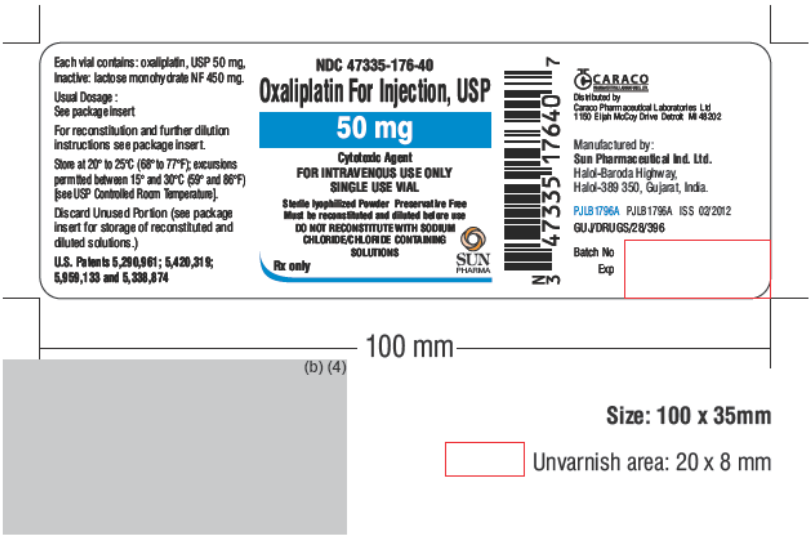

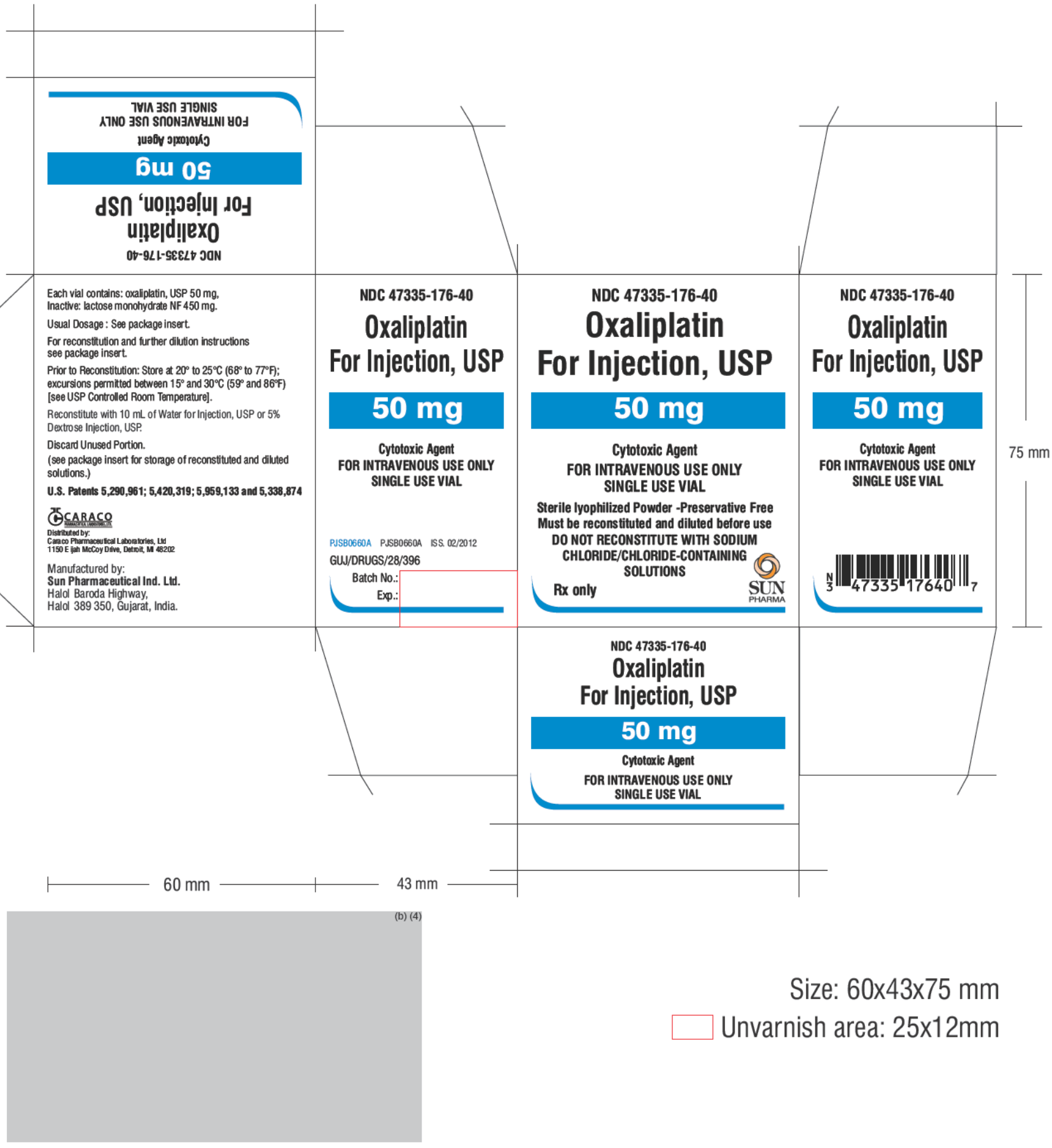

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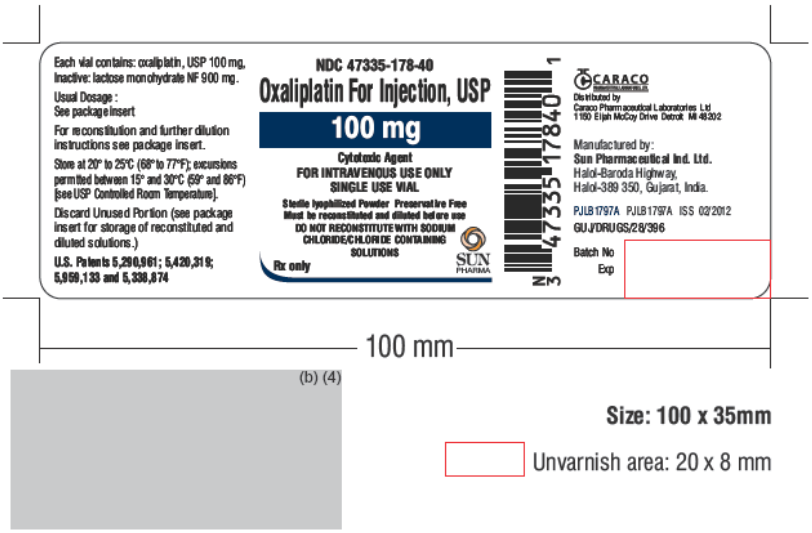

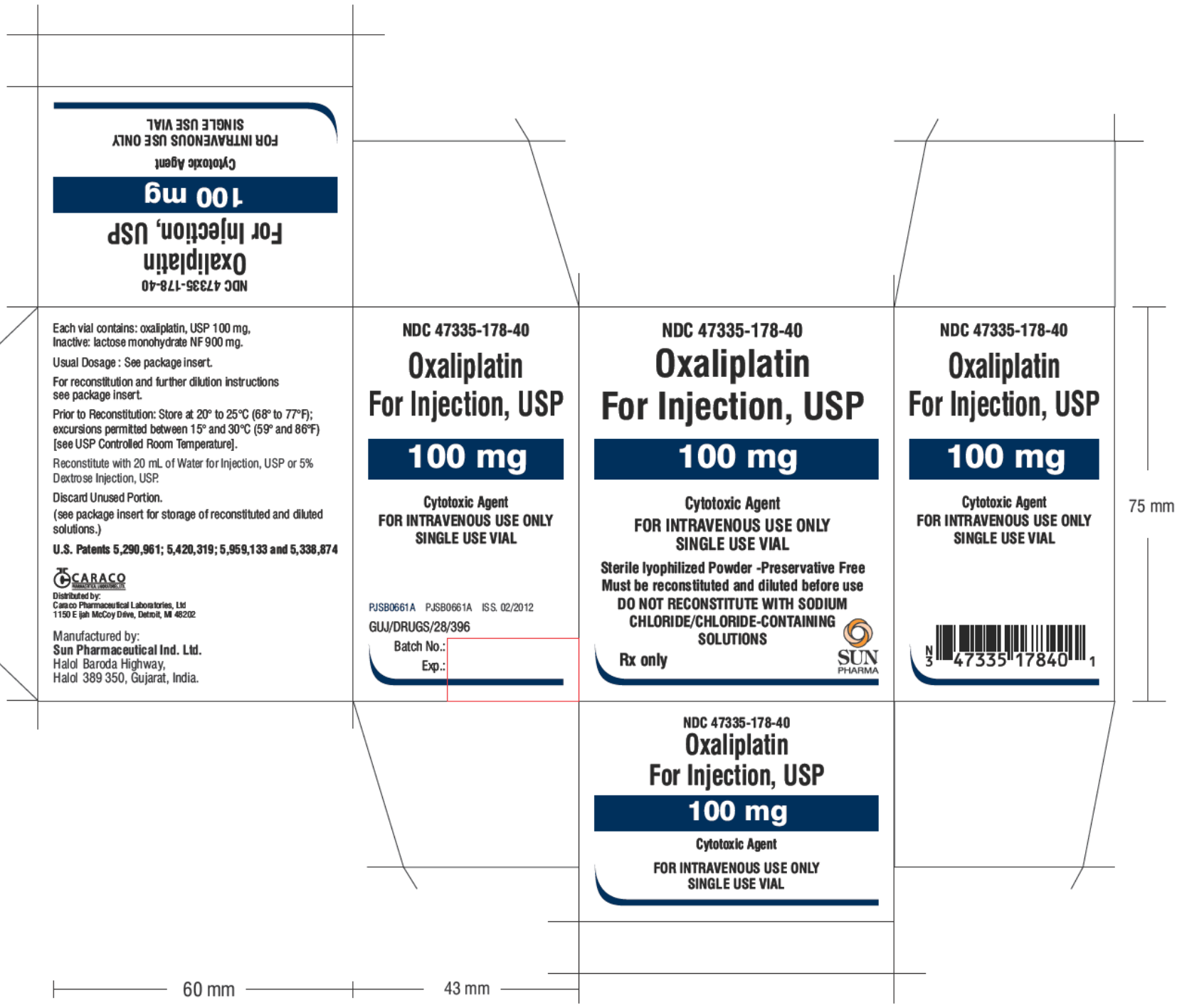

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47335-PJPI0325A
Oxaliplatin for Injection, USP
for intravenous use
50 mg and 100 mg

Do not Print in grey area

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Oxaliplatin for Injection, USP
for intravenous use
Initial U.S. Approval: 2002

WARNING: ANAPHYLACTIC REACTIONS

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

RECENT MAJOR CHANGES

DOSAGE AND ADMINISTRATION (2 2) 12/2011
WARNINGS AND PRECAUTIONS (5 1, 5 2) 12/2011

INDICATIONS AND USAGE

Oxal plat n for injection USP is a platinum based drug used in combination with infusional 5 f uorouracil /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)

DOSAGE AND ADMINISTRATION

Adm n ster oxa iplatin for injection in combination with 5 f uorouraci /leucovorin every 2 weeks (2 1)
Day 1 Oxaliplatin for njection 85 mg/m² intravenous infusion in 250 to 500 mL 5% Dextrose Injection, USP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose Injection, USP both given over 120 m nutes at the same time in separate bags using a Y line, followed by 5 f uorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5 fluorouracil 600 mg/m² intravenous nfusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22 hour continuous infusion
Day 2 leucovorin 200 mg/m² intravenous nfusion over 120 minutes, followed by 5 f uorouracil 400 mg/m² IV bolus given over 2 to 4 minutes, followed by 5 fluorourac l 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22 hour continuous infusion

Reduce the dose of oxaliplatin for injection to 75 mg/m² (adjuvant setting) or 65 mg/m² (advanced colorectal cancer) (2 2)
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 ≥ 1 5 x 10⁹/L and platelets ≥ 75 x 10⁹/L
For patients with severe renal impairment (creatinine clearance <30 mL/min), the initial recommended dose s 65 mg/m² (2 2)
Discontinue oxaliplatin for injection if there are persistent Grade 3 neurosensory events (2 2)
Never reconst tute or prepare final dilution with a sodium chloride solution or other chloride containing solutions (2 3)

DOSAGE FORMS AND STRENGTHS

Single use vials of 50 mg or 100 mg oxaliplatin as a sterile, preservative free lyophilized powder for reconstitution (3)

CONTRAINDICATIONS

Known allergy to oxa iplat n for njection or other platinum compounds (4, 5 1)

WARNINGS AND PRECAUTIONS

Allergic Reactions Monitor for development of rash, urticaria, erythema, pruritis, bronchospasm, and hypotension (5 1)
Neuropathy Reduce the dose or discontinue oxaliplatin for injection if necessary (5 2)
Pulmonary Toxic ty May need to discont nue oxaliplatin for njection until interstitial lung disease or pu monary 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, fat gue and stomatitis Other adverse reactions, including serious adverse reactions, have been reported (6 1)

To report SUSPECTED ADVERSE REACTIONS, contact CARACO Pharmaceutical Laboratories Ltd. at 1-800-818-4555 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

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

Revised: February 2012

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FULL PRESCRIBING INFORMATION

WARNING: ANAPHYLACTIC REACTIONS
Anaphylactic reactions to oxaliplatin for injection have been reported, and may occur within minutes of oxaliplatin for injection administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms of anaphylaxis *[see Warnings and Precautions (5.1)]*.

