

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Oxaliplatin Injection safely and effectively. See full prescribing information for Oxaliplatin Injection.

Oxaliplatin Injection, solution for intravenous use

Only

Initial U.S. Approval: 2002

WARNING: ANAPHYLACTIC REACTIONS

See full prescribing information for complete boxed warning. Anaphylactic reactions to Oxaliplatin Injection have been reported, and may occur within minutes of Oxaliplatin Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms. (5.1)

INDICATIONS AND USAGE

Oxaliplatin Injection is a platinum-based drug used in combination with infusional 5-fluorouracil (leucovorin), which is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.
- treatment of advanced colorectal cancer. (1)

DOSE AND ADMINISTRATION

Administer Oxaliplatin Injection in combination with 5-fluorouracil/leucovorin every 2 weeks (2.1).

Day 1: Oxaliplatin Injection 85 mg/m² intravenous infusion in 250-500 mL 5% Dextrose Injection, USP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose Injection, USP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Day 2: Leucovorin 200 mg/m² intravenous infusion over 120 minutes followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Reduce the dose of Oxaliplatin Injection to 75 mg/m² (adjunct setting) or 65 mg/m² (advanced colorectal cancer) (2.2).

FULL PRESCRIBING INFORMATION: CONTENTS

WARNING

1 INDICATIONS AND USAGE

2 DOSE AND ADMINISTRATION

2.1 Dosage

2.2 Dose Modification Recommendations

2.3 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions

5.2 Neurotoxicity

5.3 Pulmonary Toxicity

5.4 Hepatotoxicity

5.5 Use in Pregnancy

5.6 Recommended Laboratory Tests

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Nursing Mothers

8.3 Pediatric Use

- if there are persistent grade 2 neurosensory events that do not resolve.
- after recovery from grade 3/4 gastrointestinal toxicities (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. Delay next dose until neutrophils $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.
- Discontinue Oxaliplatin Injection if there are persistent Grade 2 neurosensory events. (2.2)
- Never reconstitute or prepare final dilution with a sodium chloride solution or other chloride-containing solutions. (2.3)

ADVERSE REACTIONS

Single use vials of 50 mg or 100 mg oxaliplatin as a sterile, preservative-free aqueous solution at a concentration of 5 mg/mL (5).

CONTRAINDICATIONS

Known allergy to Oxaliplatin Injection or other platinum compounds. (4, 5.1)

WARNINGS AND PRECAUTIONS

- Allergic Reactions: Monitor for development of rash, urticaria, erythema, pruritus, bronchospasm, and hypotension. (5.1)
- Neurotoxicity: Reduce the dose or discontinue Oxaliplatin Injection if necessary. (5.2)
- Pulmonary Toxicity: May need to discontinue Oxaliplatin Injection until interstitial lung disease or pulmonary fibrosis are excluded. (5.3)
- Hepatotoxicity: Monitor liver function tests. (5.4)
- Pregnancy: Fetal harm can occur when administered to a pregnant woman. Women should be apprised of the potential harm to the fetus. (5.5, 8.1)

ADVERSE REACTIONS

Most common adverse reactions (incidence $> 40\%$) were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. Other adverse reactions, including serious adverse reactions, have been reported. (8.1)

To report SUSPECTED ADVERSE REACTIONS, contact Hospira Inc. at 1-800-441-4100, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

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ADVERSE REACTIONS

8.5 Geriatric Use

8.6 Patients with Renal Impairment

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

14.1 Combination Adjuvant Therapy with Oxaliplatin Injection and Infusional 5-Fluorouracil/Leucovorin in Patients with Colon Cancer

14.2 Combination Therapy with Oxaliplatin Injection and 5-Fluorouracil/Leucovorin in Patients Previously Untreated for Advanced Colorectal Cancer

14.3 Combination Therapy with Oxaliplatin Injection and 5-Fluorouracil/Leucovorin in Previously Treated Patients with Advanced Colorectal Cancer

14.4 CLINICAL STUDIES

14.4.1 Combination Adjuvant Therapy with Oxaliplatin Injection and Infusional 5-Fluorouracil/Leucovorin in Patients with Colon Cancer

