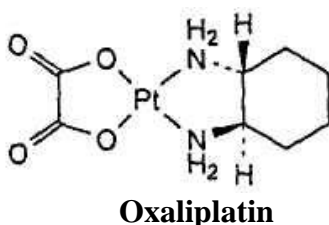

PRODUCT INFORMATION

NAME OF THE MEDICINE

Oxaliplatin Actavis 50 oxaliplatin 50mg power for injection vial
Oxaliplatin Actavis 100 oxaliplatin 100mg power for injection vial

Active. Oxaliplatin.

Inactive. Lactose



DESCRIPTION

Chemical name: [SP-4-2]-(1R,2R)- (cyclohexane-1,2-diamine- k²N,N'(oxalato (2-)-k²O¹,O²) platinum (II). Molecular formula: C₈H₁₄N₂O₄Pt. MW: 397.3. CAS: 61825-94-3. 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.

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 one to five cycles and oxaliplatin at 85 mg/m² every two weeks for one to three cycles are as follows:

Summary of platinum pharmacokinetic parameters 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} mcg/mL	AUC(0-48) mcg.h/mL	AUC(0-∞) mcg.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 AUC₍₀₋₄₈₎ and C_{max} values were determined on cycle 3 (85 mg/m²) or cycle 5 (130 mg/m²)
 Mean AUC(0-∞), V_{ss} and CL values were determined on cycle 1
 C_{max}, AUC, AUC₍₀₋₄₈₎, V_{ss} and CL values were determined by noncompartmental analysis
 T_{1/2α}, T_{1/2β} and T_{1/2γ} were determined by compartmental analysis (cycles 1-3 combined)

At the end of a two hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130 mg/m² every three weeks and steady-state was attained by cycle one in this matrix. Inter and intra-subject variability is generally low.

Biotransformation in vitro is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450 mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact drug was detectable in plasma ultrafiltrate at the end of a two 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/hour to 9.95 +/- 1.91 L/hour in renal impairment (creatinine clearance 12 to 57 mL/minute) 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 mg/m² as a two hour infusion, folinic acid 200 mg/m² over two hours, followed by an FU bolus of 400 mg/m², then an FU infusion of 600 mg/m² 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 1,108 patients were treated in the FOLFOX4 arm and 1,111 in the FU/FA arm. The median number of cycles received in both arms was 12.

In the intent to treat (ITT) population, after a median of four years follow-up, patients treated with FOLFOX4 had significantly increased disease free survival, the primary endpoint, compared to patients treated with FU/FA (see Table 1). In the subgroup 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.

Oxaliplatin Actavis

Table 1

Disease free survival and overall survival (intent to treat population)

	Disease stage	FOLFOX4	FU/FA	Hazard ratio (95% CI)
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Disease free survival 4 year probability (%) of surviving disease free (95% CI)	All	75.9 (73.4, 78.5) (n = 1, 123)	69.1 (66.3, 71.9) (n = 1, 123)	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 surviving (95% CI)	All	84.0 (81.7, 86.3) (n = 1,123)	82.4 (80.0, 84.8) (n = 1, 123)	0.89 (0.72, 1.09)
	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 1,312 patients have been enrolled in three pivotal trials for untreated (EFC7462/N9741, EFC2962) and pretreated patients (EFC2964). These studies evaluated the efficacy of oxaliplatin at the same dose intensity (85 mg/m²/two weeks) when added to different FU/FA doses and regimens, in terms of overall survival, progression free survival and tumour response.

EFC7462/N9741 was a multicentre open label randomised, three 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 two week FOLFOX4, six week IFL, or three 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 two hours, folinic acid 200 mg/m² over two hours, followed by an FU bolus of 400 mg/m², then an FU infusion of 600 mg/m² over 22 hours. Folinic acid and FU repeated on day 2. Cycle repeated every two 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 six weeks.

IROX day 1: oxaliplatin 85 mg/m² over two hours, irinotecan 200 mg/m² over 30 minutes. Cycle repeated every three 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.
 See Tables 2, 3, 4 and 5.