1 INDICATIONS AND USAGE

Oxal plat n for injection USP, used 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 DOSAGE and ADMINISTRATION

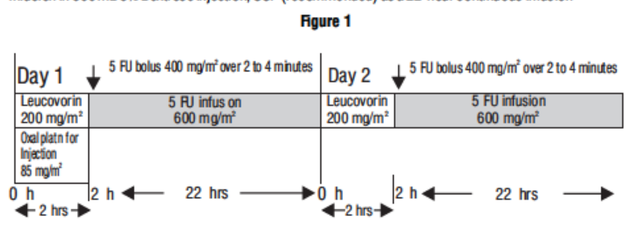
Oxal plat n for injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents Appropriate management of therapy and complications is poss b e only when adequate diagnostic and treatment facilities are readily available

2.1 Dosage
Administer oxaliplatin for injection in combination with 5 fluorourac l/ eucovorin 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 for injection 85 mg/m² intravenous infusion n 250 to 500 mL 5% Dextrose injection, USP and leucovorin 200 mg/m² intravenous infusion n 5% Dextrose Injection, USP both g ven over 120 m nutes at the same time in separate bags using a Y ine, followed by 5 fluorouracil 400 mg/m² intravenous bolus given over 2 to 4 minutes, followed by 5 fluorouracil 600 mg/m² intravenous infusion n 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 f uorouracil 400 mg/m² intravenous bo us given over 2 to 4 m nutes, followed by 5 f uorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22 hour continuous infusion

Figure 1



The administration of oxaliplatin for injection does not requ re prehydration Premedication with antiemetics, inc uding 5 HT_3 blockers with or without dexamethasone, is recommended

For information on 5 fluorouracil and leucovorin, see the respective package nserts

2.2 Dose Modification Recommendations
Prior to subsequent therapy cycles, pat ents should be evaluated for clinical toxicities and recommended laboratory tests *[see Warnings and Precautions (5 6)]* Prolongation of infusion time for oxaliplatin for injection from 2 hours to 6 hours may mitigate acute toxicities The infusion times for 5 fluorourac l and leucovorin do not need to be changed

Adjuvant Therapy in Patients with Stage III Colon Cancer
Neuropathy and other toxicities were graded using the NCI CTC scale version 1 *[see Warnings and Precautions (5 2)]*

For patients who exper ence persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin for 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/ eucovorin regimen need not be altered

A dose reduction of oxa iplatin for injection to 75 mg/m² and nfusional 5 fluorouracil to 300 mg/m² bo us 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 ≥ 1 5 x 10⁹/L and plate ets ≥ 75 x 10⁹/L

Dose Modifications in Therapy in Previously Untreated and Previously Treated Patients with Advanced Colorectal Cancer
Neuropathy was graded using a study specific neurotoxicity sca e *[see Warnings and Precautions (5 2)]* Other toxicities were graded by the NCI CTC, Version 2 0

For patients who exper ence persistent Grade 2 neurosensory events that do not resolve, a dose reduction of oxaliplatin for injection to 65 mg/m² should be considered For patients with persistent Grade 3 neurosensory events, discontinuing therapy shou d be considered The 5 fluorouracil/leucovorin reg men need not be altered

A dose reduction of oxaliplatin for injection to 65 mg/m² and 5 fluorouracil by 20% (300 mg/m² bolus and 500 mg/m² 22 hour infusion) is recommended for patients after recovery from grade 3/4 gastrointest nal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia The next dose shou d be delayed until neutrophils ≥ 1 5 x 10⁹/L and platelets ≥ 75 x 10⁹/L

Dose Modifications in Therapy for Patients with Renal Impairment
In patients with normal renal function or mild to moderate renal impairment, the recommended dose of oxaliplatin for injection s 85 mg/m² In patients with severe renal impairment, the initial recommended oxaliplatin for injection dose should be reduced to 65 mg/m² *[see Use in Specific Populations (8 6) and Clinical Pharmacology (12 3)]*

2.3 Preparation of Infusion Solution
Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions.
The lyophil zed powder is reconstituted by add ng 10 mL (for the 50 mg vial) or 20 mL (for the 100 mg vial) of Water for Injection, USP or 5% Dextrose Injection, USP **Do not administer the reconstituted solution without further dilution.** The reconstituted solution must be fur ther d luted in an infusion solution of 250 to 500 mL of 5% Dextrose Injection, USP

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)] After final di ution with 250 to 500 mL of 5% Dextrose Injection, USP, the shelf l fe is **6 hours at room temperature [20° to 25°C (68° to 77°F)] or up to 24 hours under refrigeration [2° to 8°C (36° to 46°F)].**
Oxa iplatin for injection is not light sensitive

Oxa iplatin for injection is incompatible in solution with alkal ne medications or media (such as basic solutions of 5 fluorourac l) and must not be mixed with these or administered simultaneously through the same infusion line **The infusion line should be flushed with 5% Dextrose Injection, USP prior to administration of any concomitant medication.**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration and discarded if present

Needles or intravenous administration sets containing a uminum parts that may come in contact with oxaliplatin for njection should not be used for the preparation or m xing of the drug Aluminum has been reported to cause degradation of platinum compounds

3 DOSAGE FORMS AND STRENGTHS

Oxa iplatin for injection is supplied in single use vials containing 50 mg or 100 mg of oxaliplatin as a ster le, preservative free lyophi ized powder for reconstitution

4 CONTRAINDICATIONS

Oxa iplatin for njection should not be administered to patients with a history of known a lergy to oxaliplatin for injection or other platinum compounds *[see Warnings and Precautions (5 1)]*

5 WARNINGS AND PRECAUTIONS

5.1 Allergic Reactions
See boxed warning
Grade 3/4 hypersensitivity, inc uding anaphylactic/anaphylactoid reactions, to oxaliplatin for injection has been observed in 2 to 3% of colon cancer patients These allergic reactions which can be fatal, can occur within minutes of administration and at any cyc e, and were similar in nature and severity to those reported with other platinum containing compounds, such as rash, urticaria, erythema, pruritus, and, rarely, bronchospasm and hypotension The symptoms associated with hypersensitivity reactions reported in the previously untreated patients were urticaria, pruritus, flushing of the face, diarrhea associated with oxaliplatin infusion, shortness of breath, bronchospasm, diaphoresis, chest pains, hypotension, disorientation and syncope These reactions are usually managed with standard epinephrine, corticosteroid, antihistamine therapy, and require discontinuation of therapy Rechallenge s contraindicated in these patients *[see Contraindications (4)]* Drug related deaths associated with platinum compounds from anaphylaxis have been reported

5.2 Neurologic Toxicity

Neuropathy
Oxaliplatin for injection is associated w th two types of neuropathy

An acute, reversible, primarily peripheral, sensory neuropathy that is of early onset, occurring within hours or one to two days of dosing, that resolves within 14 days, and that frequently recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received oxaliplatin for injection with 5 fluorouracil/leucovorin In any ndiv dual cyc e acute neurotoxicity was observed in approximately 30% of patients In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cyc es administered on the oxaliplatin for injection with 5 f uorouracil/leucovorin combination arm was 6

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1 to 2% (grade 3/4) of patients previously untreated for advanced colorectal cancer, and the previous y 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 dur ng the infusion of oxaliplatin for injection because cold temperature can exacerbate acute neurological symptoms

A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, 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 pat ents receiving oxaliplatin for injection w th 5 f uorouraci /leucovorin Persistent neuropathy can occur without any prior acute neuropathy event The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events These symptoms may improve in some patients upon discontinuation of oxaliplatin for injection

In the adjuvant colon cancer trial, neuropathy was graded using a prelisted 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 Patients

Grade	Definition
Grade 0	No change or none
Grade 1	Mild paresthesias, loss of deep tendon reflexes
Grade 2	Mild or moderate objective sensory loss, moderate paresthesias
Grade 3	Severe objective sensory loss or paresthesias that interfere w th function
Grade 4	Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the oxaliplatin for injection combination with a frequency of 92% (a l grades) and 13% (grade 3) At the 28 day follow up after the last treatment cycle, 60% of all patients had any grade (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 of follow up (Grade 1 17%, Grade 2 3%, Grade 3 1%)

In the advanced colorectal cancer studies, neuropathy was graded using a study spec fic 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 previous y treated patients in 74% (a l 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

Revers ble Posterior Leukoencephalopathy Syndrome
Revers ble Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0 1%) and postmarketing experience Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension *[see Adverse Reactions (6 2)]* Diagnosis of RPLS is based upon confirmation by brain imaging

5.3 Pulmonary Toxicity
Oxaliplatin for injection has been associated with pu monary 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 for injection plus infusional 5 fluorouracil/leucovorin arm compared to 4 5% (any grade) and no grade 3 and 0 1% grade 4 events in the nfusional 5 f uorouracil /leucovorin alone arm n adjuvant colon cancer patients In this study, one patient died from eosinophilic pneumonia in the oxaliplatin for injection combination arm The combined ncidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) n the oxaliplatin for injection plus 5 fluorouracil/leucovor n arm compared to 32% (any grade) and 5% (grade 3 and 4) in the rinotecan plus 5 fluorouracil/leucovorin arm of unknown duration for pat ents with previously untreated colorectal cancer In case of unexplained respiratory symptoms such as non productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, oxaliplatin for injection should be discont nued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis

5.4 Hepatotoxicity
Hepatotoxicity as evidenced n the adjuvant study, by increase n transaminases (57% vs 34%) and alkal ne phosphatase (42% vs 20%) was observed more commonly in the oxaliplatin for injection comb nation 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, perisinusoidal fibrosis, and veno occlusive lesions Hepatic vascular disorders shou d be considered, and if appropriate, shou d be investigated in case of abnormal l ver function test resu ts or portal hypertension, which cannot be explained by liver metastases *[see Clinical Trials Experience (6 1)]*

5.5 Use in Pregnancy
Pregnancy Category D
Oxaliplatin for njection may cause fetal harm when administered to a pregnant woman There are no adequate and well controlled studies of oxaliplatin for injection in pregnant women Women of childbearing potential shou d be advised to avoid becoming pregnant while receiving treatment with oxaliplatin for 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 (inc uding ALT, AST, bil rubin and creatinine) is recommended before each oxaliplatin for injection cycle *[see Dosage and Administration (2)]*

There have been reports while on study and from postmarketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in pat ents who received oxaliplatin for injection plus 5 fluorouracil/leucovorin while on anticoagulants Patients receiving oxaliplatin for injection plus 5 fluorouracil/leucovorin and requiring oral anticoagulants may require closer mon toring

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience
Serious adverse reactions includ ng anaphylaxis and a lergic 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 c inical trials of another drug and may not reflect the rates observed n 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 stud es with oxaliplatin for 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, ncrease in transam nases and alka ine phosphatase, diarrhea, emesis, fatigue and stomat t s The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatigue, neutropenia, nausea, emesis, and diarrhea *[see Warn ngs and Precautions (5)]*

