PRODUCT INFORMATION

ELOXATIN®

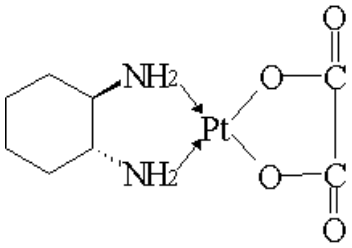
NAME OF THE MEDICINE

Non-proprietary Name

Oxaliplatin powder for injection and concentrated solution for injection.

Chemical Structure

Oxaliplatin has the following chemical structure:



CAS Number

61 825-94-3.

DESCRIPTION

Oxaliplatin is designated chemically as [*SP*-4-2]-(1*R*,2*R*)-(cyclohexane-1,2-diamine-k^2*N,N´*(oxalate (2-)-k^2*O*^{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 is a white to off-white crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and practically insoluble in ethanol.

Eloxatin powder for injection contains oxaliplatin and lactose and the concentrated solution for injection contains oxaliplatin and water for injections.

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-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 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 130mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85mg/m^2 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 85mg/m^2 Every Two Weeks or at 130mg/m^2 Every Three Weeks

Dose	**C_{max} µg/mL**	**AUC_{0-48} µg.h/mL**	**AUC µg.h/mL**	**$t_{1/2}\alpha$ h**	**$t_{1/2}\beta$ h**	**$t_{1/2}\gamma$ h**	**V_{ss} L**	**CL L/h**
85mg/m^2								
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
130mg/m^2								
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 (85mg/m^2) or Cycle 5 (130mg/m^2).
Mean AUC, V_{ss}, and CL values were determined on Cycle 1.
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 85mg/m^2 every two weeks or 130mg/m^2 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 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 $\pm$ 2.18 L/h to 9.95 $\pm$ 1.91 L/h in renal impairment (creatinine clearance 12–57mL/min) was observed together with a statistically significant decrease in distribution volume from 330 $\pm$ 40.9 to 241 $\pm$ 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 85mg/m^2 as 2 hour infusion, folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/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 surviving [95% CI]	All	84.0 [81.7, 86.3] (n=1123)	82.4 [80.0, 84.8] (n=1123)	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.

Use in combination with capecitabine

NO16968

Data from a open-label, multi-centre, randomised, controlled phase III clinical trial in patients with stage III (Dukes' C) colon cancer supports the use of capecitabine in combination with oxaliplatin (XELOX) for the adjuvant treatment of patients with colon cancer (NO16968). In this trial, 944 patients were randomised to 3 week cycles for 24 weeks with capecitabine (1000mg/m2 twice daily for 2 weeks followed by a 7 day rest period) in combination with oxaliplatin (130mg/m2 intravenous infusion over 2 hours on day 1 every 3 weeks); 942 patients were randomised to bolus 5-FU and leucovorin. In the primary analysis (ITT population), median observation time was 57 months for DFS and 59 months for OS. XELOX group had a statistical significant improvement in DFS compared to 5-FU/LV (HR=0.80, 95% CI=[0.69; 0.93]; p=0.0045). The 3 year DFS rate was 71% for XELOX versus 67% for 5-FU/LV. The analysis for the secondary endpoint of relapse free survival (RFS) supports these results with a HR of 0.78 (95% CI=[0.67; 0.92]; p=0.0024) for XELOX vs. 5-FU/LV. XELOX showed a trend towards superior OS with a HR of 0.87 (95% CI=[0.72; 1.05]; p=0.1486). The 5 year OS rate was 78% for XELOX versus 74% for 5-FU/LV.

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, EFC2962) and pretreated patients (EFC2964). These studies evaluated the efficacy of oxaliplatin at the same dose intensity (85mg/m²/2 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, 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 85mg/m^2 over 2 hours, folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Folinic acid and FU repeated on Day 2. Cycle repeated every 2 weeks.

IFL Day 1: irinotecan 125mg/m^2 over 90 minutes, folinic acid 20mg/m^2 over 15 minutes or IV push, FU bolus of 500mg/m^2 weekly x 4. Cycle repeated every 6 weeks.

IROX Day 1: oxaliplatin 85mg/m^2 over 2 hours, irinotecan 200mg/m^2 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)

EFC2962 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 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Repeated on Day 2.) to the same regimen combined with oxaliplatin at the dosage of 85mg/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 OS between the two groups, however, the study was not powered to detect a difference in OS. 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 85mg/m^2 two weekly. The two study regimens were:

Regimen 1: Day 1; folinic acid 200mg/m^2 over 2 hours, followed by a FU bolus of 400mg/m^2, then a FU infusion of 600mg/m^2 over 22 hours. Repeated on Day 2.

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

The results were as shown in Table 7.

