treat analysis n = 420) are as shown in Table 6.

The FU/FA + oxaliplatin group had a statistically significant greater response rate and longer progression free survival. There was no significant difference in overall survival between the two groups, however, the study was not powered to detect a difference in overall survival. Additionally, in both groups, post-study treatment with other agents may have influenced survival.

EFC 2964 was an open label multicentre study in which patients whose disease had progressed on one of two fluorouracil/folinic acid regimens continued on the same fluorouracil/folinic acid regimen with the addition of oxaliplatin 85 mg/m² two weekly. The two study regimens were; Regimen 1: Day 1; folinic acid 200 mg/m² over 2 hours, followed by a FU bolus of 400 mg/m², then a FU infusion of 600 mg/m² over 22 hours. Repeated on Day 2.

Regimen 2: folinic acid 500 mg/m² over 2 hours, followed by a FU infusion of 1500 mg/m² over 22 hours, repeated on Day 2.

The results were as shown in Table 7.

EFC 2961 was a multicentre, randomised, phase III study in previously untreated patients, comparing FU/FA administered as a chronomodulated infusion (FU 3500 mg/m² and folinic acid 1500 mg/m² over 5 days, with peaks at 4am) to the same regimen plus oxaliplatin 125 mg/m² given as a flat infusion. The regimen was repeated three weekly. Efficacy results are shown in Table 7a.

Table 6 (EFC 2962)	FU/FA + Oxp n = 210	FU/FA n = 210	Difference
Objective Response Rate ¹ %	49.0	21.9	p = 0.0001
[95% CI]	[42, 56]	[16,27]	
Complete	1.4	0.5	
Partial	47.6	21.4	

Table 6 (EFC 2962)	FU/FA + Oxp n = 210	FU/FA n = 210	Difference
Median progression free survival (months) ²	8.2	6.0	p = 0.0003
[95% CI]	[7.2, 8.8]	[5.5, 6.5]	(log rank)
Median survival time (months)	16	14.7	p= 0.109
[95% CI]	[14.7, 18.2]	[13.7, 18.2]	(log rank)

1. Response rate assessed according to WHO-UICC criteria.
2. Independent expert review.

Table 7 (EFC 2964)	Regimen 1 n =57	Regimen 2 n = 40	All Treated Patients n = 97
Confirmed Responses n(%) [95% CI]			
Expert assessment	13 (23%) [13-36]	7 (18%) [7-33]	20 (21%) [13-30]
Investigator assessment	11 (19%) [10-32]	10 (25%) [13-41]	21 (22%) [14-31]
Median progression free survival (months)	5.1	4.6	4.7
[95% CI]	[3.1 - 5.7]	[3.0 - 5.5]	[3.4 - 5.5]
Median overall survival (months)	11.1	10.5	11.0
[95% CI]	[8.3 -13.0]	[8.6 - 13.4]	[9.1 - 12.9]

Table 7a (EFC 2961)	FU/FA + Oxp n = 100	FU/FA n = 100	Difference
Objective Response Rate ¹ %	34	12	p < 0.001
[95% CI]	[24, 44]	[6, 20]	
Complete	1	0	
Partial	33	12	
Median progression free survival (months)	8.3	4.2	p = 0.045
[95% CI]	[6.7, 9.1]	[3.5, 6.7]	(log rank)
Median survival (months)	17.6	19.4	p = 0.82
[95% CI]	[13.1, 22.1]	[15.3, 30.5]	(log rank)

INDICATIONS

Oxaliplatin, in combination with fluorouracil and folinic acid, is indicated for:

Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of the primary tumour

Treatment of advanced colorectal cancer

CONTRAINDICATIONS

Oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin,
- are pregnant,
- are breast feeding,
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils
- $< 1.5 \times 10^9/L$ and/or platelet count of $< 75 \times 10^9/L$,
- have a peripheral sensory neuropathy with functional impairment prior to first course,
- have severely impaired renal function (creatinine clearance less than 30 mL/min).

PRECAUTIONS

General

Oxaliplatin should be administered only by or under the supervision of an experienced clinical oncologist.

