HIGHLIGHTS OF PRESCRIBING INFORMATION These highlights do not include all the information needed to use Oxaliplatin for njection, USP safely and effectively. See for

prescribing information for Oxaliplatin for Injection, USP. Oxaliplatin for Injection, USP for intravenous

Initial U.S. Approval: 2002

Rx only

WARNING: ANAPHYLACTIC REACTIONS See full prescribing information for complete Anaphylactic reactions to Oxaliplatin Injection, USP have been reported, and may occur within minutes of Oxaliplatin for Injection, USP administration, Epinephrine,

been employed to alleviate symptoms. (5.1) - RECENT MAJOR CHANGES DOSAGE AND ADMINISTRATION (2.2)

WARNINGS AND PRECAUTIONS (5.1. 5.2)

-- INDICATIONS AND USAGE --Oxaliplatin for Injection is a platinum-based drug used in combination with infusional 5-fluorouracil /leucovorin, which is indicated for:

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

----- DOSAGE AND ADMINISTRATION -----combination with 5-fluorouracil/leucovorin .

- <u>Day 1:</u> Oxaliplatin for Injection 85 mg/m<sup>2</sup> intravenous infusion in 250-500 mL 5% fetus. (5.5, 8.1)
Dextrose Injection, USP and leucovorin 200 mg/m2 intravenous infusion in 5% Dextrose tion, USP both given over 120 minutes at the same time in separate bags using a followed by 5-fluorouracil 600 mg/m<sup>2</sup> nous infusion in 500 mL 5% De Injection, USP (recommended) as a 22-hour

Day 2: leucovorin 200 mg/m² intravenous

To report SUSPECTED ADVERSE REACTIONS, 2: leucovorin 200 mg/m² intravenous sion over 120 minutes, followed by parauracii 400 mg/m² IV holus given 1-800-FDA-1088 or www.fda.gov/medwatch 5-fluorouracil 400 mg/m2 IV bolus given 600 mg/m² intravenous infusion in 500 mL and FDA approved patient labeling. 5% Dextrose Injection, USP (recommended)

· Reduce the dose of Oxaliplatin for Injection

ed colorectal cancer) (2.2): there are persistent grade 2 neurosensory events that do not resolve.

after recovery from grade 3/4 gastrointestinal toxicities (despite prophylactic treatment)

persistent Grade 3 neurosensory events. (2.2)
Never reconstitute or prepare final dilution with

a sodium chloride solution or other chloride--- 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 -

other platinum compounds. (4, 5.1) -- WARNINGS AND PRECAUTIONS --· Allergic Reactions: Monitor for development urticaria, erythema, pruritis,

bronchospasm, and hypotension. (5.1) Neuropathy: Reduce the dose or discontinue Oxaliplatin for Injection if necessary. (5.2) Pulmonary Toxicity: May need to discontinue Oxaliplatin for Injection until interstitial lung 2.3 Preparation of Infusion Solution

should be apprised of the potential harm to the ----- ADVERSE REACTIONS ---Most common adverse reactions (incidence (36-46°F)].

stomatitis. Other adverse reactions, including serious adverse reactions, have been reported.

over 2-4 minutes, followed by 5-fluorouracil See 17 for Patient Counseling Information

14.1 Combination Adjuvant Therapy with

with Stage II or III Colon Cancer

14.2 Combination Therapy with Oxaliplatin for

Advanced Colorectal Cancer

Advanced Colorectal Cancer

16 HOW SUPPLIED/STORAGE AND HANDLING

5-fluorouracil/leucovorin in Patients

Injection and 5- fluorouracil/leucovoring

in Patients Previously Untreated for

14 CLINICAL STUDIES

15 REFERENCES

16.2 Storage

16.1 How supplied

16.3 Handling and Disposal

17 1 Information for Patients

prescribing information are not listed

17 PATIENT COUNSELING INFORMATION

17.2 FDA-Approved Patient Labeling

Sections or subsections omitted from the full

Revised: December 2012 sterile, preservative-free lyophilized powder for reconstitution.