Table 6 (EFC2962)	**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	
Median progression free survival (months)[2] [95% CI]	8.2 [7.2, 8.8]	6.0 [5.5, 6.5]	p = 0.0003 (log rank)
Median survival time (months)	16	14.7	p= 0.109
[95% CI]	[14.7, 18.2]	[13.7, 18.2]	(log rank)

Table 7 (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]

1. Response rate assessed according to WHO-UICC criteria.

2. Independent expert review.

Treatment of Metastatic Colorectal Cancer

Use in combination with capecitabine, with or without bevacizumab

Study NO16966: Data from a multicentre, randomised, controlled phase III clinical study support the use of capecitabine in combination with oxaliplatin or in combination with oxaliplatin and bevacizumab (BV) for the first-line treatment of metastatic colorectal cancer (Study NO16966). The study contained two parts: an initial 2-arm part in which patients were randomised to two different treatment groups, XELOX or FOLFOX-4, and a subsequent 2x2 factorial part with four different treatment groups, XELOX + placebo (P), FOLFOX-4+P, XELOX+BV, and FOLFOX-4+BV. The treatment regimens are summarised in Table 8 below.

Table 8: Treatment regimens in Study NO16966

	Treatment	Starting Dose	Schedule
FOLFOX-4 or FOLFOX-4 + BV	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
	Placebo or bevacizumab	5 mg/kg IV 30-90 min	Day 1, prior to FOLFOX-4, every 2 weeks
XELOX or XELOX+ BV	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
	Placebo or bevacizumab	7.5 mg/kg IV 30-90 min	Day 1, prior to XELOX, every 3 weeks
5-Fluorouracil:	IV bolus injection immediately after leucovorin		

Non-inferiority of the XELOX-containing arms compared with the FOLFOX-4-containing arms in the overall comparison was demonstrated in terms of progression-free survival (PFS) in the eligible per-protocol population (EPP), with progression determined by the study investigators who were not blinded to treatment allocation (see Table 9). The criterion set for concluding non-inferiority was that the upper limit of the 97.5% confidence interval for the hazard ratio for PFS was less than 1.23. The results for OS are similar to those reported for PFS.

Table 9: Key efficacy results for the non-inferiority analysis (EPP population, Study NO16966)

Endpoint Parameter	**XELOX/XELOX+P/ XELOX+BV (n = 967)**	**FOLFOX/FOLFOX+P/ FOLFOX+BV (n = 937)**	**Hazard Ratio (97.5% CI)**
Progression-free survival Median (days) (95% CI)	241 (229; 254)	259 (245; 268)	1.05 (0.94; 1.18)
Overall survival Median (days) (95% CI)	577 (535; 615)	549 (528; 576)	0.97 (0.84; 1.14)

Study NO16966 also demonstrated superiority of the bevacizumab-containing arms over placebo-containing arms.

Study NO16967: Data from a multicenter, randomised, controlled phase III clinical study support the use of capecitabine in combination with oxaliplatin for the second-line treatment of metastatic colorectal cancer. In this trial, 627 patients with metastatic colorectal cancer who have received prior treatment with irinotecan (CPT-11) in combination with a fluoropyrimidine regimen as first-line therapy were randomised to treatment with XELOX or FOLFOX-4 (Study NO16967). The treatment regimens used in study NO16967 are summarised in Table 10 below.

Table 10: Treatment regimens in Study NO16967

	Treatment	Starting Dose	Schedule
FOLFOX-4	Oxaliplatin	85 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 2 weeks
	Leucovorin	200 mg/m^2 IV 2 h	Leucovorin on Day 1 and 2, every 2 weeks
	5-Fluorouracil	400 mg/m^2 IV bolus, 600 mg/ m^2 IV 22 h	5-fluorouracil IV bolus/infusion, each on Days 1 and 2 , every 2 weeks
XELOX	Oxaliplatin	130 mg/m^2 IV 2 h	Oxaliplatin on Day 1, every 3 weeks
	Capecitabine	1000 mg/m^2 oral bid	Capecitabine oral bid for 2 weeks (followed by 1 week off treatment)
5-Fluorouracil:	IV bolus injection immediately after leucovorin		

XELOX was demonstrated to be non-inferior to FOLFOX-4 in terms of PFS in the per-protocol population (PPP) (see Table 11). The criterion set for concluding non-inferiority was the upper limit of the 95% confidence interval for the hazard ratio for PFS was less than 1.30. The result for OS was similar to that for PFS.

Table 11: Key efficacy results for the non-inferiority analysis (PPP, Study NO16967)

Endpoint Parameter	XELOX (n = 251)	FOLFOX (n = 252)	Hazard Ratio (95% CI)
Progression-free survival Median (days) (95% CI)	154 (140; 175)	168 (145; 182)	1.03 (0.87; 1.24)
Overall survival Median (Days) (95% CI)	388 (339; 432)	401 (371; 440)	1.07 (0.88; 1.31)

Treatment of Oesophagogastric Cancer

Data from a randomised multicenter, phase III study comparing capecitabine to 5-FU and oxaliplatin to cisplatin in patients with previously untreated locally advanced or metastatic oesophagogastric cancer supports the use of oxaliplatin for the first-line treatment of advanced oesophagogastric cancer (REAL-2). In this trial, 1002 patients were randomised in a 2x2 factorial design to one of the following 4 arms:

Table 12: Treatment regimens in the REAL-2 Study

Treatment	Starting Dose	Schedule
Epirubicin (E) Cisplatin (C) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Cisplatin (C) Capecitabine (X)	50 mg/m^2 IV bolus 60 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily
Epirubicin (E) Oxaliplatin (O) 5-Fluorouracil (F)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 200 mg/m^2 continuous infusion via a central line	Day 1, every 3 weeks Day 1, every 3 weeks Daily
Epirubicin (E) Oxaliplatin (O) Capecitabine (X)	50 mg/m^2 IV bolus 130 mg/m^2 2 hour IV infusion 625 mg/m^2 bd orally	Day 1, every 3 weeks Day 1, every 3 weeks Twice daily

