

NEW ZEALAND DATA SHEET

1. OXALIPLATIN, 5 mg/mL, Concentrated Solution for Infusion

Oxaliplatin, 5 mg/mL, Concentrated Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 mL concentrate for solution for infusion contains 5 mg oxaliplatin.

Each 10 mL vial contains 50 mg oxaliplatin in concentrated solution for infusion.

Each 20 mL vial contains 100 mg oxaliplatin in concentrated solution for infusion.

For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Concentrated Solution for Infusion.

Clear, colourless solution, free from visible particles with a pH in the range of 4.5 and 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic 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.

Oxaliplatin is indicated in adults only.

4.2 Dose and method of administration

Dose

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

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

Dose modification

Prior to each treatment cycle, patients should be evaluated for toxicity and the dose of oxaliplatin adjusted accordingly (see **4.4 Special warnings and precautions for use**).

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.

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

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

Haematological toxicity

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

- Delay treatment until neutrophil count is $\geq 1.5 \times 10^9/L$ and platelet count is $\geq 75 \times 10^9/L$ and

- Reduce the 85 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)
- Reduce the 130 mg/m² oxaliplatin dose to 100 mg/m² every three weeks and FU dose by 20% (advanced treatment).

Gastrointestinal toxicity

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

- Delay treatment until resolution of the adverse reactions and

- Reduce the 85 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)
- Reduce the 130 mg/m² oxaliplatin dose to 100 mg/m² every three weeks and FU dose by 20% (advanced treatment).

Toxicity associated with fluorouracil

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

Oxaliplatin should be administered before fluorouracil.

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

Preparation and administration

Special precautions for administration

DO NOT use any injection material containing aluminium.

DO NOT administer undiluted.

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

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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 **6.6 Special precautions for disposal and other handling**).

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

For information related to precautions to be taken for handling and for instructions on dilution and preparation of infusion solution, see **6.6 Special precautions for disposal and other handling**.

4.3 Contraindications

Oxaliplatin is contraindicated in patients who:

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

4.4 Special warnings and precautions for use

General

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

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

For oxaliplatin combined with fluorouracil (with or without folinic acid), the usual dose adjustments for fluorouracil toxicities should apply (see relevant Data Sheet).

Allergic reactions

Hypersensitivity anaphylactic reactions and/or allergic reactions to oxaliplatin have been reported. These allergic reactions which may be fatal and can occur within minutes of oxaliplatin administration are similar in nature and severity to those reported with other platinum-containing compounds, such as rash, urticaria, erythema, pruritus and rarely, bronchospasm and hypotension. 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 (see **4.3 Contraindications**). Cross reactions, sometimes fatal, have been reported with all platinum compounds.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients

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receiving oxaliplatin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Neurological toxicity

Neurological toxicity (see **4.8 Undesirable 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. Dose modification may be required (see **4.2 Dose and method of administration**). 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.

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

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.

For patients who develop acute laryngopharyngeal dysaesthesia, 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.

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

Cases of Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as Posterior Reversible Encephalopathy Syndrome [PRES]) have been reported in patients receiving oxaliplatin in combination chemotherapy. RPLS is a rare, reversible, rapidly evolving neurological condition. Signs and symptoms of RPLS can include headache, altered mental functioning, seizures, hypertension, confusion, neurological disturbances and abnormal vision from blurriness to blindness, associated or not with hypertension (see **4.8 Undesirable effects**). Diagnosis of RPLS is based upon confirmation by brain imaging, preferably MRI (Magnetic Resonance Imaging).

Gastrointestinal toxicity

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic anti-emetic therapy, including 5-HT₃ antagonists and corticosteroids. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emetesis, 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 **4.8 Undesirable effects**).

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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.

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.

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 **4.8 Undesirable 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 **4.8 Undesirable effects**).

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 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 **4.8 Undesirable effects**).