Combination Adjuvant Therapy with Oxaliplatin for Injection and Infusional 5 fluorouracil/leucovorin in Patients with Colon Cancer
One thousand one hundred and eight patients w th stage II or III colon cancer, who had undergone comp ete resection of the primary tumor, have been treated in a clinical study with oxa iplat n for injection in combination with infusional 5 fluorouracil/leucovorin *[see Clinical Studies (14)]* The incidence of grade 3 or 4 adverse reactions was 70% on the oxaliplatin for injection combination arm, and 31% on the infusional 5 fluorouracil/leucovorin arm The adverse reactions in this trial are shown in the tables below Discontinuation of treatment due to adverse reactions occurred in 15% of the patients rece ving oxaliplatin for injection and infusional 5 fluorouracil/leucovorin Both 5 fluorouracil/leucovorin and oxaliplatin for injection are associated w th gastrointestinal or hematologic adverse reactions When oxaliplatin for injection is administered n combination with infusional 5 fluorouracil/leucovorin, the ncidence of these events s increased

The incidence of death w thin 28 days of last treatment, regardless of causality, was 0 5% (n 6) in both the oxal platin for injection combination and infusional 5 fluorouraci /leucovorin arms, respectively Deaths within 60 days from initiation of therapy were 0 3% (n 3) in both the oxaliplatin for injection combination and infusional 5 fluorouracil/leucovorin arms, respect vely On the oxal plat n for injection combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from ntracerebral bleeding and one from eos nophilic pneumonia On the 5 fluorouracil/leucovor n arm, one death was due to suicide, 2 from Steven Johnson Syndrome (1 patient also had sepsis), 1 unknown cause, 1 anoxic cerebral infarction and 1 probable abdominal aorta rupture

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the oxaliplatin for injection and infusional 5 fluorouracil/leucovorin arm for events with overall incidences ≥ 5% and for NCI grade 3/4 events with incidences ≥ 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)

	Oxaliplatin for Injection + 5-FU/LV N 1108		5-FU/LV N 1111	
Adverse reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	100	70	99	31
Allergy/Immunology				
Allergic Reaction	10	3	2	<1
Constitutional Symptoms/Pain				
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
Dermatology/Skin				
Skin Disorder	32	2	36	2
Injection S te Reaction[1]	11	3	10	3
Gastrointestinal				
Nausea	74	5	61	2
Diarrhea	56	11	48	7
Vomiting	47	6	24	1
Stomatitis	42	3	40	2
Anorexia	13	1	8	<1
Fever/Infection				
Fever	27	1	12	1
Infection	25	4	25	3
Neurology				
Overa l Peripheral Sensory Neuropathy	92	12	16	<1

[1] Includes thrombosis related to the catheter

The following table provides adverse reactions reported n the adjuvant therapy colon cancer clinical trial *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the oxaliplatin for injection and infusional 5 fluorouracil/leucovorin arm for events with overall incidences ≥ 5% but with incidences < 1% NCI grade 3/4 events

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

Adverse reaction (WHO/Pref)	Oxaliplatin for Injection + 5-FU/LV N 1108 All Grades (%)	5-FU/LV N 1111 All Grades (%)
Allergy/Immunology		
Rhinitis	6	8
Constitutional Symptoms/Pain/Ocular/Visual		
Epistaxis	16	12
Weight Increase	10	10
Conjunct vitis	9	15
Headache	7	5
Dyspnea	5	3
Pa n	5	5
Lacrimation Abnormal	4	12
Dermatology/Skin		
Alopecia	30	28
Gastrointestinal		
Constipation	22	19
Taste Perversion	12	8
Dyspepsia	8	5
Metabolic		
Phosphate Alka ine increased	42	20
Neurology		
Sensory Disturbance	8	1

Although specific events can vary, the overall frequency of adverse reactions was similar n men and women and in patients <65 and ≥65 years However, the follow ng grade 3/4 events were more common n females diarrhea, fatigue, granulocytopenia, nausea and vomiting In patients ≥ 65 years old, the ncidence of grade 3/4 diarrhea and granulocytopenia was higher than n younger patients Insufficient subgroup sizes prevented analysis of safety by race The following additional adverse reactions, were reported in ≥ 2% and <5% of the pat ents in the oxal plat n for injection and infusional 5 fluorouracil/leucovor n combination arm (listed in decreasing order of frequency) pain, eukopenia, we ght decrease, coughing

The number of patients who developed secondary malignancies was similar; 62 in the oxaliplatin for njection combination arm and 68 n the infusional 5 fluorourac l/ eucovorin arm An exploratory analysis showed that the number of deaths due to secondary malignancies was 1 96% in the oxaliplatin for njection combination arm and 0 98% in infusional 5 fluorouracil/leucovorin arm In addition, the number of cardiovascular deaths was 1 4% in the oxaliplatin for injection comb nation arm as compared to 0 7% in the infusional 5 fluorourac l/ eucovorin arm Clinical sign ficance of these findings is unknown

Patients Previously Untreated for Advanced Colorectal Cancer
Two hundred and fifty nine patients were treated in the oxaliplatin for injection and 5 fluorouracil/leucovor n combination arm of the randomized trial in pat ents previously untreated for advanced colorectal cancer *[see Clinical Studies (14)]* The adverse reaction profi e in this study was s milar to that seen in other studies and the adverse reactions in th s trial are shown in the tables below Both 5 fluorouracil and oxaliplatin for injection are associated with gastrointest nal and hematologic adverse reactions When oxaliplatin for injection is adm n stered in combination with 5 f uorouracil, the ncidence of these events is increased

The incidence of death w thin 30 days of treatment in the previously untreated for advanced colorectal cancer study, regardless of causality, was 3% with the oxaliplatin for injection and 5 fluorouracil/leucovor n combination, 5% w th irinotecan plus 5 fluorouracil/leucovor n, and 3% with oxa iplatin for njection plus irinotecan Deaths with n 60 days from initiation of therapy were 2 3% with the oxa iplatin for injection and 5 f uorouraci /leucovorin combination, 5 1% with ir notecan plus 5 fluorouracil/leucovor n, and 3 1% with oxaliplatin for injection plus irinotecan The follow ng table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study *[see Clinical Studies (14)]* by body system and decreasing order of frequency in the oxaliplatin for njection and 5 fluorouracil/leucovorin combination arm for events with overall incidences ≥5% and for grade 3/4 events with incidences ≥1%

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)

	Oxaliplatin for Injection + 5-FU/LV N 259		Irinotecan + 5-FU/LV N 256		Oxaliplatin for Injection + Irinotecan N 258	
Adverse reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	99	82	98	70	99	76
Allergy/Immunology						
Hypersensitivity	12	2	5	0	6	1
Cardiovascular						
Thrombosis	6	5	6	6	3	3
Hypotension	5	3	6	3	4	3
Constitutional Symptoms/Pain/Ocular/Visual						
Fatigue	70	7	58	11	66	16
Abdominal Pa n	29	8	31	7	39	10
Myalgia	14	2	6	0	9	2
Pain	7	1	5	1	6	1
Vision abnormal	5	0	2	1	6	1
Neuralgia	5	0	0	0	2	1
Dermatology/Skin						
Skin reaction hand/foot	7	1	2	1	1	0
Injection site reaction	6	0	1	0	4	1
Gastrointestinal						
Nausea	71	6	67	15	83	19
Diarrhea	56	12	65	29	76	25
Vomiting	41	4	43	13	64	23
Stomatitis	38	0	25	1	19	1
Anorexia	35	2	25	4	27	5
Constipation	32	4	27	2	21	2
Diarrhea colostomy	13	2	16	7	16	3
Gastrointestinal NOS*	5	2	4	2	3	2
Hematology/Infection						
Infection normal ANC**	10	4	5	1	7	2
Infection low ANC**	8	8	12	11	9	8
Lymphopenia	6	2	4	1	5	2
Febrile neutropenia	4	4	15	14	12	11
Hepatic/Metabolic/Laboratory/Renal						
Hyperglycemia	14	2	11	3	12	3
Hypokalemia	11	3	7	4	6	2
Dehydration	9	5	16	11	14	7
Hypoalbuminemia	8	0	5	2	9	1
Hyponatremia	8	2	7	4	4	1
Urinary frequency	5	1	2	1	3	1
Neurology						
Overall Neuropathy	82	19	18	2	69	7
Paresthesias	77	18	16	2	62	6
Pharyngo laryngeal dysesthesias	38	2	1	0	28	1
Neuro sensory	12	1	2	0	9	1
Neuro NOS*	1	0	1	0	1	0
Pulmonary						
Cough	35	1	25	2	17	1
Dyspnea	18	7	14	3	11	2
Hiccups	5	1	2	0	3	2

* Not otherwise spec fied
** Abso ute neutrophil count

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study *[see C inical Studies (14)]* by body system and decreasing order of frequency in the oxal plat n for njection and 5 fluorouracil/leucovorin combination arm for events with overall incidences ≥5% but with incidences < 1% NCI Grade 3/4 events

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

Adverse reaction (WHO/Pref)	Oxaliplatin for Injection + 5-FU/LV N 259 All Grades (%)	Irinotecan + 5-FU/LV N 256 All Grades (%)	Oxaliplatin for Injection + Irinotecan N 258 All Grades (%)
Allergy/Immunology			
Rash	11	4	7
Rhinitis al ergic	10	6	6
Cardiovascular			
Edema	15	13	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	13	6	9
Weight loss	11	9	11
Epistaxis	10	2	2
Tearing	9	1	2
Rigors	8	2	7
Dysphasia	5	3	3
Sweating	5	6	12
Arthralgia	5	5	8
Dermatology/Skin			
Alopecia	38	44	67
Flushing	7	2	5
Pruritis	6	4	2
Dry Skin	6	2	5
Gastrointestinal			
Taste perversion	14	6	8
Dyspepsia	12	7	5
Flatulence	9	6	5
Mouth Dryness	5	2	3
Hematology/Infection			
Fever normal ANC*	16	9	9
Hepatic/Metabolic/Laboratory/Renal			
Hypocalcemia	7	5	4
Elevated Creatinine	4	4	5
Neurology			
Insomnia	13	9	11
Depression	9	5	7
Dizziness	8	6	10
Anxiety	5	2	6

* Absolute neutrophil count

Adverse reactions were s milar in men and women and in patients <65 and ≥65 years, but older pat ents may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope The following additional adverse reactions, at least possibly related to treatment and potentially important, were reported in ≥ 2% and <5% of the patients in the oxaliplatin for njection and 5 f uorouraci /leucovorin combination arm (isted n decreasing order of frequency) metabolic, pneumonitis, catheter nfection, vert go, prothrombin time, pulmonary, rectal bleeding, dysuria, nail changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone pa n, pigmentation changes, and urticaria

Previously Treated Patients with Advanced Colorectal Cancer
Four hundred and fifty patients (about 150 receiving the combination of oxaliplatin for injection and 5 f uorouraci /leucovorin) were studied in a randomized trial n patients with refractory and relapsed colorectal cancer *[see Clinical Studies (14)]* The adverse reaction profile in this study was similar to that seen in other studies and the adverse reactions in this trial are shown n the tables below

Thirteen percent of patients in the oxaliplatin for injection and 5 fluorouracil/leucovorin combination arm and 18% in the 5 fluorouracil/leucovorin arm of the previous y treated study had to discontinue treatment because of adverse effects related to gastrointestinal, or hematologic adverse reactions, or neuropathies Both 5 fluorouracil and oxaliplatin for injection are associated with gastrointestinal and hematologic adverse reactions When oxa iplatin for injection is administered in combination with 5 fluorouracil, the incidence of these events is increased

The incidence of death within 30 days of treatment in the previously treated study, regardless of causality, was 5% with the oxaliplatin for injection and 5 fluorouracil/leucovorin combination, 8% with oxaliplatin for injection alone, and 7% with 5 fluorouracil/leucovorin Of the 7 deaths that occurred on the oxaliplatin for injection and 5 f uorouraci /leucovorin combination arm within 30 days of stopp ng treatment, 3 may have been treatment related, associated with gastrointestinal bleeding or dehydration

The following table provides adverse reactions reported in the previously treated study *[see Clinical Studies (14)]* by body system and in decreas ng order of frequency in the oxaliplatin for injection and 5 fluorouraci /leucovorin combination arm for events with overall incidences ≥ 5% and for grade 3/4 events with incidences ≥ 1% This table does not include hematologic and blood chemistry abnormal t es; these are shown separately below

Table 7 Adverse Reactions Reported In Previously Treated Colorectal Cancer Clinical Trial (≥5% of all patients and with ≥1% NCI Grade 3/4 events)