The primary efficacy analyses in the per-protocol population demonstrated non-inferiority in OS for capecitabine versus 5-FU-based regimens (hazard ratio 0.86, 95% CI: 0.80 to 0.99) and for oxaliplatin versus cisplatin-based regimens (hazard ratio 0.92, 95% CI: 0.80 to 1.10). The median OSl was 10.9 months in capecitabine-based regimens and 9.6 months in 5-FU-based regimens. The median OS was 10.0 months in cisplatin-based regimens and 10.4 months in oxaliplatin-based regimens.

INDICATIONS

Oxaliplatin is indicated for adjuvant treatment of stage III (Duke's C) colon cancer, in combination with fluoropyrimidine agent.

Oxaliplatin in combination with fluorouracil and folinic acid is indicated for the treatment of advanced colorectal cancer.

Oxaliplatin in combination with capecitabine, with or without bevacizumab, is indicated for the treatment of patients with metastatic colorectal cancer

Oxaliplatin in combination with epirubicin and either capecitabine or fluorouracil, is indicated for: the treatment of patients with advanced oesophagogastric 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 x 10^9/L and/or platelet count of <75 x 10^9 /L,
- have a peripheral sensory neuropathy with functional impairment prior to first course,
- have severely impaired renal function (creatinine clearance less than 30mL/min).

If contraindications exist to any of the agents in combination regimens, that agent should not be used.

PRECAUTIONS

General

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

Allergic Reactions

Anaphylactic-like reactions to Eloxatin have been reported, and may occur within minutes of Eloxatin administration. Patients with a history of allergic reactions to platinum compounds should be monitored for allergic symptoms. Allergic reactions can occur during any cycle. 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 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.

Signs and symptoms of Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension (see **ADVERSE EFFECTS**). Diagnosis of RPLS is based upon confirmation by brain imaging.

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.

Intestinal Ischaemia

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

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. If severe/life threatening diarrhoea, severe neutropenia, febrile neutropenia or severe thrombocytopenia occur, oxaliplatin must be discontinued until improvement or resolution and appropriate dose adjustments may apply.

Infection

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

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

Pulmonary Toxicity

Eloxatin 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 EFFECTS**).

Haemolytic-uraemic syndrome (HUS)

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see **ADVERSE EFFECTS)**. Oxaliplatin should be discontinued at the first signs of any evidence of microangiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH. Renal failure may be not reversible with discontinuation of therapy and dialysis may be required.

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.

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

Rhabdomyolysis
Rhabdomyolysis has been reported in patients treated with oxaliplatin, including fatal outcomes. In case of muscle pain and swelling, in combination with weakness, fever or darkened urine, oxaliplatin treatment should be discontinued. If rhabdomyolysis is confirmed, appropriate measures should be taken. Caution is recommended if medicinal products associated with rhabdomyolysis are administered concomitantly with oxaliplatin (see **INTERACTIONS WITH OTHER MEDICINES** and **ADVERSE EFFECTS**).

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

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

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, 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 ≥15mg/m². However, no effects on fertility were seen in male and female rats at doses up to 12mg/m²/day for 5 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 9mg/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 MEDICINES

In patients who have received a single dose of 85mg/m^2 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 130mg/m^2 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.

No clinically significant differences in exposure to capecitabine or its metabolites, free platinum or total platinum occured when capecitabine and oxaliplatin were administered in combination, with or without bevacizumab.

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

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

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 Eloxatin 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 EFFECTS

Fluorouracil and folinic acid (FU/FA) in combination with oxaliplatin

Table 13: 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	-
Adverse effects						
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	-

Table 14: 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 %	EFC2962				N9741			
	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
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
ALT	21.6	0.0	29.2	1.0	2.3	0	6.2	0.8
Alk. 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

NA: Not applicable

CIV – continuous intravenous infusion

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

** modified WHO toxicity grading scale

*** 14.8% febrile 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	≥1/10 (≥10%)
common	≥1/100 and <1/10 (≥1% and <10%)
uncommon	≥1/1000 and <1/100 (≥0.1% and <1.0%)
rare	≥1/10,000 and <1/1000 (≥0.01% and <0.1%)
very rare	<1/10,000 (<0.01%)

Neurological

	Adjuvant	Advanced
very common:	Sensory peripheral neuropathy, dysgeusia	Primarily sensory peripheral neuropathy (e.g. loss of deep tendon reflexes, dysaesthesia, paraesthesia Lhermitte's sign), dysgeusia
common:		Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure
rare:		Dysarthria Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES) (see **PRECAUTIONS**).

Post marketing experience with unknown frequency – convulsion.

Neurological adverse effects 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 ADMINSTRATION**).

In the adjuvant setting, for a cumulative dose of 850mg/m^2 (10 cycles) the risk of occurrence of persistent symptoms is 10% and for a cumulative dose of 1020mg/m^2 (12 cycles) the risk of occurrence is 20%.