14.4.2 Combination Therapy with Oxaliplatin Injection and 5-Fluorouracil/Leucovorin in Patients Previously Untreated for Advanced Colorectal Cancer

14.4.3 Combination Therapy with Oxaliplatin Injection and 5-Fluorouracil/Leucovorin in Previously Treated Patients with Advanced Colorectal Cancer

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

16.2 Storage

16.3 Handling and Disposal

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

17.2 FDA-Approved Patient Labeling

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLACTIC REACTIONS

Anaphylactic reactions to Oxaliplatin Injection have been reported, and may occur within minutes of Oxaliplatin Injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis (see Warnings and Precautions (5.1)).

1 INDICATIONS AND USAGE

Oxaliplatin Injection is indicated in combination with infusional 5-fluorouracil/leucovorin, is indicated for:

- adjuvant treatment of stage III colon cancer in patients who have undergone complete resection of the primary tumor.
- treatment of advanced colorectal cancer.

2 DOSE AND ADMINISTRATION

Oxaliplatin Injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate diagnostic and treatment facilities are readily available.

2.1 Dosage

Administer Oxaliplatin Injection in combination with 5-fluorouracil/leucovorin every 2 weeks. For advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles).

Day 1: Oxaliplatin Injection 85 mg/m² intravenous infusion in 250-500 mL 5% Dextrose Injection, USP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose Injection, USP both given over 120 minutes at the same time in separate bags using a Y-line, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

Day 2: Leucovorin 200 mg/m² intravenous infusion over 120 minutes, followed by 5-fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5-fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

2.2 Dose Modification Recommendations

The administration of Oxaliplatin Injection does not require prophylaxis. Premedication with antemetics, including 5-HT₃ blockers with or without dexamethasone, is recommended.

For information on 5-fluorouracil and leucovorin, see the respective package inserts.

2.3 Dose Modification Recommendations

Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests (see Warnings and Precautions (5.6)). Prolongation of infusion time for Oxaliplatin Injection from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5-fluorouracil and leucovorin do not need to be changed.

Advjuant Therapy in Patients with Stage III Colon Cancer

Neurotoxicity and other toxicities were graded using the NCI CTC scale version 1 (see Warnings and Precautions (5.2)).

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin Injection to 75 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The infusional 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin Injection to 75 mg/m² and infusional 5-fluorouracil to 300 mg/m² bolus and 500 mg/m² 22-hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

Neurotoxicity was graded using a study-specific neurotoxicity scale (see Warnings and Precautions (5.2)). Other toxicities were graded by the NCI CTC, Version 2.0.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin Injection to 65 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-fluorouracil/leucovorin regimen need not be altered.

A dose reduction of Oxaliplatin Injection to 75 mg/m² and infusional 5-fluorouracil to 300 mg/m² bolus and 500 mg/m² 22-hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils $\geq 1.5 \times 10^9/L$ and platelets $\geq 75 \times 10^9/L$.

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer

Neurotoxicity was graded using a study-specific neurotoxicity scale (see Warnings and Precautions (5.2)). Other toxicities were graded by the NCI CTC, Version 2.0.

For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin Injection to 65 mg/m² should be considered. For patients with persistent Grade 3 neurosensory events, discontinuing therapy should be considered. The 5-fluorouracil/leucovorin regimen need not be altered.

An acute syndrome of pharyngolaryngeal dysphagia seen in 1 to 2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previously treated patients, is characterized by subjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm (no stridor or wheezing). Ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin Injection because cold temperature can exacerbate acute neurological symptoms.

A persistent (> 14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hyposthesias, but may also include deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving Oxaliplatin Injection with 5-fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 1 persistent neuropathy progressed from grade 1 or 2 to grade 2. These symptoms may improve in some patients upon discontinuation of Oxaliplatin Injection.