	5-FU/LV (N 142)		Oxaliplatin for Injection (N 153)		Oxaliplatin for Injection + 5-FU/LV (N 150)	
Adverse reaction (WHO/Pref)	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Any Event	98	41	100	46	99	73
Cardiovascular						
Dyspnea	11	2	13	7	20	4
Coughing	9	0	11	0	19	1
Edema	13	1	10	1	15	1
Thromboembolism	4	2	2	1	9	8
Chest Pain	4	1	5	1	8	1
Constitutional Symptoms/Pain						
Fatigue	52	6	61	9	68	7
Back Pain	16	4	11	0	19	3
Pain	9	3	14	3	15	2
Dermatology/Skin						
Injection Site Reaction	5	1	9	0	10	3
Gastrointestinal						
Diarrhea	44	3	46	4	67	11
Nausea	59	4	64	4	65	11
Vomiting	27	4	37	4	40	9
Stomatitis	32	3	14	0	37	3
Abdom nal Pain	31	5	31	7	33	4
Anorexia	20	1	20	2	29	3
Gastroesophageal Reflux	3	0	1	0	5	2
Hematology/Infection						
Fever	23	1	25	1	29	1
Febrile Neutropenia	1	1	0	0	6	6
Hepatic/Metabolic/Laboratory/Renal						
Hypokalemia	3	1	3	2	9	4
Dehydration	6	4	5	3	8	3
Neurology						
Neuropathy	17	0	76	7	74	7
Acute	10	0	65	5	56	2
Persistent	9	0	43	3	48	6

The following table provides adverse reactions reported in the previously treated study *[see Clinical Studies (14)]* by body system and in decreas ng order of frequency in the oxaliplatin for injection and 5 fluorouraci /leucovorin combination arm for events with overa l incidences ≥ 5% but with ncidences < 1% NCI Grade 3/4 events

Table 8 - Adverse Reactions Reported In Previously Treated Colorectal Cancer Clinical Trial (≥5% of all patients but with < 1% NCI Grade 3/4 events)

Adverse reaction (WHO/Pref)	5-FU/LV (N 142) All Grades (%)	Oxaliplatin for Injection (N 153) All Grades (%)	Oxaliplatin for Injection + 5-FU/LV (N 150) All Grades (%)
Allergy/Immunology			
Rhinitis	4	6	15
Allergic Reaction	1	3	10
Rash	5	5	9
Cardiovascular			
Peripheral Edema	11	5	10
Constitutional Symptoms/Pain/Ocular/Visual			
Headache	8	13	17
Arthralgia	10	7	10
Epistax s	1	2	9
Abnormal Lacrimation	6	1	7
Rigors	6	9	7
Dermatology/Skin			
Hand Foot Syndrome	13	1	11
Flushing	2	3	10
Alopecia	3	3	7
Gastrointestinal			
Constipation	23	31	32
Dyspepsia	10	7	14
Taste Perversion	1	5	13
Mucositis	10	2	7
Flatulence	6	3	5
Hepatic/Metabolic/Laboratory/Renal			
Hematuria	4	0	6
Dysuria	1	1	6
Neurology			
Dizziness	8	7	13
Insomnia	4	11	9
Pulmonary			
Upper Resp Tract Infection	4	7	10
Pharyngitis	10	2	9
Hiccup	0	2	5

Adverse reactions were similar in men and women and in patients <65 and ≥65 years, but older pat ents may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue The fo lowing add tional adverse reactions, at least possibly related to treatment and potentially important, were reported in ≥2% and <5% of the patients in the oxaliplatin for injection and 5 fluorouracil/leucovor n combination arm (listed in decreasing order of frequency) anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritus, hemoptysis, purpura, vag nal hemorrhage, melena, somnolence, pneumonia, proct t s, involuntary muscle contractions, intestinal obstruction, g ngiv t s, tenesmus, hot flashes, enlarged abdomen, urinary ncontinence

Hematologic Changes
The following tables list the hematologic changes occurring in ≥ 5% of patients, based on laboratory values and NCI grade, w th the exception of those events occurring in adjuvant patients and anemia n the pat ents previously untreated for advanced colorectal cancer, respectively, which are based on AE reporting and NCI grade alone

Table 9 - Adverse Hematologic Reactions in Patients with Colon Cancer Receiving Adjuvant Therapy (≥5% of patients)

Hematology Parameter	Oxaliplatin for Injection + 5-FU/LV (N 1108)		5-FU/LV (N 1111)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	76	1	67	<1
Neutropenia	79	41	40	5
Thrombocytopenia	77	2	19	<1

Table 10 Adverse Hematologic Reactions in Patients Previously Untreated for Advanced Colorectal Cancer (≥5% of patients)

Hematology Parameter	Oxaliplatin for Injection + 5-FU/LV N 259		Irinotecan + 5-FU/LV N 256		Oxaliplatin for Injection + Irinotecan N 258	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	27	3	28	4	25	3
Leukopenia	85	20	84	23	76	24
Neutropenia	81	53	77	44	71	36
Thrombocytopenia	71	5	26	2	44	4

Table 11 Adverse Hematologic Reactions in Previously Treated Patients (≥5% of patients)

Hematology Parameter	5-FU/LV (N 142)		Oxaliplatin for Injection (N 153)		Oxaliplatin for Injection + 5-FU/LV (N 150)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Anemia	68	2	64	1	81	2
Leukopenia	34	1	13	0	76	19
Neutropenia	25	5	7	0	73	44
Thrombocytopenia	20	0	30	3	64	4

Thrombocytopenia and Bleeding
Thrombocytopenia was frequently reported with the combination of oxaliplatin for injection and infusional 5 fluorouracil/leucovorin The incidence of all hemorrhagic events in the adjuvant and previously treated patients was higher on the oxaliplatin for injection combination arm compared to the infusional 5 fluorouracil/leucovorin arm These events inc uded gastrointest nal bleeding, hematuria, and ep staxis In the adjuvant trial, two patients died from intracerebral hemorrhages

The incidence of Grade 3/4 thrombocytopenia was 2% in adjuvant patients with colon cancer In patients treated for advanced colorectal cancer the incidence of Grade 3/4 thrombocytopenia was 3 to 5%, and the incidence of these events was greater for the comb nation of oxaliplatin for injection and 5 fluorouracil/leucovorin over the irinotecan plus 5 f uorouraci /leucovorin or 5 fluorouraci /leucovorin control groups Grade 3/4 gastrointestinal bleeding was reported in 0 2% of adjuvant patients receiving oxaliplatin for injection and 5 fluorouracil/leucovorin In the previously untreated patients, the incidence of epistaxis was 10% in the oxaliplatin for injection and 5 fluorouracil/leucovorin arm, and 2% and 1%, respect vely, n the irinotecan plus 5 fluorourac l/ eucovorin or irinotecan plus oxaliplatin for injection arms

Neutropenia
Neutropenia was frequent y observed w th the combination of oxaliplatin for injection and 5 fluorouracil/leucovorin, with Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer, respectively In the adjuvant trial, 3 patients died from sepsis/neutropenic sepsis Grade 3 and 4 events were reported in 35% and 18% of the patients previously untreated for advanced colorectal cancer, respective y Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respect vely In adjuvant patients the incidence of either febrile neutropenia (0 7%) or documented infection with concom tant grade 3/4 neutropenia (1 1%) was 1 8% in the oxaliplatin for injection and 5 fluorouracil/leucovorin arm The incidence of febri e neutropenia in the patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the irinotecan plus 5 fluorouracil/leucovor n arm and 4% (less than 1% of cyc es) in the oxaliplatin for injection and 5 fluorouraci /leucovorin combination arm Additionally, in th s same population, infection with grade 3 or 4 neutropenia was 12% in the irinotecan plus 5 fluorouracil/leucovorin, and 8% in the oxaliplatin for injection and 5 fluorouracil/leucovorin combination The ncidence of febrile neutropenia in the previously treated patients was 1% in the 5 fluorouracil/leucovorin arm and 6% (less than 1% of cycles) in the oxaliplatin for injection and 5 fluorouracil/leucovor n combination arm

Gastrointestinal
In patients receiving the combination of oxaliplatin for njection plus infusional 5 fluorouraci /leucovorin for adjuvant treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those rece ving infusional 5 f uorouracil/leucovorin alone (see table) In pat ents previously untreated for advanced colorectal cancer rece ving the comb nation of oxaliplatin for injection and 5 fluorouracil/leucovorin, the incidence of Grade 3 and 4 vomiting and diarrhea was less compared to irinotecan plus 5 f uorouracil/leucovorin controls (see table) In previously treated patients receiving the combination of oxaliplatin for injection and 5 fluorouracil/leucovorin, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis ncreased compared to 5 fluorouraci /leucovorin controls (see table)

The incidence of gastrointestinal adverse reactions in the previous y untreated and previously treated patients appears to be sim lar across cycles Premedication w th antiemetics, including 5 HT_3 blockers, is recommended Diarrhea and mucositis may be exacerbated by the addition of oxal plat n for njection to 5 fluorouracil/leucovorin, and should be managed with appropriate supportive care Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of oxaliplatin for injection

Dermatologic
Oxaliplatin for injection did not increase the incidence of alopecia compared to 5 fluorourac l/leucovorin alone No complete alopecia was reported The nc dence of Grade 3/4 skin disorders was 2% in both the oxaliplatin for injection plus infusional 5 fluorouracil/leucovorin and the infusional 5 fluorouracil/leucovorin alone arms in the adjuvant colon cancer patients The incidence of hand foot syndrome in patients previously untreated for advanced colorectal cancer was 2% in the ir notecan plus 5 fluorouracil/leucovorin arm and 7% in the oxaliplatin for injection and 5 fluorourac l/ eucovorin combination arm The incidence of hand foot syndrome in previously treated patients was 13% in the 5 fluorouracil/leucovorin arm and 11% in the oxaliplatin for injection and 5 fluorourac l/ eucovorin combination arm

Intravenous Site Reactions
Extravasation, in some cases including necrosis, has been reported
Injection site reaction, including redness, swelling, and pain, has been reported

Anticoagulation and Hemorrhage
There have been reports while on study and from postmarketing surveillance of prolonged prothrombin time and INR occasionally associated with hemorrhage in pat ents who received oxaliplatin for injection plus 5 fluorouracil/leucovorin while on anticoagulants Patients rece ving oxa iplatin for injection p us 5 fluorouracil/leucovorin and requiring oral anticoagulants may require closer monitoring

Renal
About 5 to 10% of patients in all groups had some degree of elevation of serum creatinine The incidence of Grade 3/4 elevations in serum creatinine in the oxa iplat n for njection and 5 fluorourac l/ eucovorin combination arm was 1% in the previously treated patients Serum creatinine measurements were not reported in the adjuvant trial

Hepatic
Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to oxal plat n for injection combination therapy *[see Warnings and Precautions (5 4)]* The follow ng tables list the clinical chemistry changes associated with hepatic toxic ty occurring in ≥ 5% of patients, based on adverse reactions reported and NCI CTC grade for adjuvant patients and patients previously untreated for advanced colorectal cancer, laboratory values and NCI CTC grade for previous y treated patients

Table 12 - Adverse Hepatic Reactions in Patients with Stage II or III Colon Cancer Receiving Adjuvant Therapy (≥5% of patients)

Hepatic Parameter	Oxaliplatin for Injection + 5-FU/LV (N 1108)		5-FU/LV (N 1111)	
	All Grades (%)	**Grade 3/4 (%)**	**All Grades (%)**	**Grade 3/4 (%)**
Increase in transaminases	57	2	34	1
ALP increased	42	<1	20	<1
B lirubinaemia	20	4	20	5

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

Clinical Chemistry	Oxaliplatin for Injection + 5-FU/LV N 259		Irinotecan + 5-FU/LV N 256		Oxaliplatin for Injection + 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
A kaline Phosphatase	16	0	8	0	14	2
Total Bi irubin	6	1	3	1	3	2

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

Clinical Chemistry	5-FU/LV (N 142)		Oxaliplatin for Injection (N 153)		Oxaliplatin for Injection + 5-FU/LV (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 Bi irubin	22	6	13	5	13	1