Haemolytic-uraemic syndrome (HUS)

Haemolytic-uraemic syndrome (HUS) is a life-threatening side effect (see **4.8 Undesirable 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 not be 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 **4.8 Undesirable 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 medicine 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 **4.8 Undesirable 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,

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and those with electrolyte disturbances such as hypokalemia, hypocalcaemia, or hypomagnesaemia. In case of QT prolongation, oxaliplatin treatment should be discontinued (see **4.5 Interaction with other medicines and other forms of interaction** and **4.8 Undesirable effects**).

Cardiac disorders

Post marketing reports with oxaliplatin use include acute coronary syndrome (including myocardial infarction, coronary arteriospasm, and cardiac arrest). In case of acute coronary syndrome, treatment with oxaliplatin may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **4.8 Undesirable effects**).

Post marketing reports with oxaliplatin include cardiac arrhythmias (including bradyarrhythmia, tachycardia and atrial fibrillation). In case of cardiac arrhythmias, treatment with oxaliplatin may need to be interrupted or discontinued based on the individual benefit-risk assessment (see **4.8 Undesirable 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 **4.5 Interaction with other medicines and other forms of interaction** and **4.8 Undesirable 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 (see **4.8 Undesirable effects**).

Off-label route of administration

Do not use oxaliplatin intraperitoneally. Peritoneal haemorrhage 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.

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Hepatic Insufficiency

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

Children

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

Elderly

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

4.5 Interaction with other medicines and other forms of interaction

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

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

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

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

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 **4.4 Special warnings and precautions for use**).

Caution is advised when oxaliplatin treatment is administered concomitantly with other medicinal products known to be associated with rhabdomyolysis (see **4.4 Special warnings and precautions for use**).

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 oxaliplatin and, in particular, patients should be advised to:

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- 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.

4.6 Fertility, pregnancy and lactation

Pregnancy Category D

Reproductive toxicity studies showed no teratogenic activity in rats or rabbits at intravenous doses up to 6 and 9 mg/m²/day respectively (1/20 of the maximum recommended clinical dose, based on body surface area). However, increased embryonic deaths, decreased 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 medicine is used during pregnancy, or if the patient becomes pregnant while receiving this medicine, the patient should be apprised of the potential hazard to the fetus. Oxaliplatin is probably toxic to the human fetus at the recommended therapeutic dose, and is therefore contraindicated during pregnancy. Oxaliplatin is not recommended in women of childbearing potential not using contraceptive measures.

Fertility

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

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

Lactation

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

4.7 Effects on ability to drive and use machines

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. See **4.8 Undesirable effects** for more information.

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4.8 Undesirable effects

Table 1: 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
Anaemia	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	-

Table 2: FU/FA ± Oxaliplatin in previously untreated patients with Advanced Colorectal Cancer, all grades and grade 3-4 toxicities - all cycles - % patients

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

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

NA: Not applicable

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%)

Infections and infestations

<i>common:</i>	Neutropenic sepsis, including fatal outcomes
<i>uncommon:</i>	Sepsis, including fatal outcomes

Haematological

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

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<i>rare:</i>	Disseminated intravascular coagulation (DIC), including fatal outcomes.	Disseminated intravascular coagulation (DIC), including fatal outcomes. Autoimmune haemolytic anaemia and thrombocytopenia.
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Leucopenia and lymphopenia have been observed.

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

- Substantially increased the incidence of neutropenia and severe neutropenia (neutrophils $<1.0 \times 10^9/L$) and
- Substantially increased the incidence of thrombocytopenia (Tables 1 and 2).

Hypersensitivity

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

Metabolism and nutrition disorders

<i>very common:</i>	Anorexia, hyperglycaemia
<i>common:</i>	Hypocalcaemia

Hypernatremia has been observed.

Nervous system disorders

	Adjuvant	Advanced
<i>very common:</i>	Sensory peripheral neuropathy, dysgeusia (taste perversion), neuritis	Primarily sensory peripheral neuropathy (e.g. loss of deep tendon reflexes, dysaesthesia, paraesthesia Lhermitte's sign), dysgeusia, neuritis
<i>common:</i>		Pharyngolaryngeal dysaesthesia, jaw spasm, abnormal tongue sensation, feeling of chest pressure
<i>rare:</i>		Dysarthria, Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES) (see 4.4 Special warnings and precautions for use).