### FULL PRESCRIBING INFORMATION: CONTENTS\* 12 CLINICAL PHARMACOLOGY 12.1 Mechanism of Action WARNING 12.3 Pharmacokinetics

1 INDICATIONS AND USAGE DOSAGE AND ADMINISTRATION

2.2 Dose Modification Recommendation 2.3 Preparation of Infusion Solution DOSAGE FORMS AND STRENGTHS

CONTRAINDICATIONS 5 WARNINGS AND PRECAUTIONS 5.1 Allergic Reactions 5.2 Neurologic Toxicity

5.3 Pulmonary Toxicity

5.4 Hepatotoxicity 5.5 Use in Pregnancy

6 ADVERSE REACTIONS 6.1 Clinical Trials Experience

6.2 Postmarketing Experience

7 DRUG INTERACTIONS 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy 8.4 Pediatric Use 8.5 Geriatric Use

10 OVERDOSAGE 11 DESCRIPTION

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

1 INDICATIONS AND USAGE

Oxaliplatin for Injection, 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

treatment of advanced colorectal cance

2 DOSAGE AND ADMINISTRATION Oxaliplatin for Injection should be administered under the supervision of a qualified physician complications is possible only when adequate diagnostic and treatment facilities are readily available

**2.1 Dosage**Administer Oxaliplatin for Injection in combination with 5- fluorouracil/leucovorin every 2 weeks. For

advanced disease, treatment is recommended until disease progression or unacceptable toxicity. For adjuvant use, treatment is recommended for a total of 6 months (12 cycles): Day 1: Oxaliplatin for Injection 85 mg/m<sup>2</sup> intravenous infusion in 250-500 mL 5% Dextrose injection, JSP and leucovorin 200 mg/m² intravenous infusion in 5% Dextrose injection, USP both given over

120 minutes at the same time in separate bags using a Y-line followed by 5- fluorouracil 400 mg/m<sup>2</sup> s bolus given over 2-4 minutes, followed by 5- fluorouracil 600 mg/m² intravenous infusion in 500 mL 5% Dextrose injection, USP (recommended) as a 22-hour continuous infusion. Day 2: Leucovorin 200 mg/m² intravenous infusion over 120 minutes, followed by 5- fluorouracil 400 mg/m<sup>2</sup> intravenous bolus given over 2-4 minutes, followed by 5- fluorouracil 600 mg/m<sup>2</sup> intravenous nfusion in 500 mL 5% Dextrose injection, USP (recommended) as a 22-hour continuous infusion.

Day 1	5-FU bolus 400 mg/m² ↓ over 2-4 minutes	Day 2	5-FU bolus 400 mg/m <sup>2</sup> ↓ over 2-4 minutes
Leucovorin 200 mg/m²	5-FU infusion 600 mg/m²	Leucovorin 200 mg/m²	5-FU infusion 600 mg/m <sup>2</sup>
Oxaliplatin for Injection 85 mg/m² 0 h ←2 hrs→	2 h ← 22 hrs →	0 h ←2 hrs→	2 h ← 22 hrs →

The administration of Oxaliplatin for Injection does not require prehydration. Premedication with antiemetics, including 5-HT<sub>3</sub> blockers with or without dexamethasone, is recommended. For information on 5-fluorouracil and leucovorin, see the respective package inserts.

2.2 Dose Modification Recommendations

to 75 mg/m² (adjuvant setting) or 65 mg/m² Injection from 2 hours to 6 hours may mitigate acute toxicities. The infusion times for 5- fluorouracil Reactions (6.2)1. Diagnosis of RPLS is based upon confirm 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)1.

or grade 4 neutropenia or grade 3/4 For patients who experience persistent Grade 2 neurosensory events that do not resolve, a dose reduction of Oxaliplatin for Injection to 75 mg/m<sup>2</sup> should be considered. For patients with persistent neutrophils ≥1.5 x 10<sup>9</sup>/L and platelets ≥75 x 10<sup>9</sup>/L. and platelets ≥75

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

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

Grade 3 neurosensory events, discontinuing therapy should be considered. The 5- fluorouracil/ alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be leucovorin regimen need not be altered.

• Known allergy to Oxaliplatin for Injection or bolus and 500 mg/m² 22-hour infusion) is recommended for patients after recovery from grade 3/4 (6.1)]. astrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5 x 10<sup>9</sup>/L and platelets ≥75 x 10<sup>9</sup>/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 is  $85\ mg/m^2$ . In patients with severe renal impairment, the initial recommended Oxaliplatin for Injection dose should be reduced to 65 mg/m<sup>2</sup> [see Use in Specific Populations (8.6) and

disease or pulmonary fibrosis are excluded. (5.3)

Reconstitution or final dilution must never be performed with a sodium chloride solution or other chloride containing solutions. The lyophilized powder is reconstituted by adding 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 further diluted in an infusion administered to a pregnant woman. Women solution of 250-500 mL of 5% Dextrose Injection, USP.