Thromboembolism
The incidence of thromboembolic events n adjuvant patients w th colon cancer was 6% (1 8% grade 3/4) in the infusional 5 fluorouracil/leucovorin arm and 6% (1 2% grade 3/4) in the oxa iplat n for injection and infusional 5 fluorouracil/leucovorin combined arm, respectively The incidence was 6 and 9% of the patients previous y untreated for advanced colorectal cancer and previously treated patients in the oxaliplatin for injection and 5 f uorouracil/leucovorin combination arm, respectively

6.2 Postmarketing Experience
The following adverse reactions have been identified during postapproval use of oxaliplatin for injection Because these reactions are reported voluntar ly from a population of uncertain size, it is not always possible to reliably est mate their frequency or establ sh a causal relationship to drug exposure

Body as a whole
angioedema, anaphylactic shock

Central and peripheral nervous system disorders
loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies, fasciculations, convulsion, Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES)

Liver and Gastrointestinal system disorders
severe diarrhea/vomiting resulting in hypokalemia, colitis (includ ng *Clostridium difficile* diarrhea), metabolic acidosis; leus; intest nal obstruction, pancreatitis; veno occlusive disease of liver also known as s nusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress

Hearing and vestibular system disorders
deafness

Platelet bleeding and clotting disorders
immuno allergic thrombocytopenia
prolongation of prothrombin time and of INR in patients receiving anticoagulants

Red Blood Cell disorders
hemolytic uremic syndrome, immuno allergic hemolytic anemia

Renal disorders
Acute tubular necrosis, acute interstitial nephr t s and acute renal failure

Respiratory system disorders
pulmonary fibrosis, and other interstitial lung d seases (sometimes fatal)

Vision disorders
decrease of visual acuity, v sual field disturbance, optic neuritis and trans ent vision loss (reversible following therapy discontinuation)

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7 DRUG INTERACTIONS

No specific cytochrome P 450 based drug interaction studies have been conducted No pharmacokinetic interaction between 85 mg/m² oxaliplatin for injection and 5 fluorouracil/ eucovorin has been observed in patients treated every 2 weeks Increases of 5 fluorouracil plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² oxaliplatin for injection dosed every 3 weeks Because platinum containing species are elim nated primar ly through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds; although, this has not been specifically studied *[see Clinical Pharmacology (12 3)]*

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D

Based on direct interaction w th DNA, oxaliplatin for injection may cause fetal harm when administered to a pregnant woman There are no adequate and well controlled studies of oxal plat n for njection in pregnant women Reproduct ve toxicity studies in rats demonstrated adverse effects on fertility and embryo fetal development at maternal doses that were below the recommended human dose based on body surface area If this drug is used during pregnancy or if the patient becomes pregnant wh le taking this drug, the patient should be apprised of the potential hazard to the fetus Women of childbearing potential should be advised to avo d becoming pregnant and use effective contraception while rece ving treatment with oxal plat n for njection

Pregnant rats were administered oxa iplatin at less than one tenth the recommended human dose based on body surface area during gestation days 1 to 5 (pre implantation), 6 to 10, or 11 to 16 (during organogenesis) Oxaliplatin caused developmental mortality (increased early resorptions) when administered on days 6 to 10 and 11 to 16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6 to 10 Administration of oxaliplatin to male and fema e rats prior to mat ng resulted in 97% post implantation loss in an mals that rece ved approximate y one seventh the recommended human dose based on the body surface area

8.3 Nursing Mothers

It s not known whether oxaliplatin for injection or its derivatives are excreted in human milk Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing nfants from oxaliplatin for njection, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother

8.4 Pediatric Use

The effect veness of oxaliplatin in chi dren has not been established Oxaliplatin has been tested in 2 Phase 1 and 2 Phase 2 trials in 235 patients ages 7 months to 22 years with so id tumors (see below) and no significant activity observed

In a Phase 1/2 study, oxaliplatin was administered as a 2 hour intravenous infusion on Days 1, 8 and 15 every 4 weeks (1 cycle), for a maximum of 6 cycles, to 43 patients with refractory or relapsed malignant solid tumors, mainly neuroblastoma and osteosarcoma Twenty eight pediatric pat ents in the Phase 1 study received oxaliplatin at 6 dose levels starting at 40 mg/m² with escalation to 110 mg/m² The dose limiting toxicity (DLT) was sensory neuropathy at the 110 mg/m² dose Ffteen patients rece ved oxaliplatin at a dose of 90 mg/m² intravenous in the Phase 2 portion of the study At this dose, paresthesia (60%, G3/4 7%), fever (40%, G3/4 7%) and thrombocytopenia (40%, G3/4 27%) were the main adverse reactions No responses were observed

In a second Phase 1 study, oxaliplatin was adm n stered to 26 pediatric patients as a 2 hour intravenous infusion on day 1 every 3 weeks (1 cycle) at 5 dose levels starting at 100 mg/m² with escalation to 160 mg/m², for a maximum of 6 cycles In a separate cohort, oxaliplatin 85 mg/m² was administered on day 1 every 2 weeks, for a maximum of 9 doses Patients had metastatic or unresectable solid tumors mainly neuroblastoma and gang ioneuroblastoma No responses were observed The DLT was sensory neuropathy at the 160 mg/m² dose Based on these studies, oxaliplatin 130 mg/m² as a 2 hour intravenous nfusion on day 1 every 3 weeks (1 cycle) was used in subsequent Phase 2 studies A dose of 85 mg/m² on day 1 every 2 weeks was also found to be tolerab e

In one Phase 2 study, 43 pediatric patients with recurrent or refractory embryonal CNS tumors rece ved oxaliplatin 130 mg/m² every 3 weeks for a maximum of 12 months in absence of progressive disease or unacceptable toxicity In patients < 10 kg the oxaliplatin dose used was 4 3 mg/kg The most common adverse reactions reported were leukopenia (67%, G3/4 12%), anemia (65%, G3/4 5%), thrombocytopenia (65%, G3/4 26%), vomiting (65%, G3/4 7%), neutropenia (58%, G3/4 16%) and sensory neuropathy (40%, G3/4 5%) One partial response was observed

In a second Phase 2 study, 123 pediatric patients with recurrent so id tumors, ncluding neuroblastoma, osteosarcoma, Ewing sarcoma or peripheral PNET, ependymoma, rhabdomyosarcoma, hepatoblastoma, high grade astrocytoma, Brain stem glioma, low grade astrocytoma, malignant germ cell tumor and other tumors of nterest received oxal platin 130 mg/m² every 3 weeks for a maximum of 12 months or 17 cycles In patients < 12 months old the oxaliplatin dose used was 4 3 mg/kg The most common adverse reactions reported were sensory neuropathy (52%, G3/4 12%), thrombocytopenia (37%, G3/4 17%), anemia (37%, G3/4 9%), vomiting (26%, G3/4 4%), ALT increased (24%, G3/4 6%), AST increased (24%, G3/4 2%), and nausea (23%, G3/4 3%) Two partial responses were observed

The pharmacokinetic parameters of u trafiltrable platinum have been evaluated n 105 pediatric patients during the f rst cycle The mean c earance 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 plat num pharmacokinetic parameters in ultraf ltrate were C_{max} of 0 75 ± 0 24 mcg/mL, AUC_{0-48} of 7 52 ± 5 07 mcg·h/mL and AUC_{inf} of 8 83 ± 1 57 mcg·h/mL at 85 mg/m² of oxaliplatin and C_{max} of 1 1 ± 0 43 mcg/mL, AUC_{0-48} of 9 74 ± 2 52 mcg·h/mL and AUC_{inf} of 17 3 ± 5 34 mcg·h/mL at 130 mg/m² of oxaliplatin

8.5 Geriatric Use

No significant effect of age on the clearance of ultrafi terable platinum has been observed In the adjuvant therapy colon cancer randomized clinical trial, *[see Clinical Studies (14)]* 723 patients treated with oxaliplatin for 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 for injection combination arm compared to the infusional 5 fluorouracil/leucovor n alone arm appeared to be mainta ned across genders The effect of oxaliplatin for injection in patients ≥ 65 years of age was not conc usive Insufficient subgroup sizes prevented analysis by race

Patients ≥ 65 years of age receiving the oxaliplatin for injection combination therapy experienced more grade 3 and 4 granulocytopenia than patients < 65 years of age (45% versus 39%)

In the previously untreated for advanced colorectal cancer randomized cl nical trial *[see Clinical Studies (14)]* of oxaliplatin for injection, 160 patients treated with oxaliplatin for 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 year 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 for injection, 95 patients treated with oxa iplatin for injection and 5 fluorouracil/leucovorin were <65 years and 55 pat ents 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 stud es The incidence of diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope were h gher in patients ≥65 years old No adjustment to starting dose was required in patients ≥65 years old

8.6 Patients with Renal Impairment

The exposure (AUC) of unbound platinum in plasma ultraf ltrate tends to increase n renally impaired patients *[see Pharmacokinetics (12 3)]* Caution and close monitoring should be exercised when oxaliplatin for injection is adm n stered to patients with renal impairment The start ng oxaliplatin for injection dose does not need to be reduced in patients with m ld (creatinine clearance 50 to 80 mL/min) or moderate (creat n ne clearance 30 to 49 mL/min) renal impairment However, the starting dose of oxaliplatin for njection should be reduced in patients with severe renal impairment (creatinine clearance < 30 mL/min) *[see Dosage and Administration (2 2)]*

10 OVERDOSAGE

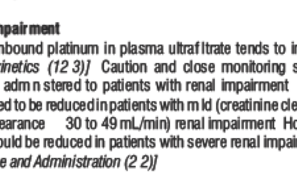
There is no known ant dote for oxaliplatin for injection overdose In addition to thrombocytopenia, the anticipated complications of an oxal plat n for injection overdose include hypersensitivity reaction, myelosuppression, nausea, vom t ng, diarrhea and neurotoxicity

Several cases of overdoses have been reported with oxaliplatin for injection Adverse reactions observed were Grade 4 thrombocytopenia (<25,000/mm³) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial musc e spasms, gastrointestinal d sorders such as nausea, vomit ng, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheez ng, chest pa n, respiratory fa lure, severe bradycardia and death

Patients suspected of receiving an overdose shou d be monitored, and supportive treatment should be adm n stered The maximum dose of oxaliplatin that has been administered in a s ngle infusion is 825 mg

11 DESCRIPTION

Oxaliplatin for njection USP is an ant neoplastic agent with the molecular formula $C_8H_{14}N_2O_4Pt$ and the chemical name of *cis* [(1 *R*,2 *R*) 1,2 cyclohexanediamine *N,N'*] [oxalato(2) *O,O'*] platinum Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2 diaminocyclohexane(DACH) and w th an oxalate ligand as a leaving group



The molecular weight is 397 3 Oxaliplatin is sl ghtly soluble in water at 6 mg/mL, very slight y soluble in methanol, and practically nsoluble in ethanol and acetone

Oxaliplatin for njection USP is supplied in vials containing 50 mg or 100 mg of oxal platin USP as a sterile, preservative free lyophilized powder for reconst tution Lactose monohydrate is present as an inact ve ingred ent at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active der vat ves via displacement of the labile oxalate ligand Several transient reactive spec es are formed, including monoaquo and diaquo DACH plat num, which cova ent y bind with macromolecules Both inter and intrastrand Pt DNA crosslinks are formed Cross inks 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 Cytotoxic ty is cell cycle nonspecific

In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma In combination with 5 fluorouracil, oxal plat n exhibits *in v tro* and *in vivo* antiproliferative activity greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)]

12.3 Pharmacokinetics

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum n plasma ultrafiltrate The decline of ultrafi terable platinum levels following oxaliplatin administration is tr phasic, character zed by two relat vely 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 s ngle 2 hour intravenous nfusion of oxaliplatin for injection at a dose of 85 mg/m² expressed as ultrafilterable platinum were C_{max} of 0 814 mcg/mL and volume of distribution of 440 L

Interpatient and intrapatient variability in ultrafiltrable platinum exposure (AUC_{0-48hr}) assessed over 3 cycles was moderate to low (23% and 6%, respectively) A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established

Distribution

At the end of a 2 hour infusion of oxaliplatin for 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 proteins are albumin and gamma globulins Platinum also binds irreversibly 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

Metabolism

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 (monochloro DACH platinum, dichloro DACH platinum, and monoaquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species

Elimination

The major route of platinum elimination is renal excretion At five days after a single 2 hour infusion of oxaliplatin for injection, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2% Platinum was cleared from plasma at a rate (10 to 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 ultrafilterable platinum The renal clearance of ultrafilterable platinum is significantly correlated with GFR