In the adjuvant colon cancer trial, neuropathy was graded using a prestudied module derived from the Neuro-Sensory section of the National Cancer Institute Common Toxicity Criteria (NCI CTC) scale, Version 1, as follows:

Table 1 - NCI CTC Grading for Neuropathy in Adjuvant Therapy

Grade	No change or none	Definition
Grade 0		Mild paresthesias, loss of deep tendon reflexes
Grade 1		Mild or moderate objective sensory loss, moderate paresthesias
Grade 2		Severe objective sensory loss or paresthesias that interfere with function
Grade 3		Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the Oxaliplatin Injection combination with a frequency of 52% (all grades) and 13% (grade 3). At the 28-day follow-up after the last treatment cycle, 60% of all patients had grade 1 (Grade 1=40%, Grade 2=16%, Grade 3=5%) peripheral sensory neuropathy decreasing to 39% at 6 months follow-up (Grade 1=31%, Grade 2=7%, Grade 3=1%) and 21% at 18 months follow-up (Grade 1=17%, Grade 2=3%, Grade 3=1%).

In the advanced colorectal cancer studies, neuropathy was graded using a study-specific neurotoxicity scale, which was different from the NCI CTC scale, Version 2.0 (see below).

Table 2 - Grading Scale for Paresthesias/Dysesthesias in Advanced Colorectal Cancer Patients

Grade	Definition
Grade 1	Resolved and did not interfere with functioning
Grade 2	Interfered with function but not daily activities
Grade 3	Pain or functional impairment that interfered with daily activities
Grade 4	Persistent impairment that is disabling or life-threatening

Overall, neuropathy was reported in patients previously untreated for advanced colorectal cancer in 82% (all grades) and 19% (grade 3/4), and in the previously treated patients in 74% (all grades) and 7% (grade 3/4) events. Information regarding reversibility of neuropathy was not available from the trial for patients who had not been previously treated for colorectal cancer.

5.3 Pulmonary Toxicity

Oxaliplatin Injection has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the Oxaliplatin Injection plus infusional 5-fluorouracil/leucovorin combination arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5-fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the Oxaliplatin Injection combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the Oxaliplatin Injection plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/leucovorin arm of unknown duration of follow-up.

Patients with unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, Oxaliplatin Injection should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

5.4 Hepatotoxicity

Hepatotoxicity as evidenced in the adjuvant study, by increases in transaminases (57% $\geq 34\%$) and alkaline phosphatase (46% $\geq 20\%$) was observed more commonly in the Oxaliplatin Injection combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, periportal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension. Such changes can be explained by liver metastases (see Clinical Trials Experience (6.1)).

5.5 Use in Pregnancy

Pregnancy Category D

Oxaliplatin Injection may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin Injection in pregnant women. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Oxaliplatin Injection (See Use in Specific Populations (8.1)).

5.6 Recommended Laboratory Tests

Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALP, AST, bilirubin and creatinine) is recommended before each Oxaliplatin Injection cycle (see Dosage and Administration (2)).

There have been reports while on study and from post-marketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in patients who received Oxaliplatin Injection plus 5-fluorouracil/leucovorin while on anticoagulants. Patients receiving Oxaliplatin Injection plus 5-fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities and hepatotoxicities can occur (see Warnings and Precautions (5.1)).

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with advanced colorectal cancer have been treated in clinical studies with Oxaliplatin Injection. The most common adverse reactions in patients with stage II or III colon cancer receiving adjuvant therapy were peripheral sensory neuropathy, neutropenia, thrombocytopenia, anemia, nausea, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea (see Warnings and Precautions (5)).

Combination Adjuvant Therapy with Oxaliplatin Injection and Infusional 5-Fluorouracil/Leucovorin in Patients with Colon Cancer

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with Oxaliplatin Injection in combination with infusional 5-fluorouracil/leucovorin (see Clinical Studies (14.1)). The incidence of grade 3 or 4 adverse reactions was 70% on the Oxaliplatin Injection combination arm, and 51% on the infusional 5-fluorouracil/leucovorin arm. The incidence of grade 3 or 4 events in the Oxaliplatin Injection combination arm for events with overall incidences $\geq 5\%$ and for grade 3/4 events with incidences $\geq 1\%$.