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

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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 **4.2 Dose and method of administration**).

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

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

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

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

In the adjuvant setting of colon cancer within 6 months after treatment cessation 87% of patients had no or mild symptoms. After up to 3 years of follow-up, about 3% of patients presented either with persisting localised paresthesias of moderate intensity (2.3%) or with paresthesias that may interfere with functional activities (0.5%).

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). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see **4.4 Special warnings and precautions for use**).

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.

Psychiatric Disorders

Depression and insomnia have been observed.

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Sensory

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

Vascular disorders

	Adjuvant	Advanced
<i>very common:</i>	Epistaxis	Epistaxis
<i>common:</i>	Deep vein thrombosis, thromboembolic events (including pulmonary embolism), hypertension	Deep vein thrombosis, thromboembolic events (including pulmonary embolism), hypertension

Haemorrhage and flushing have been observed.

Respiratory, thoracic and mediastinal disorders

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

Gastrointestinal disorders

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

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis, particularly when combining oxaliplatin with fluorouracil (see **4.4 Special warnings and precautions for use**).

Rectal haemorrhage, gastro-oesophageal reflux disease and melena have been observed.

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Addition of oxaliplatin to fluorouracil and folinic acid:

- Increased the incidence of severe nausea, vomiting, diarrhoea and stomatitis in the adjuvant setting (Table 1) and substantially increased these effects in the advanced cancer setting (Table 2).

Hepatobiliary disorders

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

Skin and subcutaneous tissue disorders

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

Moderate alopecia has been reported in 2% of patients treated with oxaliplatin as a single agent; the combination of oxaliplatin and fluorouracil did not increase the incidence of alopecia observed with fluorouracil alone. Rash erythematous, skin exfoliation, hand and foot syndrome, hyperhidrosis and nail disorder have been observed.

Musculoskeletal and connective tissue disorders

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

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

Bone pain has been observed.

Renal and urinary disorders

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

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

Haematuria, dysuria and abnormal micturition frequency have been observed.

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General disorders and Administration site conditions

Pain and injection site reaction have been observed.

Immune system

	Adjuvant	Advanced
<i>very common:</i>	Infections, fever, rigors (tremors), fatigue, asthenia	Infections, fever, rigors (tremors), fatigue, asthenia

Care of Intravenous Site

Extravasation may also result in local pain and inflammation, which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein. Injection site reactions including local pain, redness, swelling and thrombosis have been reported.

Investigations

<i>Very common:</i>	Increased bilirubin, elevation of transaminases and alkaline phosphatases activities
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Hepatic enzyme increase, blood bilirubin increase, blood lactate dehydrogenase increase, weight increase (adjuvant setting), blood creatinine increase and weight decrease (metastatic setting) have been observed.

Post marketing experience with frequency not known

The following additional adverse events were observed following the marketing of oxaliplatin concentrated solution for infusion when used with various chemotherapy regimens:

Infections and infestations

Septic shock, including fatal outcomes

Blood and lymphatic system disorders

Haemolytic uremic syndrome, autoimmune pancytopenia, pancytopenia, secondary leukaemia

Immune system disorders

Delayed hypersensitivity (see **4.4 - Special warnings and precautions for use, Allergic reactions**)

Nervous system disorders

Convulsion, ischemic and haemorrhagic cerebrovascular disorder

Cardiac disorders

QT prolongation, which may lead to ventricular arrhythmias including Torsade de Pointes, which may be fatal (see **4.4 Special warnings and precautions for use**).

Acute coronary syndrome including myocardial infarction, coronary arteriospasm, and cardiac arrest.

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Cardiac arrhythmias including bradyarrhythmia, tachycardia and atrial fibrillation.

Respiratory, thoracic and mediastinal disorders

Laryngospasm, pneumonia and bronchopneumonia, including fatal outcomes

Gastrointestinal disorders

Intestinal ischaemia, including fatal outcomes (see **4.4 Special warnings and precautions for use**), ascites.