In the advanced setting, in EFC2962, 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 874mg/m^2. Two percent were withdrawn due to persisting paraesthesia (i.e. persisting between treatment cycles), after cumulative oxaliplatin doses of 759-1100mg/m^2.

In the majority of cases, the neurological signs and symptoms improve when treatment is discontinued. Analysis of patients in EFC2962 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 913.6mg/m^2 (range: 169.7-1713.15mg/m^2). 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.

Vascular Disorders

	Adjuvant	Advanced
very common:	Epistaxis	Epistaxis
common:	Deep vein thrombosis, thromboembolic events, hypertension	Deep vein thrombosis, thromboembolic events, hypertension

Post marketing experience with unknown frequency - haemolytic uremic syndrome

Haematological

	Adjuvant	Advanced
very common:	Epistaxis, anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)	Anaemia (all grades), neutropenia (all grades), thrombocytopenia (all grades)
common	Febrile neutropenia	Febrile neutropenia
rare	Disseminated intravascular coagulation (DIC), including fatal outcomes.	Disseminated intravascular coagulation (DIC), including fatal outcomes.

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 (Tables13-14).

Gastrointestinal

	Adjuvant	Advanced
very common:	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
common:	Dyspepsia, gastrointestinal haemorrhage	Gastrointestinal haemorrhage
rare:		Colitis, including Clostridium difficile diarrhoea Pancreatitis

Addition of oxaliplatin to fluorouracil and folinic acid:

- Increased the incidence of severe nausea, vomiting, diarrhoea and stomatitis in the adjuvant setting (Table 13) and substantially increased these effects in the advanced cancer setting (Table 14).

Hepatobiliary

	Adjuvant	Advanced
very common:		Elevation of transaminases and

		alkaline phosphatases activities
very rare:	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.	Reactions related to liver sinusoidal obstruction syndrome, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis. Clinical manifestations may be portal hypertension and/or increased transaminases.

Infections and infestations

common:	Neutropenic sepsis, including fatal outcomes
uncommon:	Sepsis, including fatal outcomes

Musculoskeletal

	Adjuvant	Advanced
very common:	Arthralgia	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, injection site reactions	Skin rash (particularly urticaria), conjunctivitis, rhinitis, injection site reactions
common:	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock	Bronchospasm, sensation of chest pain, angioedema, hypotension, anaphylactic shock

Sensory

	Adjuvant	Advanced
very common:	Taste perversion	
common:	Conjunctivitis	
uncommon:		Ototoxicity
rare:	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
common:		Altered renal function
very rare:		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
common:	Rhinitis, dyspnoea, hiccups	hiccups
rare:		Acute interstitial lung disease (sometimes fatal), pulmonary fibrosis

Immune system

	Adjuvant	Advanced
very common:	Infections, fever, rigors (tremors), fatigue, asthenia	Infections, fever, rigors, (tremors), fatigue, asthenia
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.

Metabolism and nutrition disorders

common:	hypocalcaemia

Capecitabine in combination with oxaliplatin

Table 15 Summary of ADRs in ≥ 5% of patients who received capecitabine with oxaliplatin treated for adjuvant colon cancer (Study NO16968)

Body System Adverse drug reaction	**XELOX** **N=938** **All Grades %**	**5-FU/LV MAYO CLINIC** **N=657** **All Grades %**	**5-FU/LV ROSWELL PARK** **N=269** **All Grades %**
Gastrointestinal Disorders			
Diarrhoea	62	68	81
Nausea	67	53	71
*Stomatitis All	21	64	21
Vomiting	44	22	38
Abdominal pain	22	18	34
Constipation	20	12	18
Dyspepsia	9	6	14
Abdominal pain upper	8	7	8
Flatulence	5	3	11
Dry mouth	3	4	5
Nervous System Disorders			
Paraesthesia	36	2	4
Neuropathy peripheral	30	1	4
Dysgeusia	13	13	15
Headache	11	7	12
Dizziness	11	5	13

Peripheral sensory neuropathy	16	<1	4
Dysaesthesia	11	<1	<1
Lethargy	6	7	1
Hypoaesthesia	6	<1	3
General Disorders and Administration Site Conditions			
Fatigue	35	23	63
Asthenia	18	14	16
Pyrexia	12	9	16
Temperature intolerance	11	-	<1
Oedema peripheral	5	3	11
Chills	3	1	6
Skin and Subcutaneous Tissue disordErs			
Palmar-plantar Erythrodysaethesia syndrome	30	9	16
Alopecia	4	24	9
Rash	9	10	15
Dry skin	5	6	16
Pruritus	2	3	6
Blood and Lymphatic System Disorders	28	35	13
Neutropenia	18	<1	1
Thrombocytopenia	7	5	13
Anaemia	<1	5	1
Febrile neutropenia			
Metabolism and Nutrition Disorders			
Anorexia	26	15	29
Dehydration	7	4	12
Hypokalaemia	6	3	12
Decreased appetite	3	2	6
Respiratory, Thoracic and Mediastinal Disorders			
Cough	5	2	13
Oropharyngeal pain	4	6	7
Dyspnoea	7	2	6
Epistaxis	4	4	11
Dysaethesia pharynx	10	-	-
Rhinorrhoea	3	2	7
Musculoskeletal and Connective Tissue Disorders			
Pain in extremity	12	3	8
Arthralgia	4	3	10
Back pain	5	2	9
Pain in jaw	6	<1	-
Psychiatric Disorders			
Insomnia	8	7	14
Anxiety	5	3	12
Depression	4	2	9
Infections and Infestations			
Nasopharyngitis	3	3	6
Upper respiratory tract infection	3	2	7
Urinary tract infection	2	2	7
Eye disorders			
Lacrimation increased	5	8	18