Oxaliplatin Actavis **Table 2**
 Summary of time to progression – intention to treat population

EFC7462/N9741	IFL	FOLFOX4	IROX
Time to progression (TTP)	(n = 264)	(n = 267)	(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 ration (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)	

Oxaliplatin Actavis **Table 3**
 Summary of overall survival – intention to treat population

EFC7462/N9741	IFL	FOLFOX4	IROX
Overall survival	(n = 264)	(n = 267)	(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 ration (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)	

Oxaliplatin Actavis **Table 4**
 Summary of confirmed overall response – patients (N, %) with measureable disease

EFC7462/N9741	IFL	FOLFOX4	IROX
Overall response	n = 212	n = 210	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 = 0.0252

^aPatients 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

Oxaliplatin Actavis

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)

EFC2962 was a multinational multicentre randomised phase III study in previously untreated patients, comparing a two weekly fluorouracil bolus plus infusion and high dose folinic acid (FU/FA regimen, day 1: folinic acid 200 mg/m² over two hours, followed by an FU bolus of 400 mg/m², then an 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 nine 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 shown in Table 6.

Oxaliplatin Actavis

Table 6

Confirmed responses after independent radiological review in study EFC2962

	FU/FA + oxp n = 210	FU/FA N = 210	Difference
Objective response rate* % (95% CI)	49.0 (42, 56)	21.9 (16, 27)	p = 0.0001
Complete	1.4	0.5	
Partial	47.6	21.4	
Median progression free survival (months)** (95% CI)	8.2 (7.2, 8.8)	6.0 (5.5, 6.5)	p = 0.0003 (log rank)

Median survival time (months) (95% CI)	16 (14.7, 18.2)	14.7 (13.7, 18.2)	p = 0.109 (log rank)
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*Response rate assessed according to WHO-UICC criteria

**Independent expert review

oxp = oxaliplatin

FU/FA = fluorouracil and folinic acid

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.

EFC2964 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 twice weekly. The two study regimens were as follows.

Regimen 1, day 1: folinic acid 200 mg/m² over two hours, followed by an FU bolus of 400 mg/m², then an FU infusion of 600 mg/m² over 22 hours. Repeated on day 2.

Regimen 2: folinic acid 500 mg/m² over two hours, followed by an FU infusion of 1,500 mg/m² over 22 hours, repeated on day 2.

The results are shown in Table 7.

Oxaliplatin Actavis

Table 7

Confirmed responses in study EFC2964

	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) [95% CI]	5.1 [3.1 – 5.7]	4.6 [3.0 – 5.5]	4.7 [3.4 – 5.5]
Median overall survival (months) [95% CI]	11.1 [8.3 – 13.0]	10.5 [8.6 – 13.4]	11.0 [9.1 – 12.9]

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 breastfeeding.
- 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 a severely impaired renal function (creatinine clearance less than 30 mL/minute).

PRECAUTIONS

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

Allergic reactions. Anaphylactic-like reactions to oxaliplatin have been reported, and may occur within minutes of oxaliplatin 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 Effects) of oxaliplatin should be carefully monitored, especially if coadministered 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 two hour infusion, the next oxaliplatin infusion should be administered over six 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 antiemetic therapy, including 5HT₃-antagonists and corticosteroids. Dehydration, ileus, intestinal obstruction, hypokalaemia, 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. Oxaliplatin has been associated with pulmonary fibrosis (0.7% of study patients), which may be fatal. In the case of unexplained respiratory symptoms such as nonproductive 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 Effects).

Hepatic toxicity. Reactions related to liver sinusoidal obstruction syndrome, including nodular regenerative hyperplasia, have been reported (see Adverse Effects). 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.

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

Use in the 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. 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 greater than or equal to 15 mg/m². However, no effects on fertility were seen in male and female rats at doses up to 12 mg/m²/day for five days/cycle.

Use in pregnancy.

Category D - Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

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 fetal 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 breastfeeding women.

Interactions with other medicines

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 three 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 intravenous line. There are 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 doctor for appropriate management.

Patients and caregivers should be informed of the expected side effects of oxaliplatin 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.

ADVERSE EFFECTS

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

	Arm A FOLFOX 4 n = 1,108			Arm B FU/FA n = 1,111		
	All	Grade 3	Grade 4	All	Grade 3	Grade 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
Aneamia	75.6	0.7	0.1	66.9	0.3	-
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
Febrile neutropenia	0.7	0.7	-	0.1	0.1	-

FU/FA = fluouracil and folinic acid

NA = Not applicable

Oxaliplatin Actavis

Table 9

FU/FA ± oxaliplatin in previously untreated patients with advanced colorectal cancer, all grades and grade 3 to 4 toxicities – all cycles - % patients