Table 3 - Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	Oxaliplatin + 5-FU/LV (N=1108)	Irinotecan + 5-FU/LV (N=256)	Oxaliplatin + Irinotecan (N=258)
All Grades (%)	71	6	7
Grade 3/4 (%)	16	0	0
All Grades (%)	99	82	98
Grade 3/4 (%)	70	70	99

Table 4 - Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 5 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 6 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 7 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 8 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 9 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 10 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Adverse Reaction (WHO/Pre)	All Grades (%)	Grade 3/4 (%)
Allergic/Immunology	12	2
Cardiovascular	11	3
Hypersensitivity	6	5
Thrombosis	5	3
Hypotension	5	3

Table 11 - Adverse Reactions Reported in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial (< 5% of all patients and with < 1% NCI Grade 3/4 events)

Table 13 – Adverse Hepatic – Clinical Chemistry Abnormalities in Patients Previously Untreated for Advanced Colorectal Cancer (≥ 5% of patients)

Clinical Chemistry	Oxaliplatin + 5-FU/FLV (N=259)		irinotecan + 5-FU/FLV (N=256)		Oxaliplatin + irinotecan (N=258)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
ALT (SGPT-ALAT)	6	1	2	0	5	2
AST (SGOT-ASAT)	17	1	2	1	11	1
Alkaline Phosphatase	16	0	8	0	14	2
Total Bilirubin	6	1	3	1	3	2

Table 14 – Adverse Hepatic – Clinical Chemistry Abnormalities in Previously Treated Patients (≥ 5% of patients)

Clinical Chemistry	5-FU/FLV (N=142)		Oxaliplatin (N=153)		5-FU/FLV (N=150)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
ALT (SGPT-ALAT)	28	3	36	1	31	0
AST (SGOT-ASAT)	39	2	54	4	47	0
Total Bilirubin	22	6	13	5	13	1

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.7 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean plasma pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mg/L, AUC_{0-24} of 7.52 ± 5.07 mg·h/mL, and AUC_{0-48} of 15.7 mg·h/mL. In the inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean plasma pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mg/L, AUC_{0-24} of 7.52 ± 5.07 mg·h/mL, and AUC_{0-48} of 15.7 mg·h/mL. In the inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean plasma pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mg/L, AUC_{0-24} of 7.52 ± 5.07 mg·h/mL, and AUC_{0-48} of 15.7 mg·h/mL.

The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population pharmacokinetic analysis was 4.7 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean plasma pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mg/L, AUC_{0-24} of 7.52 ± 5.07 mg·h/mL, and AUC_{0-48} of 15.7 mg·h/mL. In the inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean plasma pharmacokinetic parameters in ultrafiltrate were C_{max} of 0.75 ± 0.24 mg/L, AUC_{0-24} of 7.52 ± 5.07 mg·h/mL, and AUC_{0-48} of 15.7 mg·h/mL.

8.5 Geriatric Use
No significant effect of age on the clearance of ultrafiltrable platinum has been observed. In the adjuvant therapy for cancer randomized clinical trial, *See Clinical Studies (14)* 723 patients treated with Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin were <65 years and 400 patients were ≥ 65 years. A descriptive subgroup analysis demonstrated that the improvement in DFS for the Oxaliplatin Injection combination arm compared to the infusional 5-fluorouracil/leucovorin alone arm appeared to be maintained across genders. The effect of Oxaliplatin Injection in patients ≥ 65 years of age was not conclusive. Insufficient subgroup sizes prevented analysis by race. Patients ≥ 65 years of age receiving the Oxaliplatin Injection combination therapy received more grade 3-4 granulocytopenia than patients < 65 years of age (46% versus 39%).