Allergic Reactions

Anaphylactic-like reactions to *Oxallicord Concentrate for Solution for Infusion* have been reported, and may occur within minutes of *Oxallicord Concentrate for Solution for Infusion* administration. Patients with a history of allergic reactions to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-type reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Rechallenge with oxaliplatin is contraindicated.

Neurological Toxicity

Neurological toxicity (see **ADVERSE REACTIONS**) of oxaliplatin should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before initiation of each administration, and periodically thereafter. It is not known whether patients with pre-existing medical conditions associated with peripheral nerve damage have a reduced threshold for oxaliplatin induced peripheral neuropathy.

For patients who develop acute laryngopharyngeal dysaesthesias, during or within 48 hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours. To prevent such dysaesthesia, advise the patient to avoid exposure to cold and to avoid ingesting cold food and/or beverages during or within 48 hours following oxaliplatin administration.

Gastrointestinal Toxicity

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic anti-emetic therapy, including 5-HT₃ antagonists and corticosteroids. Dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with fluorouracil.

Haematological Toxicity

Monitor haematological toxicity with a full blood count and white cell differential count prior to starting therapy and before each subsequent course. Idiosyncratic haematological toxicity may occur, especially in patients who have received previous myelotoxic treatment.

Pulmonary Toxicity

Oxallicord Concentrate for Solution for Infusion has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. 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 **ADVERSE REACTIONS**).

Hepatic Toxicity

Reactions related to liver sinusoidal obstruction syndrome, including nodular regenerative hyperplasia, have been reported (see **ADVERSE REACTIONS**). In the case of abnormal liver function test results or portal hypertension which could not be explained by liver metastases, reactions related to liver sinusoidal obstruction syndrome should be investigated, and very rare cases of drug induced hepatic vascular disorders should be considered.

Renal Impairment

Oxaliplatin has not been studied in patients with severe renal impairment. It is therefore contraindicated in patients with severe renal impairment.

There is limited information on safety in patients with moderately impaired renal function, and administration should only be considered after suitable appraisal of the benefit/risk for the patient, however, treatment may be initiated at the normally recommended dose. In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

There is no need for dose adjustment in patients with mild renal dysfunction.

Hepatic Insufficiency

Oxaliplatin has not been studied in patients with severe hepatic impairment. No increase in oxaliplatin 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.

Children

Oxaliplatin is not recommended for use in children as safety and efficacy have not been established in this group of patients.

Elderly

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Carcinogenicity, mutagenicity and impairment of fertility

Oxaliplatin was shown to be mutagenic and clastogenic in mammalian test systems *in vitro* and *in vivo*. The carcinogenic potential of oxaliplatin has not been studied, but compounds with similar mechanisms of action and genotoxicity profiles have been reported to be carcinogenic. Oxaliplatin should be considered a probable carcinogen.

In dogs dosed with oxaliplatin, a decrease in testicular weight accompanied with testicular hypoplasia approaching aplasia was seen at doses ≥ 15 mg/m². However, no effects on fertility were seen in male and female rats at doses up to 12 mg /m²/day for 5 days/cycle.

Use in Pregnancy

Category D. Reproductive toxicity studies showed no teratogenic activity in rats or rabbits at intravenous doses up to 6 and 9 mg/m²/day respectively (1/20 of the maximum recommended clinical dose, based on body surface area). However, increased embryonic deaths, decreased foetal weight and delayed ossifications were observed in rats. Related compounds with similar mechanisms of action have been reported to be teratogenic. There are no adequate and well- controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the foetus. Oxaliplatin is probably toxic to the human foetus at the recommended therapeutic dose, and is therefore contraindicated during pregnancy.

As with other cytotoxic agents, effective contraceptive measures should be taken in potentially fertile patients prior to initiating chemotherapy with oxaliplatin.

Use in Lactation

There are no data on the excretion of oxaliplatin into milk of animals or humans. Oxaliplatin is contraindicated in breast feeding women.

Interactions with other drugs

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of fluorouracil, no change in the level of exposure to fluorouracil has been observed. However, in patients dosed with fluorouracil weekly and oxaliplatin 130 mg/m² every 3 weeks, increases of 20% in fluorouracil plasma concentrations have been observed.