** stomatitis, mucosal inflammation, mucosal ulceration, mouth ulceration*

Table 16 shows the most frequent ADRs (≥5%) reported in patients with metastatic colorectal cancer who received first-line (Study NO16966) or second-line (Study NO16967) treatment with capecitabine in combination with oxaliplatin (XELOX). In Study NO16966, the pooled XELOX versus FOLFOX-4 comparison includes pooled safety data from the XELOX arm of the initial 2-arm part of the study and the XELOX+placebo (P) arm of the 2x2 factorial part of the study versus the pooled safety data from the FOLFOX-4 arm of the initial 2-arm part of the study and the FOLFOX-4+P arm of the 2x2 factorial part of the study (see **CLINICAL TRIALS**). The intensity of adverse events was graded according to the toxicity categories of the NCI CTCAE grading system.

Table 16: Summary of ADRs in ≥ 5 % of patients who received first-line or second-line treatment with capecitabine and oxaliplatin for metastatic colorectal cancer (Study NO16966 and Study NO16967)

	XELOX[a] n=966		FOLFOX-4 [b] n=957	
Body System	**All Grades**	**Grade 3/4**	**All Grades**	**Grade 3/4**
Adverse drug reaction	**%**	**%**	**%**	**%**
Gastrointestinal Disorders				
Nausea	60	4	60	3
Diarrhoea	60	19	53	9
Vomiting	41	4	35	3
Stomatitis	18	<1	34	2
Abdominal pain	18	2	15	2
Constipation	13	<1	18	1
Dyspepsia	8	-	10	<1
Abdominal pain upper	5	<1	5	<1
Nervous System Disorders				
Paraesthesia	36	4	35	3
Neuropathy peripheral	17	3	17	2
Peripheral sensory neuropathy	15	2	16	2
Dysgeusia	11	-	14	-
Neuropathy	13	2	12	2
Dysaesthesia	12	1	13	2
Dizziness	9	<1	8	-
Headache	8	<1	8	<1
Lethargy	8	2	8	<1
Hypoaesthesia	8	<1	6	<1
General Disorders and Administration Site Conditions				
Fatigue	36	5	41	7
Asthenia	17	3	18	3
Pyrexia	11	<1	17	1
Temperature intolerance	7	<1	7	<1
Blood and Lymphatic System Disorders				
Neutropenia	24	6	54	40
Thrombocytopenia	19	5	21	3
Anaemia	10	1	10	1
Metabolism and Nutrition Disorders				
Anorexia	26	2	24	2
Hypokalaemia	7	5	5	2

Body System Adverse drug reaction	XELOX[a] n=966 All Grades %	 Grade 3/4 %	FOLFOX-4 [b] n=957 All Grades %	 Grade 3/4 %
Dehydration	6	3	4	2
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	28	5	9	1
Rash	5	<1	7	<1
Respiratory,Thoracic and Mediastinal Disorders				
Dysaesthesia pharynx	12	2	6	<1
Epistaxis	5	-	10	-
Dyspnoea	7	1	5	1
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	8	<1	3	<1
Pain in jaw	5	<1	4	<1
Investigations				
Weight decreased	7	<1	4	<1
Psychiatric Disorders				
Insomnia	5	<1	5	<1

[a] XELOX: capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and oxaliplatin (130 mg/m^2 as a 2-hour infusion on day 1 every three weeks).

[b] FOLFOX-4: leucovorin (200 mg/m^2 as a 2-hour infusion on days 1 and 2 every two weeks), 5-FU (400 mg/m^2 as a bolus injection, 600 mg/m^2 as a 22 hour infusion on days 1 and 2 every two weeks), and oxaliplatin (85 mg/m^2 as a 2 hour infusion on day 1 every two weeks).

Rare or uncommon ADRs reported for the combination of capecitabine with oxaliplatin are consistent with ADRs reported for capecitabine monotherapy or oxaliplatin monotherapy (see Product Information for capecitabine).

Capecitabine in combination with oxaliplatin and bevacizumab

Table 17 shows the most frequent ADRs (≥ 5%) reported in a phase III trial (Study NO16966) of patients with metastatic colorectal cancer who received first-line treatment with capecitabine in combination with oxaliplatin and bevacizumab (XELOX+BV). The comparison of XELOX+BV versus FOLFOX-4+BV includes safety data from the XELOX+BV arm and the FOLFOX-4+BV arm of the 2x2 factorial part of the study. The intensity of adverse events was graded according to the toxicity categories of the NCI CTCAE grading system.