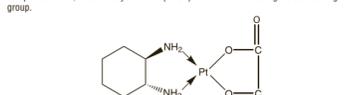
In the previously untreated for advanced colorectal cancer randomized clinical trial *See Clinical Studies (14)* of Oxaliplatin Injection, 160 patients treated with Oxaliplatin Injection and 5-fluorouracil/leucovorin were <65 years and 99 patients were ≥ 65 years. The same efficacy improvements in response rate, time to tumor progression, and overall survival were observed in the ≥ 65 years old patients as in the overall study population. In the previously treated for advanced colorectal cancer randomized clinical trial *See Clinical Studies (14)* of Oxaliplatin Injection, 95 patients treated with Oxaliplatin Injection and 5-fluorouracil/leucovorin were <65 years and 55 patients were ≥ 65 years. The rates of overall adverse reactions, including grade 3 and 4 events, were similar across and within arms in the different age groups in all studies. The incidence of diarrhea, dehydration, neutropenia, leukopenia, and thrombocytopenia were similar in patients ≥ 65 years old. No adjustment to starting dose was required in patients ≥ 65 years old.

8.6 Patients with Renal Impairment
The safety and effectiveness of the combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin in patients with renal impairment has not been established. The combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin should be used with caution in patients with preexisting renal impairment since the primary route of platinum elimination is renal. Clearance of ultrafiltrable platinum is decreased voluntarily from a population of patients with renal impairment. A pharmacodynamic relationship between plasma ultrafiltrate levels and clinical safety and effectiveness has not been established. *See Adverse Reactions (6.1) and Clinical Pharmacology (12.3)*.

10 OVERDOSEAGE
There is no known antidote for Oxaliplatin Injection overdose. In addition to thrombocytopenia, the anticipated complications of an Oxaliplatin Injection overdose include hypersensitivity reactions, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity. Several cases of overdose have been reported with Oxaliplatin Injection. Adverse reactions observed were Grade 4 thrombocytopenia (< 25,000/mm³) without any bleeding, anemia, sensory neuropathy such as paresthesia, dyesthesia, laryngospasm and facial muscle spasms, gastrointestinal toxicity such as nausea, vomiting, stomatitis, flatulence, abdominal cramping and Grade 4 intestinal obstruction. Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death.

Patients suspected of receiving an overdose should be monitored, and supportive treatment should be administered. The maximum dose of oxaliplatin that has been administered in a single infusion is 825 mg.

11 DESCRIPTION
Oxaliplatin Injection is an antineoplastic agent with the molecular formula C₁₂H₁₆N₂O₇PI and the chemical name of (1R,2R)-2-(2-cyanoethoxy)ethane-1,1'-diyl bis(oxalate(2-)). Oxaliplatin is an oxaloplatin complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.



The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone. Oxaliplatin Injection is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free solution. The solution is clear, colorless to light yellow, and has a pH of 4.0. Oxaliplatin is a complex of platinum, 1,2-diaminocyclohexane (DACH) and with an oxalate ligand as a leaving group.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the diablo oxalate ligand. Several transient reactive species are formed, including monoquo and diaquo DACH platinum, which covalently bind with macromolecules. Both monoquo and diaquo DACH platinum are cytotoxic. Oxalate anions are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription, resulting in cell cycle arrest. Women of childbearing potential should be advised to avoid becoming pregnant and use effective contraception while receiving treatment with Oxaliplatin Injection.

12.2 Pharmacokinetics
The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafiltrable platinum levels following oxaliplatin administration is biphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$: 0.43 hours and $t_{1/2\beta}$: 16.8 hours) and a long terminal elimination phase ($t_{1/2\gamma}$: 391 hours). Pharmacokinetic parameters obtained after a single 2-hour intravenous infusion of Oxaliplatin Injection at a dose of 85 mg/m² expressed as ultrafiltrable platinum were C_{max} of 0.814 mg/mL and volume of distribution of 440 L. Interpatient and inpatient variability in ultrafiltrable platinum exposure (AUC_{0-24}) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between plasma ultrafiltrate levels and clinical safety and effectiveness has not been established.

12.3 Distribution
At the end of a 2-hour infusion of Oxaliplatin Injection, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding partners are albumin and gamma-globulins. Platinum also binds reversibly and accumulates (approximately 2-fold) in erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m² every two weeks.

12.4 Excretion
Oxaliplatin undergoes rapid and extensive nonenzymatic biotransformation. There is no evidence of cytochrome P450-mediated metabolism in vitro. Up to 17 platinum-containing derivatives have been observed in plasma ultrafiltrate samples from patients, including several cytotoxic species (monoquo DACH platinum, dichloro DACH platinum, and monoquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species.