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

Oxaliplatin is incompatible with chloride containing solutions and basic solutions (including fluorouracil), therefore oxaliplatin should not be mixed with these or administered simultaneously via the same IV line. There is no data for compatibility with other drugs.

The lack of Cytochrome P450 mediated metabolism indicates that oxaliplatin is unlikely to modulate the P450 metabolism of concomitant medications through a competitive mechanism.

Advice to Patients

Patients must be adequately informed of the risk of diarrhoea/emesis and neutropenia after oxaliplatin/fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

Patients and caregivers should be informed of the expected side effects of ***Oxaliccord Concentrate for Solution for Infusion*** and, in particular, patients should be advised to:

- Avoid cold foods and drinks and cover skin prior to exposure to cold during or within 48 hours following oxaliplatin administration, since neurological effects may be precipitated or exacerbated by exposure to cold.
- Contact their doctor immediately if they develop fever, particularly in association with persistent diarrhoea or evidence of infection since this may indicate low blood count.
- Contact their doctor if persistent vomiting, diarrhoea, signs of dehydration, cough or breathing difficulties or signs of allergic reaction occur.

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

ADVERSE REACTIONS

Table 8: FU/FA ± Oxaliplatin in adjuvant treatment of colon cancer - EFC3313 (MOSAIC), all grades and grade 3-4 toxicities - all cycles - % patients

	Arm A FOLFOX4 N=1108			Arm B FU/FA N=1111		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Laboratory						
Granulocytopenia	78.9	28.8	12.3	39.9	3.7	1.0
Thrombocytopenia	77.4	1.5	0.2	19.0	0.2	0.2
Anemia	75.6	0.7	0.1	66.9	0.3	-

	Arm A FOLFOX4 N=1108			Arm B FU/FA N=1111		
	All	Gr 3	Gr 4	All	Gr 3	Gr 4
Adverse events						
Paraesthesia	92.0	12.4	NA	15.6	0.2	NA
Nausea	73.7	4.8	0.3	61.1	1.5	0.3
Diarrhoea	56.3	8.3	2.5	48.4	5.1	1.5
Vomiting	47.2	5.3	0.5	24.0	0.9	0.5
Stomatitis/mucositis	42.1	2.8	0.1	39.7	2.1	0.2
Skin disorder	31.5	1.4	0.6	35.5	1.7	0.7
Alopecia	30.2	NA	NA	28.1	NA	NA
Fever	27.3	0.7	0.3	12.2	0.4	0.2
Infection	25.2	3.3	0.7	24.9	2.3	0.6
Injection site reaction	11.1	2.6	0.5	10.4	3.1	0.2
Allergic reaction	10.3	2.3	0.6	1.9	0.1	0.1
Thrombosis/phlebitis	5.7	1.0	0.2	6.5	1.7	0.1
Neutropenic sepsis	1.1	0.6	0.4	0.1	-	0.1
Feile neutropenia	0.7	0.7	-	0.1	0.1	-

Table 9: FU/FA ± Oxaliplatin in previously untreated patients with Advanced Colorectal Cancer, all grades and grade 3-4 toxicities - all cycles - % patients

Incidence of Toxicity by patient %	EFC 2961				EFC 2962				N9741			
	N=100 Control arm q 3w FU CM 5- day		N=99 Oxaliplatin 125 q 3w FU CM 5- day		N=208 Control arm q 2w FU bolus + CIV		N=209 Oxaliplatin 85 q 2w FU bolus + CIV		N=256 Irinotecan 125 q 6w FU bolus x 4 weekly		N=259 FOLFOX4 Oxaliplatin 85 q 2w FU bolus + CIV	
	All Gr.	Gr. 3-4	All Gr.	Gr. 3- 4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4
Paraesthesias [†]	20.0	0.0	91.9	45	11.5	0.0	67.0	16.7	15.6	2.3	77.2	17.8
Laryngopharyngeal dysesthesia	N/A	N/A	N/A	N/A	NA [†]	NA [†]	NA [†]	NA [†]	1.2	0	38.2	1.5
Neurosensory	N/A	N/A	N/A	N/A	NA [†]	NA [†]	NA [†]	NA [†]	2.3	0	12.0	0.8
Nausea	NA*	NA*	NA*	NA*	53.4	1.9	72.2	5.7	67.2	14.5	71.0	6.2
Vomiting	64.0	2.0	88.9	25.3**	29.3	1.9	54.1	5.7	43.4	13.3	40.9	3.5
Diarrhoea	49.0	5.0	85.9	43.4**	43.8	5.3	58.9	12.0	65.2	28.5	56.0	11.6
Stomatitis	59.0	4.0	61.6	10.1	35.6	1.4	44.0	5.7	25.0	0.8	37.5	0