Table 17: Summary of ADRs reported in ≥ 5% of patients with metastatic colorectal cancer who received first-line treatment with XELOX+BV (Study NO16966)

Body System Adverse drug reaction	XELOX+BV[a] (N=353) All Grades %	 Grade 3/4 %	FOLFOX-4+BV[b] (N=341) All Grades %	 Grade 3/4 %
Gastrointestinal Disorders				
Nausea	64	6	62	3
Diarrhoea	62	21	60	12
Vomiting	44	5	37	6
Stomatitis	29	2	40	4

Body System Adverse drug reaction	XELOX+BV[a] (N=353) All Grades %	 Grade 3/4 %	FOLFOX-4+BV[b] (N=341) All Grades %	 Grade 3/4 %
Constipation	14	-	21	-
Abdominal pain	15	3	16	<1
Abdominal pain upper	7	-	6	-
Dyspepsia	6	-	11	<1
Nervous System Disorders				
Paraesthesia	37	5	39	6
Neuropathy peripheral	20	5	18	3
Peripheral sensory neuropathy	18	2	21	5
Neuropathy	14	2	13	3
Dysaesthesia	13	3	12	1
Dysgeusia	12	<1	14	-
Headache	12	<1	13	<1
Dizziness	7	<1	7	<1
Lethargy	8	<1	7	1
General Disorders and Administration Site Conditions				
Fatigue	36	7	37	6
Asthenia	21	7	26	4
Pyrexia	12	-	15	<1
Temperature intolerance	9	-	6	-
Blood and Lymphatic System Disorders				
Neutropenia	20	7	55	40
Thrombocytopenia	13	3	13	3
Anaemia	7	<1	11	1
Skin and Subcutaneous Tissue Disorders				
Palmar-plantar erythrodysaesthesia syndrome	39	12	13	2
Rash	7	-	10	-
Dry skin	6	-	4	-
Respiratory, Thoracic and Mediastinal Disorders				
Dysaesthesia pharynx	10	1	4	-
Epistaxis	8	-	29	<1
Dyspnoea	6	2	6	<1
Rhinorrhoea	5	-	4	-
Dysphonia	5	-	6	-
Metabolism and Nutrition Disorders				
Anorexia	28	3	26	2
Hypokalaemia	6	3	5	2
Dehydration	6	3	4	1
Vascular Disorders				
Hypertension	12	3	16	3
Musculoskeletal and Connective Tissue Disorders				
Pain in extremity	10	-	7	<1
Investigations				
Weight decreased	8	<1	7	-

Body System Adverse drug reaction	XELOX+BV[a] (N=353)		FOLFOX-4+BV[b] (N=341)	
	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
Psychiatric Disorders				
Insomnia	5	-	4	-

[a] XELOX+BV: capecitabine (1000 mg/m^2 twice daily for 2 weeks followed by a 7-day rest period) and oxaliplatin (130 mg/m^2 as a 2-hour infusion on day 1 every three weeks), and bevacizumab (7.5 mg/kg on day 1 every three weeks).

[b] FOLFOX-4+BV: leucovorin (200 mg/m^2 as a 2-hour infusion on days 1 and 2 every two weeks), 5-FU (400 mg/m^2 as a bolus injection, 600 mg/m^2 as a 22 hour infusion on days 1 and 2 every two weeks), and oxaliplatin (85 mg/m^2 as a 2 hour infusion on day 1 every two weeks), and bevacizumab (5 mg/kg on day 1 every two weeks).

Rare or uncommon ADRs reported for the combination of capecitabine with oxaliplatin and bevacizumab are consistent with ADRs reported for capecitabine monotherapy or oxaliplatin monotherapy or bevacizumab combination therapy (see Product Information for capecitabine or bevacizumab).

Epirubicin in combination with oxaliplatin and either fluorouracil or capecitabine

Table 18: Summary of the most common Grade 3/4 haematological ADRs reported in patients treated with oxaliplatin and epirubicin in combination with fluorouracil (EOF) or capecitabine (EOX) for advanced oesophagogastric cancer

The table also lists ADRs reported in the other arms of this trial, using cisplatin and epirubicin in combination with fluorouracil (ECF) or capecitabine (ECX).

Body System Adverse Drug Reaction	ECF n = 236	ECX n = 229	EOF n = 231	EOX n = 232
	Grade 3/4 %	Grade 3/4 %	Grade 3/4 %	Grade 3/4 %
Blood And Lymphatic System Disorders				
Neutropenia	41.7	51.1	29.9	27.6
Leucopenia	19.5	21.0	13.4	13.8
Anaemia	13.1	10.5	6.5	8.6
Thrombocytopenia	4.7	4.8	4.3	5.2
Febrile neutropenia	9.3	6.7	8.5	7.8

Table 19: Summary of the most common Grade 3/4 non-haematological ADRs reported in patients treated with oxaliplatin and epirubicin in combination with fluorouracil (EOF) or capecitabine (EOX) for advanced oesophagogastric cancer

The table also lists ADRs reported in the other arms of this trial, using cisplatin and epirubicin in combination with fluorouracil (ECF) or capecitabine (ECX).