Pharmacokinetics in Special Populations

Pediatric

[See Use In Specific Patient Populations (8 4)]

Renal Impairment

A study was conducted in 38 patients with advanced GI cancer and varying degrees of renal impairment Patients in the normal (creatinine clearance (CrCL) > 80 mL/min, N 11), mild (CrCL 50 to 80 mL/min, N 13), and moderate (CrCL 30 to 49 mL/min, N 10) groups were treated with 85 mg/m² oxaliplatin for injection and those in the severe (CrCL < 30 mL/min, N 4) group were treated with 65 mg/m² oxaliplatin for injection The mean AUC of unbound platinum was 40%, 95%, and 342% higher in the mild, moderate, and severe groups, respectively, than in the normal group Mean C_{max} of unbound platinum appeared to be similar among the normal, mild and moderate renal function groups, but was 38% higher in the severe group than in the normal group Caution should be exercised in renally impaired patients *[see Use in Specific Populations (8 6)]* The starting dose of oxaliplatin for injection should be reduced in patients with severe renal impairment *[see Dosage and Administration (2 2)]*

Drug Drug Interactions

No pharmacok netic interaction between 85 mg/m² of oxaliplatin for injection and infusional 5 fluorouracil has been observed in patients treated every 2 weeks, but increases of 5 fluorourac l plasma concentrations by approximately 20% have been observed with doses of 130 mg/m² of oxaliplatin for injection administered every 3 weeks *In vitro*, platinum was not displaced from plasma proteins by the following medications erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel *In vitro*, oxaliplatin is not metabolized by, nor does it inhibit, human cytochrome P450 isoenzymes No P450 mediated drug drug nteractions are therefore anticipated in patients S nce platinum containing species are elim nated pr marily through the kidney, clearance of these products may be decreased by coadministration of potentially nephrotoxic compounds, a though this has not been spec fical y 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 mutagenic to mammalian cells *in v tro* (L5178Y mouse lymphoma assay) Oxaliplatin was clastogenic both *in vitro* (chromosome 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 mat ng w th females that received two cycles of oxal plat n 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 oxal plat n 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 bas s

14 CLINICAL STUDIES

14.1 Combination Adjuvant Therapy with Oxaliplatin for Injection and Infusional 5-fluorouracil/leucovorin in Patients with Colon Cancer

An international, multicenter, random zed study compared the efficacy and evaluated the safety of oxaliplatin for injection in combination with an infusional schedule of 5 fluorouracil/leucovorin to infusional 5 fluorouraci /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 object ve of the study was to compare the 3 year disease free survival (DFS) in patients receiv ng oxaliplatin for njection and infusional 5 fluorouracil/leucovorin to those receiv ng 5 fluorouracil/ eucovorin alone Patients were to be treated for a total of 6 months (i e , 12 cyc es) 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 h stologically proven stage II (T_3 T_4 N0 M0; Dukes' B2) or III (any T N_{1-2} M0; Dukes' C) colon carcinoma (with the inferior pole of the tumor above the peritoneal ref ection, i e , ≥15 cm from the anal margin) and undergone (w thin 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 embryogenic ant gen (CEA) < 10 ng/mL Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were ne igib e for th s trial

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

Table 15 - Dosing Regimens in Adjuvant Therapy Study

Treatment Arm	Dose	Regimen
Oxa iplatin for Injection + 5 FU/LV (FOLFOX4) (N 1123)	Day 1 Oxaliplatin for Injection 85 mg/m² (2 hour infusion) + LV 200 mg/m² (2 hour nfusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion) Day 2 LV 200 mg/m² (2 hour infusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion)	every 2 weeks 12 cycles
5 FU/LV (N 1123)	Day 1 LV 200 mg/m² (2 hour infusion), fo lowed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion) Day 2 LV 200 mg/m² (2 hour infusion), fo lowed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion)	every 2 weeks 12 cycles

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

Table 16 - Patient Characteristics in Adjuvant Therapy Study

	Oxaliplatin for Injection + Infusional 5 FU/LV N 1123	Infusional 5 FU/LV N 1123
Sex Male (%)	56 1	52 4
Female (%)	43 9	47 6
Median age (years)	61	60
<65 years of age (%)	64 4	66 2
≥65 years of age (%)	35 6	33 8
Karnofsky Performance Status (KPS) (%)		
100	29 7	30 5
90	52 2	53 9
80	4 4	3 3
70	13 2	11 9
≤60	0 6	0 4
Primary s te (%)		
Colon inc uding cecum	54 6	54 4
Sigmoid	31 9	33 8
Recto sigmoid	12 9	10 9
Other including rectum	0 6	0 9
Bowel obstruction (%)		
Yes	17 9	19 3
Perforation (%)		
Yes	6 9	6 9
Stage at Random zation (%)		
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 (%)		
T1	0 5	0 7
T2	4 5	4 8
T3	76	75 9
T4	19	18 5
Staging N (%)		
N0	40 2	39 9
N1	39 4	39 4
N2	20 4	20 7
Staging M (%)		
M1	0 4	0 8

Table 17 - Dosing in Adjuvant Therapy Study

	Oxaliplatin for Injection + Infusional 5 FU/LV N 1108	Infusional 5 FU/LV N 1111
Median Relative Dose Intensity (%)		
5 FU	84 4	97 7
Oxal plat n for Injection	80 5	N/A
Median Number of Cycles	12	12
Median Number of cycles with oxaliplatin for injection	11	N/A

The fo low ng 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

Table 18 - Summary of DFS analysis - ITT analysis

Parameter	Oxaliplatin for Injection + Infusional 5 FU/LV	Infusional 5 FU/LV
Overa l		
N	1123	1123
Number of events relapse or death (%)	304 (27 1)	360 (32 1)
Disease free survival % [95% CI]*	73 3 [70 7, 76]	67 4 [64 6, 70 2]
Hazard ratio [95% CI]**	0 8 [0 68, 0 93]	
Stratified Logrank test	p 0 003	
Stage III (Dukes' C)		
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]	58 9 [55 2, 62 7]
Hazard ratio [95% CI]**	0 78 [0 65, 0 93]	
Logrank test	p 0 005	
Stage II (Dukes' B2)		
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 favors Oxaliplatin for Injection + Infusional 5 fluorouracil/leucovorin

In the overall and stage III colon cancer populations DFS was statistically significantly improved in the oxaliplatin for 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 for 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 for injection and infusional 5 fluorouracil/leucovorin combination and infusional 5 fluorouracil/leucovorin alone in Stage III patients

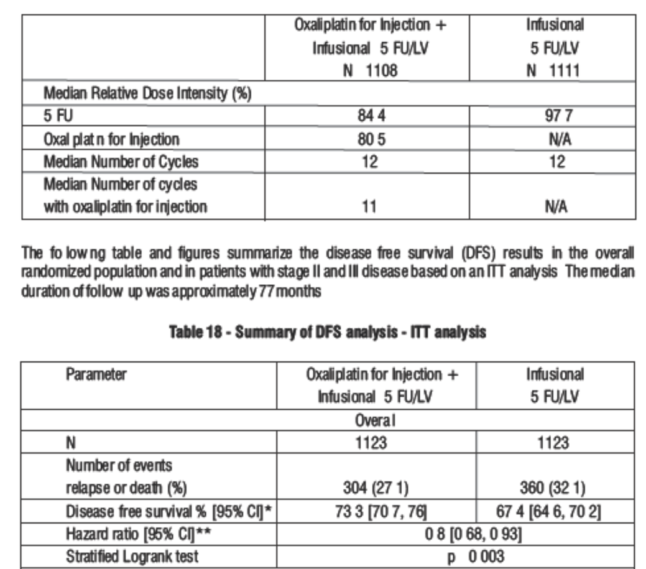


Figure 2 - DFS Kaplan-Meier curves by treatment arm (cutoff: 1 June 2006) ITT population

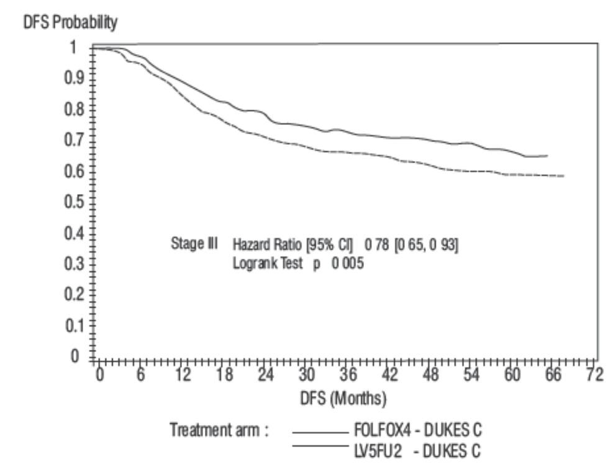


Figure 3 - DFS Kaplan-Meier curves by treatment arm in Stage III patients (cutoff: 1 June 2006) ITT population

The following table summarizes the overall survival (OS) results n the overall random zed population and in pat ents with stage II and III disease, based on the ITT analysis

Table 19 - Summary of OS analysis - ITT analysis

Parameter	Oxaliplatin for Injection +Infusional 5 FU/LV	Infusional 5 FU/LV
Overa l		
N	1123	1123
Number of death events (%)	245 (21 8)	283 (25 2)
Hazard ratio* [95% CI]	0 84 [0 71, 1]	
Stage III (Dukes' C)		
N	672	675
Number of death events (%)	182 (27 1)	220 (32 6)
Hazard ratio* [95% CI]	0 8 [0 65, 0 97]	
Stage II (Dukes' B2)		
N	451	448
Number of death events (%)	63 (14)	63 (14 1)
Hazard ratio* [95% CI]	1 [0 7, 1 41]	

* A hazard ratio of less than 1 favors Oxaliplatin for Injection + Infusional 5 fluorouracil/leucovorin
Data cut off for overall survival 16 January 2007

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

A North American, mu ticenter, open label, randomized controlled study was sponsored by the National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer Treatment Group (NCCTG) The study had 7 arms at different times during its conduct, four of which were closed due to e ther changes in the standard of care, toxicity, or simplification During the study, the control arm was changed to irinotecan plus 5 fluorouracil/leucovorin The results reported below compared the efficacy and safety of two experimental regimens, oxaliplatin for njection in combination w th infusional 5 fluorouracil/leucovor n and a comb nation of oxaliplatin for injection plus irinotecan, to an approved control regimen of irinotecan p us 5 fluorouracil/leucovorin in 795 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer After completion of enrollment, the dose of ir notecan plus 5 fluorouracil/leucovorin was decreased due to toxicity Patients had to be at east 18 years of age, have known locally advanced, locally recurrent, or metastatic colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent, histologically proven colorectal adenocarcinoma, measurable or evaluable disease, with an ECOG performance status 0, 1, or 2 Patients had to have granulocyte count ≥ 1 5 x 10⁹/L, platelets ≥ 100 x 10⁹/L, hemoglobin ≥ 9 gm/dL, creatinine ≤ 1 5 x ULN, total bilirubin ≤ 1 5 mg/dL, AST ≤ 5 x ULN, and a kaline phosphatase ≤ 5 x ULN Pat ents may have received adjuvant therapy for resected Stage II or III disease w thout recurrence within 12 months The patients were stratified for ECOG performance status (0, 1 vs 2), prior adjuvant chemotherapy (yes vs no), prior immunotherapy (yes vs no), and age (<65 vs ≥ 65 years) Although no post study treatment was specified in the protocol, 65 to 72% of patients received additional post study chemotherapy after study treatment discontinuation on all arms Fifty eight percent of patients on the oxaliplatin for injection p us 5 f uorouraci /leucovorin arm received an rinotecan containing regimen and 23% of patients on the irinotecan plus 5 fluorouracil/leucovorin arm received oxa iplatin containing regimens Oxaliplatin was not commercially available during the trial

The following table presents the dosing regimens of the three arms of the study

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

Treatment Arm	Dose	Regimen
Oxa iplatin for Injection + 5 FU/LV (FOLFOX4) (N 267)	Day 1 Oxaliplatin for Injection 85 mg/m² (2 hour infusion) + LV 200 mg/m² (2 hour infusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion) Day 2 LV 200 mg/m² (2 hour infusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion)	every 2 weeks
Irinotecan + 5 FU/LV (IFL) (N 264)	Day 1 irinotecan 125 mg/m² as a 90 min infusion + LV 20 mg/m² as a 15 min infusion or intravenous push, followed by 5 FU 500 mg/m² intravenous bolus weekly x 4	every 6 weeks
Oxaliplatin for Injection + Irinotecan (IROX) (N 264)	Day 1 Oxaliplatin for Injection 85 mg/m² ntravenous (2 hour infusion) + irinotecan 200 mg/m² ntravenous over 30 minutes	every 3 weeks