Incidence of Toxicity by patient %	EFC 2961				EFC 2962				N9741			
	N=100 Control arm q 3w FU CM 5- day		N=99 Oxaliplatin 125 q 3w FU CM 5- day		N=208 Control arm q 2w FU bolus + CIV		N=209 Oxaliplatin 85 q 2w FU bolus + CIV		N=256 Irinotecan 125 q 6w FU bolus x 4 weekly		N=259 FOLFOX4 Oxaliplatin 85 q 2w FU bolus + CIV	
	All Gr.	Gr. 3-4	All Gr.	Gr. 3- 4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4	All Gr.	Gr. 3-4
Anaemia	74.0	2.0	83.8	3.0	80.8	2.4	85.2	3.3	28.1	4.3	27.0	2.7
Neutropenia	8.0	1.0	30.3	2.0	30.8	7.2	74.6	43.1	80.1	46.1***	82.2	54.1***
Thrombocytopenia	0.0	0.0	7.1	0.0	28.8	0.0	75.6	2.4	26.2	2.7	71.4	4.6
Fever without neutropenia	19.0	5.0	12.1	7.1	14.9	0.0	33.0	0.0	8.6	0.4	16.2	0.8
Infection	5.0	4.0	2.0	0.0	27.9	1.0	31.6	1.0	5.1	0.8	9.7	3.5
Asthenia	6.0	4.0	3.0	1.0	21.6	3.4	23.4	4.3	NA	NA	NA	NA
Fatigue	0.0	0.0	0.0	0.0	7.2	0.5	12.9	1.0	58.2	10.5	70.3	6.6
Alopecia	4.0	NA	4.0	NA	19.2	NA	17.7	NA	44.1	0	37.5	0
Skin	38.0	1.0	39.4	0.0	32.2	0.5	28.7	0.0	NA	NA	NA	NA
AST	75.0	1.0	91.9	5.1	23.1	0.0	46.4	0.5	2.0	0.4	17.4	1.2
ALT	22.0	1.0	47.5	1.0	21.6	0.0	29.2	1.0	2.3	0	6.2	0.8
Alk. phosphatase	85.0	14.0	82.8	19.2	39.9	1.4	56.5	1.4	7.0	0	16.2	0
Creatinine increase	26.0	0.0	9.1	0.0	8.2	0.5	4.8	0.5	3.5	0.4	4.2	0

NA: Not applicable

* nausea-vomiting are reported together in that study (WHO toxicity grading scale)

CIV - continuous intravenous infusion

** modified WHO toxicity grading scale

*** 14.8% feile neutropenia reported in the IFL arm and 4.2% in the FOLFOX4 arm

† Various studies used different data convention. Break down data collection by laryngopharyngeal dysesthesia and neurosensory was not done in EFC2962.

Note: *very common* $\geq 1/10$ ($\geq 10\%$)

common $\geq 1/100$ and $< 1/10$ ($\geq 1\%$ and $< 10\%$)

uncommon $\geq 1/1000$ and $< 1/100$ ($\geq 0.1\%$ and $< 1.0\%$)

rare $\geq 1/10,000$ and $< 1/1000$ ($\geq 0.01\%$ and $< 0.1\%$)

very rare $< 1/10,000$ ($< 0.01\%$)

Neurological

	Adjuvant	Advanced
<i>very common:</i>	Sensory peripheral neuropathy, dysgeusia	Primarily sensory peripheral neuropathy (e.g. loss of deep tendon reflexes, dysaesthesia, paraesthesia Lhermitte's sign), dysgeusia
<i>common:</i>		Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure
<i>rare:</i>		Dysarthria

Post marketing experience with unknown frequency – convulsion.