Incidence of toxicity by patient %	EFPC2962				N9741			
	n = 208		n = 209		n = 256		N = 259	
	All grades	Grades 3 - 4	All grades	Grades 3 - 4	All grades	Grades 3 - 4	All grades	Grades 3 - 4
	Control arm q 2 w FU bolus + CIV		Oxaliplatin 85 q 2 w FU bolus + CIV		Irinotecan 125 q 6 w FU bolus x 4 weekly		FOLFOX4 Oxaliplatin 85 q 2 w FU bolus + CIV	
Paraesthesias**	11.5	0.0	67.0	16.7	15.6	2.3	77.2	17.8
Laryngopharyngeal dysesthesia	NA	NA	NA	NA	1.2	0	38.2	1.5
Neurosensory	NA	NA	NA	NA	2.3	0	12.0	0.8
Nausea	53.4	1.9	72.2	5.7	67.2	14.5	71.0	6.2
Vomiting	29.3	1.9	54.1	5.7	43.4	13.3	40.9	3.5
Diarrhoea	43.8	5.3	58.9	12.0	65.2	28.5	56.0	11.6
Stomatitis	35.6	1.4	44.0	5.7	25.0	0.8	37.5	0
Anaemia	80.8	2.4	85.2	3.3	28.1	4.3	27.0	2.7
Neutropenia	30.8	7.2	74.6	43.1	80.1	46.1*	82.2	54.1*
Thrombocytopenia	28.8	0.0	75.6	2.4	26.2	2.7	71.4	4.6
Fever without neutropenia	14.9	0.0	33.0	0.0	8.6	0.4	16.2	0.8
Infection	27.9	1.0	31.6	1.0	5.1	0.8	9.7	3.5
Asthenia	21.6	3.4	23.4	4.3	NA	NA	NA	NA
Fatigue	7.2	0.5	12.9	1.0	58.2	10.5	70.3	6.6
Alopecia	19.2	NA	17.7	NA	44.1	0	37.5	0
Skin	32.2	0.5	28.7	0.0	NA	NA	NA	NA
AST	23.1	0.0	46.4	0.5	2.0	0.4	17.4	1.2
AST	21.6	0.0	29.2	1.0	2.3	0	6.2	0.8
Alkaline phosphatase	39.9	1.4	56.5	1.4	7.0	0	16.2	0

Creatinine increase	8.2	0.5	4.8	0.5	3.5	0.4	4.2	0
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*14.8% febrile neutropenia reported in the IFL (Irinotecan FU/LV) and 4.2% in the FOLFAX4 arm
 **Various studies used different data convention. Breakdown data collection by laryngopharyngeal dysaesthesia and neurosensory was not done in EFC2962
 NA: not applicable
 CIV continuous intravenous infusion

Note.

Very common: greater than or equal to 1/10 (greater than or equal to 10%),
 Common: greater than or equal to 1/100 and < 1/10 (greater than or equal to 1% and < 10%),
 Uncommon: greater than or equal to 1/1,000 and < 1/100 (greater than or equal to 0.1% and < 1%),
 Rare: greater than or equal to 1/10,000 and < 1/1,000 (greater than or equal to 0.01% and < 0.1%),
 Very rare: < 1/10,000 (< 0.01%).

Neurological.

	Adjuvant	Advanced
Very common	Sensory peripheral neuropathy	Primarily sensory peripheral neuropathy (e.g. loss of deep tendon reflexes, dysaesthesia, paraesthesia, Lhermitte's sign)
Common		Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure
Rare		Dysarthria

Neurological adverse effects are the dose limiting toxicity. A primarily sensory peripheral neuropathy occurs in 85 to 95% of patients. These symptoms usually develop at the end of the two 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 (ten cycles) the risk of occurrence of persistent symptoms is 10% and for a cumulative dose of 1,020 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. 2% were withdrawn

due to persisting paraesthesia (i.e. persisting between treatment cycles), after cumulative oxaliplatin doses of 759-1,100 mg/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 to 1,713.15 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.

Haematological.

	Adjuvant	Advanced
Very common	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 x 10⁹/L); and
- substantially increased the incidence of thrombocytopenia (see Tables 8 and 9).

Gastrointestinal.

	Adjuvant	Advanced
Very common	Diarrhoea, nausea, vomiting,	Diarrhoea, nausea, vomiting,

	stomatitis, anorexia, abdominal pain, mucositis, constipation	stomatitis, anorexia, abdominal pain, mucositis, dehydration, ileus, intestinal obstruction, hypokalaemia, metabolic acidosis, constipation
Common	Dyspepsia	
Rare		Colitis, including <i>Clostridium difficile</i> diarrhoea

Addition of oxaliplatin to fluorouracil and folinic acid:

- increased the incidence of severe nausea, vomiting, diarrhoea and stomatitis in the adjuvant setting (see Table 9) and substantially increased these effects in the advanced cancer setting (see Table 10).