Esophagitis

Duodenal ulcer, and complications, such as duodenal ulcer haemorrhage or perforation, which can be fatal (see **4.4 Special warnings and precautions for use**).

Hepatobiliary

Focal nodular hyperplasia, hepatic failure

Skin and subcutaneous tissue disorders

Hypersensitivity vasculitis

Injury, poisoning, and procedural complications

Fall and fall-related injuries

Musculoskeletal and connective tissue disorders

Rhabdomyolysis, including fatal outcomes (see **4.4 Special warnings and precautions for use**).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents (Platinum compounds), ATC Code: L01XA03

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Mechanism of action

Oxaliplatin is an antineoplastic medicine belonging to a new class of platinum based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (DACH) and an oxalate group. Oxaliplatin is a single enantiomer, the Cis-[oxalato(trans-1-1,2-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.

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of individual active compounds have not been determined. The pharmacokinetics of ultrafiltrable platinum, representing a mixture of all unbound, active and inactive platinum species, following a two hour infusion of oxaliplatin at 130 mg/m² every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m² every two weeks for 1 to 3 cycles are as follows:

Table 3: Summary of platinum pharmacokinetic parameter estimates in ultrafiltrate following multiple doses of oxaliplatin at 85 mg/m² every two weeks or at 130 mg/m² every three weeks

Dose	C _{max} µg/mL	AUC ₀₋₄₈ µg.h/mL	AUC µg.h/mL	t _{1/2 α} h	T _{1/2 β} h	t _{1/2 γ} h	V _{ss} L	CL L/h
85 mg/m²								
Mean	0.814	4.19	4.68	0.43	16.8	391	440	17.4
SD	0.193	0.647	1.40	0.35	5.74	406	199	6.35
130 mg/m²								
Mean	1.21	8.20	11.9	0.28	16.3	273	582	10.1
SD	0.10	2.40	4.60	0.06	2.90	19.0	261	3.07

Mean AUC₀₋₄₈ and C_{max} values were determined on Cycle 3 (85 mg/m²) or Cycle 5 (130 mg/m²).

Mean AUC, V_{ss}, and CL values were determined on Cycle 1.

C_{max}, AUC, AUC₀₋₄₈, V_{ss} and CL values were determined by non-compartmental analysis.

t_{1/2 α}, t_{1/2 β} and t_{1/2 γ} were determined by compartmental analysis (Cycles 1-3 combined).

Distribution

At the end of a 2-hour infusion, 15% of the administered platinum is present in the systemic circulation, the remaining 85% being rapidly distributed into tissues or eliminated in the urine. Irreversible binding to red blood cells and plasma, results in half-lives in these matrices that are close to the natural turnover of red blood cells and serum albumin. No accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks or 130 mg/m² every three weeks and steady state was attained by cycle one in this matrix. Inter- and intra-subject variability is generally low.

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Biotransformation

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 medicine 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.

Excretion

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration. By day 5, approximately 54% of the total dose was recovered in the urine and < 3% in the faeces.

A significant decrease in clearance of ultrafilterable platinum from 17.6 ± 2.18 L/h to 9.95 ± 1.91 L/h in renal impairment (creatinine clearance 12 - 57 mL/min) was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 L. The effect of severe renal impairment on platinum clearance has not been evaluated.

CLINICAL TRIALS

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

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

EFC3313 (MOSAIC)

EFC3313 (MOSAIC) was an international, multicentre, open-label, randomised phase III study comparing two treatment regimens (FOLFOX4 versus FU/FA) as adjuvant treatment of Duke's stage B2/C colon cancer. FOLFOX4 - Day 1; Oxaliplatin 85mg/m² as 2 hour infusion, folinic acid 200 mg/m² over 2 hours, followed by a FU bolus of 400 mg/m², then a FU infusion of 600 mg/m² over 22 hours. Folinic acid and FU repeated on Day 2. 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 4). 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.

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Table 4: 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.