Neurological adverse reactions are the dose-limiting toxicity. A primarily sensory peripheral neuropathy occurs in 85-95% of patients. These symptoms usually develop at the end of the 2-hour oxaliplatin infusion or within a few hours, abate spontaneously within the next hours or days, and frequently recur with further cycles. They may be precipitated by or exacerbated by exposure to cold temperatures or objects. They usually present as transient paraesthesia, dysaesthesia and hypoaesthesia. There may be functional impairment such as difficulty in executing fine movements. The duration of symptoms increases with the number of treatment cycles. Symptoms usually recede between courses of treatment.

If symptoms persist or pain or functional impairment develops, the dose should be reduced or treatment discontinued (see **DOSAGE AND ADMINISTRATION**).

In the adjuvant setting, for a cumulative dose of 850 mg/m² (10 cycles) the risk of occurrence of persistent symptoms is 10% and for a cumulative dose of 1020 mg/m² (12 cycles) the risk of occurrence is 20%.

In the advanced setting, in EFC 2962, 16% of patients receiving oxaliplatin + FU/FA developed paraesthesia and associated functional impairment lasting longer than two weeks, after a median cumulative oxaliplatin dose of 874 mg/m². Two percent were withdrawn due to persisting paraesthesia (i.e. persisting between treatment cycles), after cumulative oxaliplatin doses of 759-1100 mg/m².

In EFC2961, 13% developed parasthesia and functional impairment, with a median onset of 6 months or after a cumulative oxaliplatin dose of 1100mg/m².

In the majority of cases, the neurological signs and symptoms improve when treatment is discontinued. Analysis of patients in EFC 2962 showed that of the 34 patients who developed Grade 3 neurotoxicity (the maximum grade in that study), 25 (73.5%) had an improvement of their symptoms in a median time of 13.2 weeks. Eight of the 34 patients (23%) had complete resolution of their symptoms. The mean duration of the Grade 3 neurotoxicity was 13.6 weeks. The mean cumulative oxaliplatin dose at date of onset was 913.6 mg/m² (range: 169.7-1713.15 mg/m²). The median follow-up time for these 34 patients was 55.71 weeks.

An acute pharyngolaryngeal dysaesthesia syndrome occurs in 1% to 2% of patients. It often occurs on exposure to cold and changes in temperature. It is characterised by subjective sensations of dysphagia and dyspnoea, feeling of suffocation, without evidence of respiratory distress (no cyanosis or hypoxia, laryngospasm or bronchospasm).

Other symptoms occasionally observed, particularly of cranial nerve dysfunction may be either associated with other symptoms, or also may occur in isolation, 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 spasm/muscle contractions - involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain.

	Adjuvant	Advanced
<i>very common:</i>	Epistaxis	Epistaxis
<i>common:</i>	Deep vein thrombosis, thromboembolic events, hypertension	Deep vein thrombosis, thromboembolic events, hypertension

Haematological

	Adjuvant	Advanced
<i>very common:</i>	Epistaxis, anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)	Anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)

In both adjuvant and advanced cancer treatment, addition of oxaliplatin to fluorouracil and folinic acid:

Substantially increased the incidence of neutropenia and severe neutropenia (neutrophils $<1.0 \times 10^9/L$) and

Substantially increased the incidence of thrombocytopenia (Tables 8-9).

Gastrointestinal

	Adjuvant	Advanced
<i>very common:</i>	Diarrhoea, nausea, vomiting, stomatitis, anorexia, abdominal pain, mucositis, constipation	Diarrhoea, nausea, vomiting, stomatitis, anorexia, abdominal pain, mucositis, dehydration, ileus, intestinal obstruction, hypokalemia, metabolic acidosis, constipation
<i>common:</i>	Dyspepsia, Gastrointestinal haemorrhage	Gastrointestinal haemorrhage
<i>rare:</i>		Colitis, including Clostridium difficile diarrhoea

Addition of oxaliplatin to fluorouracil and folinic acid:

Increased the incidence of severe nausea, vomiting, diarrhoea and stomatitis in the adjuvant setting (Table 8) and substantially increased these effects in the advanced cancer setting (Table 9).