Body System Adverse Drug Reaction	ECF n = 234	ECX n = 234	EOF n = 225	EOX n = 227
	Grade 3/4 %	Grade 3/4 %	Grade 3/4 %	Grade 3/4 %
Infections and infestations				
Infection	11.9	5.1	11.5	8.4
Nervous System Disorders				
Peripheral Neuropathy	0.4	1.7	8.4	4.4
Vascular Disorders				
Thromboembolism	18.1	14.9	8.5	8.4

Body System Adverse Drug	**ECF** **n = 234**	**ECX** **n = 234**	**EOF** **n = 225**	**EOX** **n = 227**
Gastrointestinal Disorders				
Stomatitis	1.3	1.7	4.4	2.2
Nausea/vomiting	10.2	7.7	13.8	11.4
Diarrhoea	2.6	5.1	10.7	11.9
Skin And Subcutaneous Tissue Disorders				
Palmar-Plantar Erythrodysaesthesia	4.3	10.3	2.7	3.1
Alopecia (grade 1- 2)	44.2†	47.4□†	27.7 †	28.8□†
General Disorders and Administration Site Conditions				
Lethargy	16.6	15.5	12.9	24.9
Fever	3.4	4.3	2.6	4.4

† grade 2 only

Post marketing experience with frequency not known:

The following additional adverse events were observed following the marketing of Eloxatin when used with various chemotherapy regimens:

- Infections and infestations

Septic shock, including fatal outcomes

- Respiratory, thoracic and mediastinal disorders

Laryngospasm

- Cardiac disorders

QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see **PRECAUTIONS**).

- Gastrointestinal disorders

Intestinal ischaemia, including fatal outcomes (see **PRECAUTIONS).**
Duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see **PRECAUTIONS**).

- Musculoskeletal and connective tissue disorders

Rhabdomyolysis, including fatal outcomes (see **PRECAUTIONS**).

DOSAGE AND ADMINISTRATION

Dosage

In combination with fluorouracil and folinic acid for adjuvant treatment of colon cancer, the recommended dose of oxaliplatin is 85 mg/m^2 intravenously repeated every two weeks for 12 cycles (6 months).

In combination with capecitabine for adjuvant treatment of colon cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended doses of capecitabine see **CLINICAL TRIALS**.

In combination with fluorouracil and folinic acid for the treatment of advanced colorectal cancer, the recommended dose of oxiplatin is 85mg/m^2 intravenously repeated every two weeks.

In combination with capecitabine with or without bevacizumab, for the treatment of metastatic colorectal cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended dose of capecitabine and bevacizumab, see **CLINICAL TRIALS**.

In combination with epirubicin and either fluororuracil or capecitabine, for the treatment of oesophagogastric cancer, the recommended dose of oxaliplatin is 130 mg/m^2, administered as an intravenous infusion over 2 hours on day 1 of a three week cycle. For the recommended doses of epirubicin, capecitabine and fluorouracil, see **CLINICAL TRIALS**.

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 x 10^9/L or platelets <75 x 10^9/L) is present before starting treatment or prior to the next course:

- Delay treatment until neutrophil count is ≥1.5 x 10^9/L and platelet count is ≥75 x 10^9/L and

- Reduce the 85mg/m^2 oxaliplatin dose to 75mg/m² every two weeks and FU dose by 20% (adjuvant treatment)

- Reduce the 85mg/m^2 oxaliplatin dose to 65mg/m² every two 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 effects and

- Reduce the 85mg/m^2 oxaliplatin dose to 75mg/m² every two weeks and FU dose by 20% (adjuvant treatment)

- Reduce the 85mg/m^2 oxaliplatin dose to 65mg/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).

Oxaliplatin should be administered before fluorouracil.

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

Toxicity associated with capecitabine, epirubicin and bevacizumab

See relevant Product Information for capecitabine, epirubicin and bevacizumab associated toxicities.

Dose Modifications for Haematological Toxicity used in Studies NO16966 and NO16967

Table 20: Dose Modifications for Febrile Neutropenia, "XELOX" Arm

	Grade 3 ANC < 1.0x10^9/L with fever ≥ 38.5˚C	Grade 4 ANC <1.0x10^9/L with fever ≥ 38.5˚C and life threatening sepsis
1st occurrence	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine at 50% of original dose + oxaliplatin 85mg mg/m^2
2nd occurrence	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine at 50% of original dose + oxaliplatin 85 mg/m^2	Treatment stopped permanently

Treatment (including bevacizumab/placebo) was not to start unless toxicity (except anemia) was resolved to grade ≤ 1(eg, ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L)

Table 21: Dose Modifications for Neutropenia, "XELOX" Arm

	Grade 2 1.0≤ANC<1.5x10^9/L	Grade 3 0.5≤ANC<1.0x10^9/L	Grade 4 ANC<0.5x10^9/L
1st occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 100 mg/m^2	Capecitabine 50% of original dose + oxaliplatin 85 mg/m^2
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment stopped permanently
3rd occurrence	No dose adjustment	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine monotherapy at 75% of original dose	Not applicable

Laboratory value at start of a treatment cycle: Treatment start was delayed (including bevacizumab/placebo) until ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L, and the patient had recovered from non-hematologic toxicity to baseline or grade ≤ 1, then treatment was started with doses indicated above.