12.5 Elimination
The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of Oxaliplatin Injection at 160 mg/m² for a maximum of 12 cycles, in a separate study, excretion of ultrafiltrable platinum was 100%. Platinum was cleared from plasma at a rate (10–17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR: 7.5 L/h). There was no significant effect of gender on the clearance of ultrafiltrable platinum. The renal clearance of ultrafiltrable platinum is significantly correlated with GFR.

Pharmacokinetics in Special Populations
Renal Impairment
The AUC_{0-24} of platinum in the plasma ultrafiltrate increases as renal function decreases. The AUC_{0-24} of platinum in patients with mild (creatinine clearance, CL_{cr} ≥ 80 mL/min), moderate (CL_{cr} 30 to 80 mL/min) and severe renal (CL_{cr} < 30 mL/min) impairment was increased by 1.5, 2.0, and 2.5-fold, respectively, compared to patients with normal renal function (CL_{cr} ≥ 80 mL/min). *See Adverse Reactions (6.1), Drug Interactions (7) and Use in Specific Populations (8.6)*.

Drug-Drug Interactions
No pharmacokinetic interaction between 85 mg/m² of Oxaliplatin Injection and infusional 5-fluorouracil has been observed in patients treated every 2 weeks, but increases of 5-fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² of Oxaliplatin Injection administered every 3 weeks. *In vitro*, platinum was not displaced from plasma proteins by the following compounds: erythronium, salicylate, valproic acid, griseofulvin, and pivalate. *In vivo*, oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes. No P450-mediated drug-drug interactions are therefore anticipated in patients. Since platinum-containing species are eliminated primarily through the kidney, clearance of these products may be decreased by co-administration of potentially nephrotoxic compounds, although this has not been specifically studied.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin. Oxaliplatin was not mutagenic to bacteria (Ames test) but was potent to mammalian cells in *in vitro* (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both *in vitro* (chromosome 12 aberration in human lymphocytes) and *in vivo* (mouse bone marrow micronucleus assay).

In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days every 21 days for a total of three cycles prior to mating with females that received two cycles of oxaliplatin on the same schedule. A dose of 2 mg/kg/day (less than one-seventh the recommended human dose on a body surface area basis) did not affect pregnancy rate, but caused developmental mortality (increased early resorptions, decreased live fetuses, decreased live births) and delayed growth (decreased fetal weight).

Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level was not identified. This daily dose is approximately one-sixth of the recommended human dose on a body surface area basis.

14 CLINICAL STUDIES
14.1 Combination Adjuvant Therapy with Oxaliplatin Injection and Infusional 5-Fluorouracil/Leucovorin in Patients with Colon Cancer
An international, multicenter, randomized study compared the efficacy and evaluated the safety of Oxaliplatin Injection in combination with an infusional schedule of 5-fluorouracil/leucovorin to infusional 5-fluorouracil/leucovorin alone, in patients with stage II (Dukes' B2) or III (Dukes' C) colon cancer who had undergone complete resection of the primary tumor. The primary objective of the study was to compare the 5-year disease-free survival (DFS) in patients receiving Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin combination to infusional 5-fluorouracil/leucovorin alone. Patients were to be treated for a total of 6 months (i.e., 12 cycles). A total of 2246 patients were randomized: 1123 patients per study arm. Patients in the study had to be between 18 and 75 years of age, have histologically proven stage II (T₁₋₃, N0, M0; Dukes' B2) or III (T₄, N0, M0; Dukes' C) colon carcinoma with the inferior pole of the tumor above the peritoneal reflection, i.e., ≥ 15 cm from the anal margin and undergone (within 7 weeks prior to randomization) complete resection of the primary tumor without gross or microscopic evidence of residual disease. Patients had to have had no prior chemotherapy, immunotherapy or radiotherapy, and have an ECOG performance status of 0, 1, or 2 (KPS ≥ 60%), absolute neutrophil count (ANC) > 1.5x10⁹/L, platelets ≥ 100x10⁹/L, serum creatinine ≤ 1.25 x ULN, total bilirubin < 2 x ULN, AST/ALT < 2 x ULN and carcino-embryonic antigen (CEA) < 10 ng/mL. Patients with preexisting neuropathy (NCI grade ≥ 1) were ineligible for this trial.