Hepatobiliary

	Adjuvant	Advanced
<i>very common:</i>		Elevation of transaminases and alkaline phosphatases activities
<i>very rare:</i>	Reactions related to liver sinusoidal obstruction syndrome, including peliosis, hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	Reactions related to liver sinusoidal obstruction syndrome, including peliosis, hepatitis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Musculoskeletal

	Adjuvant	Advanced
<i>very common:</i>		Back pain*, arthralgia

* Back pain. If associated with haemolysis, which has been rarely reported, should be investigated.

Hypersensitivity

	Adjuvant	Advanced
<i>very common:</i>	Skin rash (particularly urticaria), conjunctivitis, rhinitis	Skin rash (particularly urticaria), conjunctivitis, rhinitis
<i>common:</i>	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock

Sensory

	Adjuvant	Advanced
<i>very common:</i>	Taste perversion	
<i>common:</i>	Conjunctivitis	
<i>uncommon:</i>		Ototoxicity
<i>rare:</i>	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation)	Deafness, optic neuritis, loss of visual acuity, visual field disturbances, transient vision loss (reversible following therapy discontinuation)

Renal

	Adjuvant	Advanced
<i>common:</i>		Altered renal function
<i>very rare:</i>		Renal tubular necrosis

In clinical and post-marketing setting: *very rare* - Acute tubular necrosis, acute interstitial nephritis, and acute renal failure

Respiratory

	Adjuvant	Advanced
Very common	Cough	Cough
<i>common:</i>	Rhinitis, dyspnoea, hiccups	hiccups
<i>rare:</i>		Acute interstitial lung disease, pulmonary fibrosis

Immune system

	Adjuvant	Advanced
<i>very common:</i>	Infections, fever, rigors (tremors), fatigue, asthenia	Infections, fever, rigors (tremors), fatigue, asthenia
<i>common:</i>	Febrile neutropenia	Febrile neutropenia
<i>rare:</i>		Autoimmune haemolytic anaemia and thrombocytopenia

Skin

	Adjuvant	Advanced
<i>very common:</i>	Alopecia, rash	
<i>common:</i>		Alopecia, rash

Moderate alopecia has been reported in 2% of patients treated with oxaliplatin as a single agent; the combination of oxaliplatin and fluorouracil did not increase the incidence of alopecia observed with fluorouracil alone.

DOSAGE AND ADMINISTRATION

Dosage

In combination with fluorouracil and folinic acid the recommended dose for the treatment of advanced colorectal cancer is 85 mg/m² intravenously repeated every two weeks, or 130mg/m² repeated every three weeks.

In combination with fluorouracil and folinic acid the recommended dose for adjuvant treatment is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

Dosage Modification

Prior to each treatment cycle, patients should be evaluated for toxicity and the dose of oxaliplatin adjusted accordingly.

Neurological Toxicity

If acute neurological reactions occur e.g. acute pharyngolaryngeal dysaesthesia, increase the oxaliplatin infusion time from 2 hours to 6 hours. This decreases C_{\max} by 30% and may lessen acute toxicities.

If sensory loss or paraesthesia persists longer than 7 days or interferes with function (grade 2 toxicity), reduce oxaliplatin dose by 25%.

If sensory loss or paraesthesia interferes with activities of daily living (grade 3 toxicity), oxaliplatin should be discontinued.

Haematological Toxicity

If haematological toxicity (neutrophils $<1.5 \times 10^9/L$ or platelets $<75 \times 10^9/L$) is present before starting treatment or prior to the next course:

- Delay treatment until neutrophil count is $\geq 1.5 \times 10^9/L$ and platelet count is $\geq 75 \times 10^9/L$ and
 - Reduce the $85 \text{mg}/\text{m}^2$ oxaliplatin dose to $75 \text{mg}/\text{m}^2$ every two weeks and FU dose by 20% (adjuvant treatment)
 - Reduce the $85 \text{mg}/\text{m}^2$ oxaliplatin dose to $65 \text{mg}/\text{m}^2$ every two weeks and FU dose by 20% (advanced treatment)
 - Reduce the $130 \text{mg}/\text{m}^2$ oxaliplatin dose to $100 \text{mg}/\text{m}^2$ every three weeks and FU dose by 20% (advanced treatment).
 -