Treatment of Advanced Colorectal Cancer

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

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

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

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

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

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

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

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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 5: 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)
FOLFOX4 vs. IFL: P=0.0014
IROX vs. IFL: P=0.8295

Hazard Ratio (95% confidence interval)
FOLFOX4 vs. IFL: 0.74 (0.61-0.89)
IROX vs. IFL: 1.02 (0.85-1.23)

Table 6: 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)
FOLFOX4 vs. IFL: P< 0.0001
IROX vs. IFL: P=0.0252

Hazard Ratio (95% confidence interval)
FOLFOX4 vs. IFL: 0.65 (0.53-0.80)
IROX vs. IFL: 0.79 (0.65-0.97)

Table 7: 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

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Table 8: Number of deaths - treated patients N (%)

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

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

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

EFC 2964 was an open label multicentre study in which patients whose disease had progressed on one of two fluorouracil/folinic acid regimens continued on the same fluorouracil/folinic acid regimen with the addition of oxaliplatin 85 mg/m² two weekly. The two study regimens were;

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

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

The results were as shown in Table 10.

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

Efficacy results are shown in Table 11.

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Table 9

EFC 2962	FU/FA + Oxp n = 210	FU/FA n = 210	Difference
Objective Response Rate ¹ % [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) ² [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)

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

Table 10

EFC 2964	Regimen 1 n = 57	Regimen 2 n = 40	All Treated Patients n = 97
Confirmed Responses n (%) [95% CI]			
Expert assessment	13 (23%) [13-36]	7 (18%) [7-33]	20 (21%) [13-30]
Investigator assessment	11 (19%) [10-32]	10 (25%) [13-41]	21 (22%) [14-31]
Median progression free survival (months) [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]

Table 11

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

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

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections

6.2 Incompatibilities

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 medicines.

6.3 Shelf life

36 months from the date of manufacture stored at or below 25 °C.

If unopened vial is frozen, do not freeze for longer than 2 days.

48 hours diluted in glucose 5 % injection stored at 2° - 8° C (Refrigerate. Do not freeze).

12 hours diluted in glucose 5 % injection stored at 25 ° C (Do not freeze).

6.4 Special precautions for storage

Unopened vial: Store below 25°C. If frozen, do not freeze for longer than 2 days.

For storage conditions after dilution of the medicine, see section 6.3.

6.5 Nature and contents of container

50 mg/10 mL - 1 vial with 10 mL concentrate (Type I clear glass) with chlorobutyl elastomer stopper.

100 mg/20 mL - 1 vial with 20 mL concentrate (Type I clear glass) with chlorobutyl elastomer stopper.

Pack size: 1 vial per box

6.6 Special precautions for disposal and other handling

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.

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Preparation of infusion solution

Dilution before infusion

Withdraw the required amount of concentrate solution from the vial(s) and then dilute with 250 mL to 500 mL of 5% glucose injection to give an oxaliplatin concentration between 0.2 mg/mL and 2 mg/mL; concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.

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 12 hours at 25°C.

From a microbiological and chemical 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. Inspect visually prior to use. Only clear solutions without particles should be used.

The product is for single use in one patient only. Discard any residue.

NEVER use sodium chloride solution for either reconstitution or dilution.

Infusion

The administration of oxaliplatin does not require prehydration. Oxaliplatin diluted in 250 to 500 mL of a glucose 5% injection must be infused either by central venous line or peripheral vein over 2 to 6 hours. When oxaliplatin is administered with fluorouracil, the oxaliplatin infusion should precede that of fluorouracil.

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

7. MEDICINE SCHEDULE

Prescription medicine

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8. SPONSOR

Alchemy Health Limited
120 Ngapuhi Road
Remuera
Auckland 1050
NEW ZEALAND

Medical enquiries: 0508 ALCHEMY (0508 252436)

9. DATE OF FIRST APPROVAL

15 December 2022

10. DATE OF REVISION OF THE TEXT

11 September 2023

Summary Table of Changes

Section changed	Summary of new information
6.3	Shelf life increased from '30 months from the date of manufacture stored at or below 25 °C' to '36 months from the date of manufacture stored at or below 25 °C'.