Hepatobiliary.

	Adjuvant	Advanced
Very common		Elevation of transaminases and alkaline phosphatases activities
Very rare	Reactions related to liver sinusoidal obstruction syndrome, including peliosis, nodular regenerative hyperplasia, perisinusoidal fibrosis and portal hypertension	Reactions related to liver sinusoidal obstruction syndrome, including peliosis, nodular regenerative hyperplasia, perisinusoidal fibrosis and portal hypertension

Musculoskeletal.

	Adjuvant	Advanced
Very common		Back pain*, arthralgia

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

Hypersensitivity.

	Adjuvant	Advanced
Very common	Skin rash (particularly urticaria), conjunctivitis, rhinitis	Skin rash (particularly urticaria), conjunctivitis, rhinitis
Common	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic

	shock	shock
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Sensory.

	Adjuvant	Advanced
Very common	Taste perversion	
Common	Conjunctivitis	
Uncommon		Ototoxicity
Rare		Deafness, optic neuritis, loss of visual acuity

Renal.

	Adjuvant	Advanced
Common		Altered renal function
Very rare		Renal tubular necrosis

In clinical and postmarketing setting: *very rare* - Acute tubulo-interstitial nephropathy leading to acute renal failure.

Respiratory.

	Adjuvant	Advanced
Common	Rhinitis, dyspnoea	
Rare		Acute interstitial lung disease, pulmonary fibrosis

Immune system.

	Adjuvant	Advanced
Very common	Infections, fever, rigors (tremors)	Infections, fever, rigors (tremors)
Common	Febrile neutropenia	Febrile neutropenia
Rare		Autoimmune haemolytic anaemia and thrombocytopenia

Skin.

	Adjuvant	Advanced
Very common	Alopecia, rash	
Common		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.

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 (six 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 two to six hours. This decreases C_{max} by 30% and may lessen acute toxicities.

If sensory loss or paraesthesia persists longer than seven 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 x 10⁹/L or platelets < 75 x 10⁹/L) is present before starting treatment or prior to the next course:

- delay treatment until neutrophil count is greater than or equal to 1.5 x 10⁹/L and platelet count is greater than or equal to 75 x 10⁹/L; and
- reduce the 85 mg/m² oxaliplatin dose to 75 mg/m² every two weeks and FU dose by 20% (adjuvant treatment);
- reduce the 85 mg/m² oxaliplatin dose to 65 mg/m² every two weeks and FU dose by 20% (advanced treatment).

Gastrointestinal toxicity.

If grade 3 to 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 mg/m² oxaliplatin dose to 75 mg/m² every two weeks and FU dose by 20% (adjuvant treatment);
- reduce the 85 mg/m² oxaliplatin dose to 65 mg/m² every two 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, Section 9b).

Oxaliplatin should be administered before fluorouracil.

Oxaliplatin is administered as a two to six 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 5-fluorouracil, basic solutions trometamol and folinic acid). A Y-tube may be used (see Infusion, below).

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

Reconstitution of the solution. Water for injections or 5% glucose solution should be used to reconstitute the powder.

– For a vial of 50 mg: add 10 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

– For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

Do not administer the reconstituted solution without further dilution.

From a microbiological and chemical point of view, the reconstituted solution should be diluted immediately with 5% glucose solution.

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.

Dilution before infusion. Withdraw the required amount of reconstituted solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5% glucose solution to give an oxaliplatin concentration not less than 0.2 mg/ml.

Administer by IV infusion.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C. From a microbiological point of view, this infusion preparation should be used immediately.

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

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

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

NEVER use sodium chloride solution for either reconstitution or dilution.

Infusion

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

OVERDOSAGE

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

The National Poisons Centre, telephone number 0800 POISON (0800 764 766), should be contacted for advice on the management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Powder for solution for infusion (sterile, vials): 50 mg, 100 mg.

Reconstituted solution for injection: to be diluted immediately.

Diluted solution for injection: may be stored at temperatures between 2-8°C (refrigerate, do not freeze) for not more than 24 hours.

Store below 25°C. Do not freeze.

MEDICINE CLASSIFICATION

Prescription medicine.

NAME AND ADDRESS OF THE SPONSOR

Australian Sponsor:

Actavis Australia Pty Ltd
225 George Street
Sydney NSW 2000
ABN 43 122 896 468

New Zealand Sponsor:

CSL Biotherapies (NZ) Ltd
666 Great South Road, Penrose
Auckland 1544, New Zealand

Ph: 0800 502 757

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