Gastrointestinal Toxicity

If grade 3-4 gastrointestinal reactions occur, as assessed according to US *National Cancer Institute* criteria:

- Delay treatment until resolution of the adverse reactions and
 - Reduce the $85 \text{mg}/\text{m}^2$ oxaliplatin dose to $75 \text{mg}/\text{m}^2$ every two weeks and FU dose by 20% (adjuvant treatment)
 - Reduce the $85 \text{mg}/\text{m}^2$ oxaliplatin dose to $65 \text{mg}/\text{m}^2$ every two weeks and FU dose by 20% (advanced treatment)
 - Reduce the $130 \text{mg}/\text{m}^2$ oxaliplatin dose to $100 \text{mg}/\text{m}^2$ every three weeks and FU dose by 20% (advanced treatment).

Toxicity associated with fluorouracil

Dose adjustments should also be made for fluorouracil associated toxicities (see relevant product information).

Oxaliplatin should be administered before fluorouracil.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 mL of 5% glucose injection.

Preparation and Administration:

SPECIAL PRECAUTIONS FOR ADMINISTRATION

DO NOT use any injection material containing aluminium

DO NOT administer undiluted

DO NOT mix or administer with sodium chloride injection or any other solution containing chlorides

DO NOT mix with any other medication or administer simultaneously by the same infusion line (in particular fluorouracil and folic acid). A Y-tube may be used (see Infusion)

USE ONLY the recommended diluents (see below).

Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed.

Handling

As with other potentially toxic compounds, caution should be exercised when handling and preparing oxaliplatin solutions.

The handling of this cytotoxic agent by health care personnel requires every precaution to guarantee the protection of the handler and their surroundings. It is essential to use appropriate protective clothing, including protective goggles, mask and gloves. Pregnant women must be warned to avoid handling cytotoxic agents. If oxaliplatin concentrate, premixed solution or infusion solution should come into contact with skin, mucous membranes or eyes, wash immediately and thoroughly with water.

Preparation of Infusion Solution

Dilution before Infusion

The reconstituted solution **MUST** be further diluted in an infusion solution of 250-500 mL of 5% glucose injection. From a microbiological and chemical point of view, this infusion preparation should be used immediately. Inspect visually prior to use. Only clear solutions without particles should be used. The product is for single use in one patient only. Discard any residue. **NEVER** use sodium chloride solution for either reconstitution or dilution.

Infusion

The administration of oxaliplatin does not require prehydration. Oxaliplatin diluted in 250 to 500 mL of a glucose 5% injection must be infused either by central venous line or peripheral

vein over 2 to 6 hours. When oxaliplatin is administered with fluorouracil, the oxaliplatin infusion should precede that of fluorouracil.

Oxaliplatin can be co-administered with folinic acid infusion using a Y-tube placed immediately before the site of injection. The drugs should not be combined in the same infusion bag. Folinic acid must be diluted using isotonic infusion solutions such as 5% glucose solution but NOT sodium chloride solutions or alkaline solutions.

Flush the line after oxaliplatin administration.

While oxaliplatin has minimal to no vesicant potential, extravasation may result in local pain and inflammation which may be severe and lead to complications especially when oxaliplatin is infused through a peripheral vein. In case of oxaliplatin extravasation, the infusion must be stopped immediately and the usual local symptomatic treatment initiated.

Disposal

All materials that have been used for reconstitution, for dilution and administration must be destroyed according to local statutory requirements

POISONING AND OVERDOSAGE

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.

PRESENTATION:

Oxallicord Concentrate for Solution for Infusion is available in 50 mg/10 ml and 100 mg/20 ml vials. Keep the vial in the outer carton in order to protect from light. Store below 25°C. Do not freeze.

MEDICINE CLASSIFICATION

Prescription medicine

NAME AND ADDRESS OF SPONSOR:

Distributed in New Zealand by:

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Remuera, Auckland
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DATE OF PREPARATION

27th August 2010.