The following table shows the dosing regimens for the two arms of the study.

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/FLV (FOLFFOX4) (N=1123)	Day 1: Oxaliplatin: 85 mg/m ² (2-hour infusion) + LV 200 mg/m ² (2-hour infusion), followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion)	every 2 weeks 12 cycles
5-FU/FLV (N=1123)	Day 1: LV 200 mg/m ² (2-hour infusion), followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion)	every 2 weeks 12 cycles

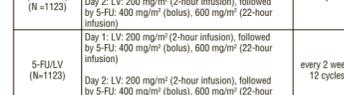


Figure 2 – DFS Kaplan-Meier curves by treatment arm (cutoff: 1 June 2006) – ITT population

The following tables show the baseline characteristics and dosing of the patient population entered into this study. The baseline characteristics were well balanced between arms.

Parameter	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
Sex: Male (%)	56.1	52.4
Female (%)	43.9	47.6
Median age (years)	61.0	60.0
<65 years of age (%)	64.6	66.2
≥65 years of age (%)	35.4	33.8

Primary site	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
Colon including cecum	54.6	54.4
Sigmoid	31.9	33.8
Recto sigmoid	12.9	10.9
Other including rectum	0.5	0.9

Stage at Randomization (%)	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
II (T=3-4 N=0, M=0)	40.1	39.9
III (T=any, N=1-2, M=0)	59.6	59.3
IV (T=any, N=any, M=1)	0.4	0.8

Staging – T (%)	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
T1	0.5	0.7
T2	45.0	43.8
T3	42.0	43.9
T4	19.0	18.5

Staging – N (%)	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
N0	40.2	39.9
N1	39.4	39.4
N2	20.4	20.7
N3	0.4	0.8

Parameter	Oxaliplatin + Infusional 5-FU/FLV (N=1108)	Infusional 5-FU/FLV (N=1111)
Median Relative Dose Intensity (%)	84.4	97.7
Oxaliplatin Injection	80	N/A
Median Number of Cycles	12.5	12
Median Number of cycles with Oxaliplatin Injection	11	N/A

The following table and figures summarize the disease-free survival (DFS) results in the overall randomized population and in patients with stage II and III disease based on an ITT analysis. The median duration of follow-up was approximately 77 months.

Parameter	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
N	1123	1123
Number of events – relapse or death (%)	304 (27.1)	300 (26.7)
Disease-free survival % [95% CI]	73.3 [70.7, 76.0]	67.4 [64.6, 70.2]
Hazard ratio [95% CI] **	0.80 [0.68, 0.93]	
Stratified Logrank test	p=0.003	

Parameter	Stage III (Dukes' C) (N=672)	675
N	672	675
Number of events – relapse or death (%)	226 (33.6)	271 (40.1)
Disease-free survival % [95% CI]	66.4 [62.7, 70.0]	58.9 [55.2, 62.7]
Hazard ratio [95% CI] **	0.78 [0.65, 0.93]	
Logrank test	p=0.005	

Parameter	Stage II (Dukes' B2) (N=451)	448
N	451	448
Number of events – relapse or death (%)	78 (17.3)	89 (19.9)
Disease-free survival % [95% CI]	83.7 [80.2, 87.1]	79.9 [76.2, 83.7]
Hazard ratio [95% CI] **	0.84 [0.62, 1.14]	
Logrank test	p=0.258	

Data cut off for disease free survival 1 June 2006
**Disease-free survival at 5 years
** A hazard ratio of less than 1.00 favors Oxaliplatin Injection + Infusional 5-fluorouracil/leucovorin.

In the overall and stage III colon cancer populations DFS was statistically significantly improved in the Oxaliplatin Injection combination arm compared to infusional 5-fluorouracil/leucovorin alone. However, a statistically significant improvement in DFS was not noted in Stage II patients.

Figure 2 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone for the overall population (ITT analysis). Figure 3 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone in Stage II patients.