Table 22: Dose Modifications for Thrombocytopenia and Anemia, "XELOX" Arm

Thrombocytopenia	Platelets ≥ 25 - < 75x10^9/L	Platelets ≥ 10 - < 25x10^9/L	Platelets < 10 x10^9/L
1st occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 100 mg/m^2	Capecitabine 50% of original dose + oxaliplatin 85 mg/m^2
2nd occurrence	No dose adjustment	Capecitabine 75% of original dose + oxaliplatin 85 mg/m^2	Treatment was stopped permanently unless it was in the best interest of the patient to be treated with capecitabine monotherapy at 50% of original dose
3rd occurrence	No dose adjustment	Capecitabine 50% of original dose + oxaliplatin	Treatment was stopped permanently

Thrombocytopenia	Platelets ≥ 25 - < 75x10^9/L	Platelets ≥ 10 - < 25x10^9/L	Platelets < 10 x10^9/L
		85 mg/m^2	
Anemia (non-hemolytic) anytime during treatment	Hemoglobin 8.0 - < 10.0 g/dL	Hemoglobin 6.5 - < 8.0 g/dL	Hemoglobin < 6.5 g/dL
any occurrence	No dose adjustment (could be managed by transfusion)	No dose adjustment (could be managed by transfusion)	No dose adjustment (could be managed by transfusion)

Treatment did not start unless toxicity (except anemia) was resolved to grade ≤ 1(eg, ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L)

Laboratory value at start of a treatment cycle: Treatment start was delayed (including bevacizumab/placebo) until ANC ≥ 1.5 x10^9/L, platelets ≥ 75x10^9/L, and recovery from non-hematologic toxicity to baseline or grade ≤ 1, then treatment was started with doses indicated above.

Dose Modifications for Non-haematological Toxicity used in Study NO16966

Table 23: Dose Modifications for Non-hematologic Adverse Events, "XELOX" Arm

Toxicity	Grade	Dose Adjustment
* Allergic reactions	3 or 4	Stop treatment permanently
* Respiratory symptoms indicative of pulmonary fibrosis	any	Interrupt treatment and investigate cause of symptoms
* Interstitial pulmonary fibrosis not present at baseline	any	Stop treatment permanently
Nausea and/or vomiting despite premedication with an effective antiemetic therapy	3	100 mg/m^2
Nausea and/or vomiting	4	100 mg/m^2
Diarrhoea	3 or 4	100 mg/m^2
Stomatitis	3	No dose reduction
Stomatitis	4	100 mg/m^2
Skin toxicity (retreatment delayed until recovery to Grade ≤ 1)	3 or 4	No dose reduction

* No dose adjustment for capecitabine (if in the best interest of the patient)

Dose Modifications used in the REAL-2 Study

Oxaliplatin was delayed for 1 week if neutrophil count < 1.0 x109/L, platelet count < 75 x109/L or the patient had persistent grade 1 or 2 neuropathy. After recovery from grade 2-4 thrombocytopenia or grade 3/4 neutropenia, the dose of oxaliplatin was reduced to 100 mg/m^2. On recovery of persistent grade 1/2 neuropathy between cycles or grade 3/4 neuropathy for 7-14 days, the dose of oxaliplatin was reduced to 100 mg/m^2. In the event of persistent grade 3/4 neuropathy, further oxaliplatin was omitted and carboplatin could be substituted at the investigators discretion. If laryngeal dysaesthesia occurred, subsequent oxaliplatin was administered as a 6-h infusion. If grade 3/4 diarrhoea or stomatitis occurred despite appropriate fluoropyrimidine dose reductions, subsequent oxaliplatin was reduced to 100 mg/m^2.

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 folinic 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

(i) Reconstitution of the Solution

The lyophilised powder is reconstituted by adding 10mL (for the 50mg vial) or 20mL (for the 100mg vial) of Water for Injections or 5% glucose injection. The resulting solution contains 5mg of oxaliplatin per mL. **Do not administer the reconstituted solution without further dilution**.

Chemical and physical in-use stability has been demonstrated for 48 hours at 2-8°C and 30°C. From a microbiological point of view, the reconstituted solution should be diluted immediately with 5% glucose injection. If not diluted 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. Reconstitution should take place in controlled and validated aseptic conditions. Inspect visually prior to use. Only clear solutions without particles should be used. Contains no antimicrobial agent. Product is for single use only. Discard any residue.

(ii) Dilution before Infusion

For both the Concentrate and Lyophilised Presentations

The reconstituted solution or the concentrate **MUST** be further diluted in an infusion solution of 250-500mL of 5% glucose injection. From a microbiological point of view, this infusion preparation should be used immediately. To reduce microbiological hazard, use as soon as practicable after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally be no longer than 24 hours at 2°C to 8°C. Reconstitution should take place in controlled and validated aseptic conditions.

For concentrate presentation only

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 8°C and for 24 hours at 25°C. From a microbiological point of view, this infusion preparation should be used immediately.

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

For both the concentrate and lyophilised presentations

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 500mL 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.

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 Poisons Information Centre, telephone number 131 126, should be contacted for advice on the management of an overdosage.

PRESENTATION AND STORAGE CONDITIONS

Eloxatin is available as a sterile lyophilised powder for infusion▲ in 50mg and 100mg vials or a concentrated solution for infusion in 50mg/10mL, 100mg/20mL and 200mg/40mL vials. Store below 30ºC. Do not freeze.

▲ Not marketed.

NAME AND ADDRESS OF THE SPONSOR

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NSW 2113

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE ARTG

27th February 2001

DATE OF MOST RECENT AMENDMENT

30th June 2015