The following table presents the demographics of the patient population entered into this study

Table 21 - Patient Demographics in Patients Previously Untreated for Advanced Colorectal Cancer Clinical Trial

	Oxaliplatin for Injection + 5 FU/LV N 267	Irinotecan + 5 FU/LV N 264	Oxa iplat n for Injection + Irinotecan N 264
Sex Male (%)	58 8	65 2	61
Female (%)	41 2	34 8	39
Median age (years)	61	61	61
<65 years of age (%)	61	62	63
≥65 years of age (%)	39	38	37
ECOG (%)			
0 1	94 4	95 5	94 7
2	5 6	4 5	5 3
Involved organs (%)			
Colon only	0 7	0 8	0 4
Liver only	39 3	44 3	39
Liver + other	41 2	38 6	40 9
Lung only	6 4	3 8	5 3
Other (inc uding lymph nodes)	11 6	11	12 9
Not reported	0 7	1 5	1 5
Prior radiation (%)	3	1 5	3
Prior surgery (%)	74 5	79 2	81 8
Prior adjuvant (%)	15 7	14 8	15 2

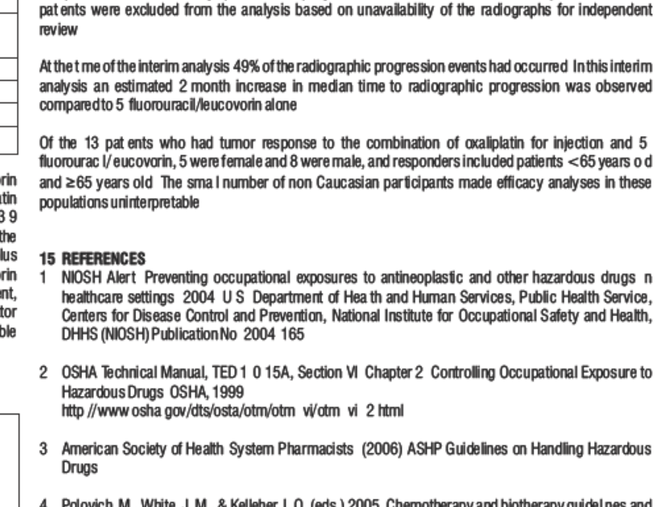
The length of a treatment cycle was 2 weeks for the oxaliplatin for injection and 5 fluorouracil/leucovorin regimen; 6 weeks for the irinotecan p us 5 fluorouracil/leucovorin regimen; and 3 weeks for the oxaliplatin for injection plus irinotecan regimen The median number of cycles administered per patient was 10 (23 9 weeks) for the oxaliplatin for injection and 5 fluorourac l/ eucovorin regimen, 4 (23 6 weeks) for the rinotecan p us 5 f uorouraci /leucovorin regimen, and 7 (21 weeks) for the oxaliplatin for njection plus rinotecan regimen Patients treated with the oxaliplatin for injection and 5 fluorouracil/leucovorin combination had a significantly longer time to tumor progression based on investigator assessment, longer overall survival, and a s gnificantly higher confirmed response rate based on investigator assessment compared to patients given irinotecan plus 5 fluorouracil/leucovorin The following table summarizes the efficacy results

Table 22 - Summary of Efficacy

	Oxaliplatin for Injection + 5 FU/LV N 267	Irinotecan +5 FU/LV N 264	Oxaliplatin for Injection + Irinotecan N 264
Survival (ITT)			
Number of deaths N (%)	155 (58 1)	192 (72 7)	175 (66 3)
Median survival (months)	19 4	14 6	17 6
Hazard Ratio and (95% confidence interval)	0 65 (0 53 to 0 8)*		
P value	<0 0001*		
TTP (ITT, investigator assessment)			
Percentage of progressors	82 8	81 8	89 4
Median TTP (months)	8 7	6 9	6 5
Hazard Ratio and (95% confidence interva)***	0 74 (0 61 to 0 89)*		
P value	0 0014*		
Response Rate (invest gator assessment)**			
Pat ents with measurable disease	210	212	215
Complete response N (%)	13 (6 2)	5 (2 4)	7 (3 3)
Partial response N (%)	82 (39)	64 (30 2)	67 (31 2)
Complete and partial response N (%)	95 (45 2)	69 (32 5)	74 (34 4)
95% confidence interval	(38 5 to 52)	(26 2 to 38 9)	(28 1 to 40 8)
P value	0 008*		

* Compared to irinotecan plus 5 fluorouracil/leucovorin (IFL) arm
** Based on all patients with measurable disease at baseline
*** The numbers in the response rate and TTP analysis are based on unblinded investigator assessment
**** A hazard ratio of less than 1 favors Oxaliplatin for Injection + Infusional 5 fluorouracil/leucovorin

Figure 4 illustrates the Kaplan Meier survival curves for the comparison of oxaliplatin for injection and 5 fluorouracil/leucovorin combination and oxaliplatin for injection plus irinotecan to irinotecan plus 5 fluorouracil/leucovorin



* Log rank test comparing Oxaliplatin for Injection plus 5 FU/LV to Irinotecan plus 5 FU/LV

Figure 4 - Kaplan-Meier Overall Survival by treatment arm

A descriptive subgroup analys s demonstrated that the improvement in surv val for oxaliplatin for injection plus 5 fluorouracil/leucovorin compared to irinotecan p us 5 fluorouracil/leucovorin appeared to be maintained across age groups, prior adjuvant therapy, and number of organs invo ved An estimated survival advantage in oxal plat n for injection plus 5 fluorouracil/leucovor n versus irinotecan plus 5 f uorouraci /leucovorin was seen in both genders; however it was greater among women than men Insufficient subgroup sizes prevented analysis by race

14.3 Combination Therapy with Oxaliplatin for Injection and 5-fluorouracil/leucovorin in Previously Treated Patients with Advanced Colorectal Cancer

A multicenter, open label, randomized, three arm controlled study was conducted in the US and Canada comparing the efficacy and safety of oxa iplatin for injection in combination with an infusional schedule of 5 fluorouracil/leucovorin to the same dose and schedule of 5 fluorourac l/ eucovorin alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/progressed dur ng or within 6 months of f rst line therapy with bolus 5 fluorouracil/leucovorin and irinotecan The study was intended to be analyzed for response rate after 450 patients were enrolled Survival will be subsequently assessed in all patients enrolled in the completed study Accrual to this study is complete, with 821 pat ents enrolled Patients in the study had to be at east 18 years of age, have unresectable, measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky performance status > 50% Pat ents had to have SGOT(AST) and SGPT(ALT) ≤ 2x the institution s upper imit of normal (ULN), un ess l ver metastases were present and documented at baseline by CT or MRI scan, in which case ≤ 5x ULN was permitted Patients had to have alkaline phosphatase ≤ 2x the institution s ULN, unless liver metastases were present and documented at baseline by CT or MRI scan, in which cases ≤ 5x ULN was permitted Prior radiotherapy was permitted if it had been completed at least 3 weeks before randomization

The dos ng regimens of the three arms of the study are presented in the table below

Table 23 - Dosing Regimens in Refractory and Relapsed Colorectal Cancer Clinical Trial

Treatment Arm	Dose	Regimen
Oxaliplatin for Injection + 5 FU/LV (N 152)	Day 1 Oxaliplatin for Injection 85 mg/m² (2 hour infusion) + LV 200 mg/m² (2 hour infusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion) Day 2 LV 200 mg/m² (2 hour infusion), followed by 5 FU 400 mg/m² (bo us), 600 mg/m² (22 hour infusion)	every 2 weeks
5 FU/LV (N 151)	Day 1 LV 200 mg/m² (2 hour nfusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion) Day 2 LV 200 mg/m² (2 hour nfusion), followed by 5 FU 400 mg/m² (bolus), 600 mg/m² (22 hour infusion)	every 2 weeks
Oxaliplatin for Injection (N 156)	Day 1 Oxaliplatin for Injection 85 mg/m² (2 hour nfusion)	every 2 weeks

Patients entered into the study for evaluation of response must have had at least one unidimensional lesion measuring ≥ 20mm using conventional CT or MRI scans, or ≥ 10mm us ng a spiral CT scan Tumor response and progression were assessed every 3 cyc es (6 weeks) using the Response Evaluation Criteria in Solid Tumors (RECIST) until radiological documentation of progression or for 13 months follow ng the first dose of study drug(s), whichever came first Conf rmed responses were based on two tumor assessments separated by at least 4 weeks

The demographics of the patient population entered into this study are shown in the tab e below

Table 24 - Patient Demographics in Refractory and Relapsed Colorectal Cancer Clinical Trial

	5 FU/LV (N 151)	Oxaliplatin for Injection (N 156)	Oxa iplatin for Injection + 5 FU/LV (N 152)
Sex Male (%)	54 3	60 9	57 2
Female (%)	45 7	39 1	42 8
Median age (years)	60	61	59
Range	21 to 80	27 to 79	22 to 88
Race (%)			
Caucasian	87 4	84 6	88 8
Black	7 9	7 1	5 9
Asian	1 3	2 6	2 6
Other	3 3	5 8	2 6
KPS (%)			
70 to 100	94 7	92 3	95 4
50 to 60	2 6	4 5	2
Not reported	2 6	3 2	2 6
Prior radiotherapy (%)	25 2	19 2	25
Prior pelvic radiation (%)	18 5	13 5	21 1
Number of metastatic sites (%)			
1	27 2	31 4	25 7
≥2	72 2	67 9	74 3
Liver nvolvement (%)			
Liver only	22 5	25 6	18 4
Liver + other	60 3	59	53 3

The median number of cycles administered per patient was 6 for the oxal plat n for injection and 5 fluorouraci /leucovorin comb nation and 3 each for 5 fluorouracil/leucovor n alone and oxa iplatin for injection alone

Patients treated with the comb nation of oxaliplatin for injection and 5 fluorourac l/ eucovorin had an increased response rate compared to patients g ven 5 fluorouracil/leucovorin or oxa iplatin alone The efficacy results are summarized in the tables below

Table 25 - Response Rates (ITT Analysis)

Best Response	5 FU/LV (N 151)	Oxal platin for Injection (N 156)	Oxaliplatin for Injection + 5 FU/LV (N 152)
CR	0	0	0
PR	0	2 (1%)	13 (9%)
p value	0 0002 for 5 FU/LV vs Oxal platin for Injection + 5 FU/LV		
95% CI	0 to 2 4%	0 2 to 4 6%	4 6 to 14 2%

Table 26 - Summary of Radiographic Time to Progression*

Arm	5 FU/LV (N 151)	Oxaliplatin for Injection (N 156)	Oxaliplatin for Injection + 5 FU/LV (N 152)
No of Progressors	74	101	50
No of patients w th no radiological evaluation beyond basel ne	22 (15%)	16 (10%)	17 (11%)
Median TTP (months)	2 7	1 6	4 6
95% CI	1 8 to 3	1 4 to 2 7	4 2 to 6 1

*This is not an ITT analysis Events were imited to radiographic disease progression documented by independent review of radiographs Clinical progression was not nc uded in th s analysis, and 18% of pat ents were excluded from the analysis based on unavailability of the radiographs for independent review

At the t me 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 pat ents who had tumor response to the combination of oxaliplatin for injection and 5 fluorourac l/ eucovorin, 5 were female and 8 were male, and responders included patients <65 years o d and ≥65 years old The sma l number of non Caucasian participants made efficacy analyses in these populations uninterpretable

15 REFERENCES

1 NIOSH Alert Preventing occupational exposures to antineoplastic and other hazardous drugs n healthcare settings 2004 U S Department of Hea th and Human Services, Public Health Service, Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health, DHHS (NIOSH) Publication No 2004 165

2 OSHA Technical Manual, TED 1 0 15A, Section VI Chapter 2 Controlling Occupational Exposure to Hazardous Drugs OSHA, 1999
http //www osha gov/dts/osta/otm/otm vi/otm vi 2 html