Figure 3 – DFS Kaplan-Meier curves by treatment arm in Stage II patients (cutoff: 1 June 2006) – ITT population

The following table summarizes the overall survival (OS) results in the overall randomized population and in patients with stage II and III disease based on an ITT analysis.

Parameter	Oxaliplatin + Infusional 5-FU/FLV (N=1123)	Infusional 5-FU/FLV (N=1123)
N	1123	1123
Number of death events (%)	245 (21.8)	283 (25.2)
Hazard ratio [95% CI]	0.84 [0.71, 1.00]	

Parameter	Stage III (Dukes' C) (N=672)	675
N	672	675
Number of death events (%)	182 (27.1)	220 (32.6)
Hazard ratio [95% CI]	0.80 [0.65, 0.97]	

Parameter	Stage II (Dukes' B2) (N=451)	448
N	451	448
Number of death events (%)	63 (14.0)	63 (14.1)
Hazard ratio [95% CI]	1.00 [0.70, 1.41]	

** A hazard ratio of less than 1.00 favors Oxaliplatin Injection + Infusional 5-fluorouracil/leucovorin.
**Based on all patients with measurable disease at baseline
The numbers in the response rate and TTP analysis are based on unblinded investigator assessment.

Figure 4 illustrates the Kaplan-Meier survival curves for the comparison of Oxaliplatin Injection and 5-fluorouracil/leucovorin combination and Oxaliplatin Injection plus irinotecan to irinotecan plus 5-fluorouracil/leucovorin.

Arm	5-FU/FLV (N=151)	Oxaliplatin + 5-FU/FLV (N=156)	Oxaliplatin + Irinotecan + 5-FU/FLV (N=264)
No. of Progressors	74	101	50
No. of patients with no radiological evaluation beyond baseline	22 (15%)	16 (10%)	17 (6%)
Median TTP (months)	0	2.7	1.6
95% CI	18-3.0	1.4-2.7	4.2-6.1

*This is not an ITT analysis. Events were limited to radiographic disease progression documented by independent review of radiographs. Clinical progression was not included in this analysis, and 18% of patients were excluded from the analysis based on unavailability of the radiographs for independent review.

At the time of the interim analysis 49% of the radiographic progression events had occurred. In this interim analysis an estimated 2-month increase in median time to radiographic progression was observed compared to 5-fluorouracil/leucovorin alone. Of the 13 patients who had tumor response to the combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin, 5 were female and 8 were male, and responders included patients < 65 years old and ≥ 65 years old. The small number of non-Caucasian participants made efficacy analyses in these populations uninterpretable.

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16 HOW SUPPLIED/STORAGE AND HANDLING
16.1 New Sampling Occupational Exposure to Hazardous Drugs. OSHA, 1999. http://www.osha-slc.gov/otsa/otm/volm_vt_m_vx_2.html
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16.2 HOW SUPPLIED/STORAGE AND HANDLING
Oxaliplatin Injection is supplied in clear, glass, single use vials containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free aqueous solution at a concentration of 5 mg/mL. Tactic Acid, NF. Water for Injection, USP and Sodium Hydroxide, NF are used as inactive ingredients. Each vial contains 50 mg of oxaliplatin and 100 mg of sodium chloride. NDC 61703-383-18: 50 mg/10 mL, single use vial individually packaged in a carton. NDC 61703-383-22: 100 mg/20 mL, single use vial individually packaged in a carton.

Table 20 – Dosing Regimens in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin + 5-FU/FLV (FOLFFOX4) (N=264)	Day 1: Oxaliplatin: 85 mg/m ² (2-hour infusion) + LV 200 mg/m ² (2-hour infusion), followed by 5-FU: 400 mg/m ² (bolus), 600 mg/m ² (22-hour infusion)	every 2 weeks
irinotecan + 5-FU/FLV (IRI) (N=264)	Day 1: irinotecan 125 mg/m ² as a 90-min infusion + LV 200 mg/m ² as a 15-min infusion intravenously weekly, followed by 5-FU 500 mg/m ² intravenous bolus weekly x 4	every 6 weeks
Oxaliplatin + irinotec		