3 American Society of Health System Pharmacists (2006) ASHP Guidelines on Handling Hazardous Drugs

4 Polovich, M , White, J M , & Kelleher, L O (eds) 2005 Chemotherapy and biotherapy guidel nes and recommendations for practice (2nd ed) Pittsburgh, PA Oncology Nursing Society

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Oxal platin for Injection USP is supplied in clear, glass, single use vials with gray elastomeric stoppers and aluminum flip off sea s conta n ng 50 mg or 100 mg of oxaliplatin as a sterile, preservative free lyophilized powder for reconstitution Lactose monohydrate is also present as an inact ve ingred ent

NDC 47335 176 40 50 mg single use vial with grey flip off seal individually packaged in a carton
NDC 47335 178 40 100 mg sing e use vial with green flip off seal individually packaged in a carton

16.2 Storage

Store under normal lighting conditions at 20° to 25°C (68° to 77°F); excursions permitted between 15° and 30°C (59° and 86°F) [see USP Controlled Room Temperature]

16.3 Handling and Disposal

As with other potentially toxic anticancer agents, care should be exercised in the hand ing and preparation of infusion solutions prepared from oxaliplatin for injection The use of gloves is recommended If a solution of oxaliplatin for injection contacts the skin, wash the skin immediately and thoroughly with soap and water If oxaliplatin for injection contacts the mucous membranes, flush thoroughly with water

Procedures for the handling and disposal of anticancer drugs should be considered Several guidelines on the subject have been published *[see References (15)]* There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Patients and patients' caregivers should be informed of the expected side effects of oxaliplatin for injection, particularly its neurologic effects, both the acute, reversible effects and the persistent neurosensory toxicity Patients should be informed that the acute neurosensory toxicity may be precipitated or exacerbated by exposure to cold or cold objects Patients should be instructed to avoid cold drinks, use of ice, and should cover exposed skin prior to exposure to cold temperature or cold objects

Patients must be adequately informed of the risk of low blood cell counts and instructed to contact their physician immediately should fever, particularly if associated with persistent diarrhea, or evidence of infection develop

Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of dehydration, cough or breathing difficulties occur, or signs of allergic reaction appear

No studies on the effects on the ability to drive and use machines have been performed However oxaliplatin treatment resulting in an increased risk of dizziness, nausea and vomiting, and other neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the ability to drive and use machines

Vision abnormalities, in particular transient v sion loss (revers b e following therapy discontinuation), may affect patients' ability to drive and use mach nes Therefore, pat ents shou d be warned of the potential effect of these events on the ability to drive or use machines

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17.2 FDA-Approved Patient Labeling

See Patient Information provided separately

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PATIENT INFORMATION

OXALIPLATIN FOR INJECTION, USP FOR INTRAVENOUS USE

Read this patient information leaflet carefully before you start receiving oxaliplatin for injection. There may be new information. It will help you learn more about oxaliplatin for injection. This leaflet does not take the place of talking to your doctor about your medical condition or your treatment. Ask your doctor about any questions you have.

What is the most important information I should know about oxaliplatin for injection?

Serious side effects can happen in people taking oxaliplatin for injection, including:

- **Serious allergic reactions. Oxaliplatin for injection can cause serious allergic reactions, including allergic reactions that may cause death.** Oxaliplatin for injection is a platinum base medicine. Serious allergic reactions including death can occur in people who take oxaliplatin for injection and who have had previous allergic reactions to platinum medicines. Serious allergic reactions can happen within a few minutes of your infusion or any time during your treatment with oxaliplatin for injection.

Get emergency help right away if you:

- **have trouble breathing.**
- **feel like your throat is closing up.**

Call your doctor right away if you have any of the following signs or symptoms of an allergic reaction:

- rash
- flushed face
- hives
- itching
- swelling of your lips or tongue
- sudden cough
- dizziness or feel faint
- sweating
- chest pain

See "What are the possible side effects of oxaliplatin for injection" for information about other serious side effects.

What is oxaliplatin for injection?

Oxaliplatin for injection is an anti-cancer (chemotherapy) medicine that is used with other anti-cancer medicines called 5-fluorouracil and leucovorin to treat people with:

- stage III colon cancer after surgery to remove the tumor
- advanced colon or rectal cancer (colo-rectal cancer).

Oxaliplatin for injection with infusional 5-fluorouracil and leucovorin was shown to lower the chance of colon cancer returning when given to patients with stage III colon cancer after surgery to remove the tumor. Oxaliplatin for injection also increases survival in patients with stage III colon cancer. Oxaliplatin for injection with infusional 5-fluorouracil and leucovorin was also shown to increase survival, shrink tumors and delay growth of tumors in some patients with advanced colorectal cancer.

It is not known if oxaliplatin for injection works in children.

Who should not use oxaliplatin for injection?

- Do not use oxaliplatin for injection if you are allergic to any of the ingredients in oxaliplatin for injection or other medicines that contain platinum. Cisplatin and carboplatin are other chemotherapy medicines that also contain platinum. See the end of this leaflet for a complete list of the ingredients in oxaliplatin for injection.

Ask your doctor if you are not sure if you take a medicine that contains platinum.

What should I tell my doctor before treatment with oxaliplatin for injection?

Before receiving oxaliplatin for injection, tell your doctor if you:

- have kidney problems
- have any other medical conditions
- have had any allergic reactions to any medicines
- are pregnant or plan to become pregnant. Oxaliplatin for injection may harm your unborn child. You should avoid becoming pregnant while taking oxaliplatin for injection. Talk with your doctor about how to avoid pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if oxaliplatin passes into your breast milk. You and your doctor should decide whether you will stop breastfeeding or not take oxaliplatin for injection.

Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Know the medicines you take. Keep a list of them and show it to your doctor and pharmacist when you get a new medicine.

How is oxaliplatin for injection given to me?

Oxaliplatin for injection is given to you through your veins (blood vessels).

- Your doctor will prescribe oxaliplatin for injection in an amount that is right for you.
- Your doctor will treat you with several medicines for your cancer.
- It is very important that you do exactly what your doctor and nurse have taught you to do.
- Some medicines may be given to you before oxaliplatin for injection to help prevent nausea and vomiting.
- Oxaliplatin for injection is given with 2 other chemotherapy medicines, leucovorin and 5-fluorouracil.
- Each treatment course is given to you over 2 days. You will receive oxaliplatin for injection on the first day only.
- There are usually 14 days between each chemotherapy treatment course.

<u>Treatment Day 1:</u>

Oxaliplatin for injection and leucovorin are given through a thin plastic tube put into a vein (intravenous infusion or I.V.) and given for 2 hours. You will be watched by a healthcare provider during this time.

Right after the oxaliplatin for injection and leucovorin are finished, 2 doses of 5-fluorouracil will be given. The first dose is given right away into your I.V. tube. The second dose will be given into your I.V. tube over the next 22 hours, using a pump device.

<u>Treatment Day 2:</u>

You will not get oxaliplatin for injection on Day 2. Leucovorin and 5-fluorouracil will be given the same way as on Day 1.

During your treatment with oxaliplatin for injection:

- It is important for you to keep all appointments. Call your doctor if you must miss an appointment. There may be special instructions for you.
- Your doctor may change how often you get oxaliplatin for injection, how much you get, or how long the infusion will take.
- You and your doctor will discuss how many times you will get oxaliplatin for injection.

The 5-fluorouracil will be given through your I.V. with a pump. If you have any problems with the pump or the tube, call your doctor, your nurse, or the person who is responsible for your pump. Do not let anyone other than a healthcare provider touch your infusion pump or tubing.

What activities should I avoid while on treatment with oxaliplatin for injection?

- Avoid cold temperatures and cold objects. Cover your skin if you must go outside in cold temperatures.
- Do not drink cold drinks or use ice cubes in drinks.
- Do not put ice or ice packs on your body.

See "How can I reduce the side effects caused by cold temperatures?" for more information.

Talk with your doctor and nurse about your level of activity during treatment with oxaliplatin for injection. Follow their instructions.

What are the possible side effects of oxaliplatin for injection?

Oxaliplatin for injection can cause serious side effects, including:

- **Serious allergic reactions.** See "What is the most important information I should know about oxaliplatin for injection?"
- **Nerve problems.** Oxaliplatin for injection can affect how your nerves work and make you feel. Tell your doctor right away if you get any signs of nerve problems listed below:
  - Very sensitive to cold temperatures and cold objects
  - Trouble breathing, swallowing, or saying words, jaw tightness, odd feelings in your tongue, or chest pressure
  - Pain, tingling, burning (pins and needles, numb feeling) in your hands, feet, or around your mouth or throat, which may cause problems walking or performing activities of daily living.
- **Reversible Posterior Leukoencephalopathy (RPLS).** RPLS is a rare condition that affects the brain. Tell your doctor right away if you have any of the following signs and symptoms of RPLS:
  - headache
  - confusion or a change in the way you think
  - seizures
  - vision problems, such as blurriness or vision loss. You should not drive, operate heavy machines, or engage in dangerous activities if you have vision problems while receiving oxaliplatin for injection.

The first signs of nerve problems may happen with the first treatment. The nerve problems can also start up to 2 days after treatment. If you develop nerve problems, the amount of oxaliplatin for injection in your next treatment may be changed or oxaliplatin for injection treatment may be stopped.

For information on ways to lessen or help with the nerve problems, see the end of this leaflet, "How can I reduce the side effects caused by cold temperatures?"

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- **Lung problems (interstitial fibrosis).** Tell your doctor right away if you get a dry cough and have trouble breathing (shortness of breath) before your next treatment. These may be signs of a serious lung disease.
- **Liver problems (hepatotoxicity).** Your doctor will do blood tests to check your liver.
- **Harm to an unborn baby. Oxaliplatin for injection may cause harm to your unborn baby.** See "What should I tell my doctor before treatment with oxaliplatin for injection?"

The most common side effects of oxaliplatin for injection include:

- Decreased blood counts: Oxaliplatin for injection can cause a decrease in neutrophils (a type of white blood cells important in fighting in bacterial infections), red blood cells (blood cells that carry oxygen to the tissues), and platelets (important for clotting and to control bleeding).
- High blood pressure (hypertension)
- Infection Call your doctor right away if you get any of the following signs of infection:
  - Fever (temperature of 100.5° F or greater)
  - Chills or shivering
  - Cough that brings up mucus
  - Burning or pain on urination
  - Pain on swallowing
  - Sore throat
  - Redness or swelling at intravenous site
- Bleeding or bruising. Tell your doctor about any signs or symptoms of bleeding or bruising.
- Nausea
- Vomiting
- Diarrhea
- Constipation
- Mouth sores
- Stomach pain
- Decreased appetite
- Tiredness
- Injection site reactions. Reactions may include redness, swelling, pain, tissue damage at the site of injection.
- Hair loss (alopecia)
- Dehydration (too much water loss). Call you doctor if you have signs of dehydration including:
  - tiredness
  - thirst
  - dry mouth
  - lightheadedness (dizziness)
  - decreased urination

Tell your doctor if you have any side effect that bothers your or that does not go away. These are not all the possible side effects of oxaliplatin for injection. For more information, ask your doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How can I reduce the side effects caused by cold temperatures?

- Cover yourself with a blanket while you are getting your oxaliplatin for injection infusion.
- Do not breathe deeply when exposed to cold air.
- Wear warm clothing in cold weather at all times. Cover your mouth and nose with a scarf or a pull-down cap (ski cap) to warm the air that goes to your lungs.
- Wear gloves when taking things from the freezer or refrigerator.
- Drink fluids warm or at room temperature.
- Always drink through a straw.
- **Do not** use ice chips if you have nausea or mouth sores. Ask your healthcare provider or doctor about what you can use.
- Be aware that most metals are cold to touch, especially in the winter. These include your car door and mailbox. Wear gloves to touch cold objects.
- Do not run the air-conditioning at high levels in the house or in the car in hot weather.
- If your body gets cold, warm-up the affected part. If your hands get cold, wash them with warm water.
- Always let your healthcare provider or doctor know **before** your next treatment how well you did since your last visit.

This list is not complete and your healthcare provider or doctor may have other useful tips for helping you with these side effects.

General information about the safe and effective use of oxaliplatin for injection

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet.

This patient information leaflet summarizes the most important information about oxaliplatin for injection. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about oxaliplatin for injection that is written for health professionals.

What are the ingredients in oxaliplatin for injection?

Active ingredient: oxaliplatin USP
Powder for solution for infusion inactive ingredients: lactose monohydrate

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