After reconstitution in the original vial, the solution may be stored up to 24 hours under refrigeration [2-8°C (36-46°F)]. After final dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life 6 ADVERSE REACTIONS is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C 6.1 Clinical Trials Experience

≥ 40%) were peripheral sensory neuropathy, Oxaliplatin for Injection is not light sensitive.

Y-line, followed by 5-fluorouracil 400 mg/m² intrombocytopenia, infrombocytopenia, anemia, oxaliplatin for Injection is incompatible in solution with alkaline medications or media (such as basic solutions of 5-fluorouracil) and must not be mixed with these or administered simultaneously through phosphatase, diarrhea, emesis, fatigue and 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 aluminum parts that may come in contact with Oxaliplatin for Injection should not be used for the preparation or mixing of the drug. Aluminum has

> 3 DOSAGE FORMS AND STRENGTHS Oxaliplatin for Injection is supplied in single-use vials containing 50 mg or 100 mg of oxaliplatin as a

been reported to cause degradation of platinum compounds.

4 CONTRAINDICATIONS Oxaliplatin for Injection should not be administered to patients with a history of known allergy to

Oxaliplatin for Injection or other platinum compounds [see Warnings and Precautions (5.1)].

5 WARNINGS AND PRECAUTIONS

13 NONCLINICAL TOXICOLOGY 5.1 Allergic Reactions See boxed warning 13.1 Carcinogenesis,

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to Oxaliplatin for Injection has been observed in 2-3% of colon cancer patients. These allergic reactions which can be fatal. has been observed in 2-3% of colon cancer patients. These allergic reactions which can be ratal, can occur within minutes of administration and at any cycle, 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, Oxaliplatin for Injection and Infusional 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 is contraindicated in these patients [see Contraindications (4)]. Drug-related deaths associated with

platinum compounds from anaphylaxis have been reported 14.3 Combination Therapy with Oxaliplatin for Injection and 5- fluorouracil/leucovorin 5.2 Neurologic Toxicity

Previously Treated Patients with Neuropathy Oxaliplatin for Injection is associated with 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 recui 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 individual cycle acute neurotoxicity was observed in approximately 30% of patient 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 cycles administered on the Oxaliplatin for Injection with 5- fluorouracil/leucovorin combination arm was 6.

An acute syndrome of pharyngolaryngeal dysesthesia seen in 1-2% (grade 3/4) of patients previous untreated for advanced colorectal cancer, and the previously treated patients is characterized by bjective sensations of dysphagia or dyspnea, without any laryngospasm or bronchospasm stridor or wheezing), Ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplati Injection because cold temperature can exacerbate acute neurological symptoms

A persistent (>14 days) primarily peripheral sensory neuronathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include deficits in propriception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving Oxaliplatin for Injection with 5- fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persisten uropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patient 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:

Mild paresthesias, loss of deep tendon reflexes Mild or moderate objective sensory loss, moderate pare Grade 3 Severe objective sensory loss or paresthesias that interfere with function Grade 4 Not applicable

Peripheral sensory neuropathy was reported in adjuvant patients treated with the Oxaliplatin fo Injection combination with a frequency of 92% (all 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-specific neurotoxicity scale, which was different from the NCI CTC scale, Version 2.0 (see below)

Table 2 - Grading Scale for Paresthesias/Dysesthesias in Advanced Colorectal Cancer Patients Interfered with function but not daily activities
Pain or functional impairment that interfered with daily activities Persistent impairment that is disabling or life-threatening

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

Reversible Posterior Leukoencephalopathy Syndrome Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES, Posterior Reversible Encephalopathy Syndrome) has been observed in clinical trials (< 0.1%) and postmarketing Prior to subsequent therapy cycles, patients should be evaluated for clinical toxicities and recommended laboratory tests [see Warnings and Precautions (5.6)]. Prolongation of infusion time for Oxaliplatin for

5.3 Pulmonary Toxicity xaliplatin for Injection has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade ally or the data. The operation of the overall frequency of adverse reactions was similar in men compared to 4.5% (any grade) and no grade 4 events in the Oxaliplatin for Injection plus infusional 5- fluorouracil/levencevorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5- fluorouracil/levencevorin arm and women and in patients <65 and ≥65 years. However, the following grade 3/4 events were more

leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic common in females: diarrhea, fatigue, granulocytopenia, nausea and vomiting. In patients ≥65 years onia in the Oxaliplatin for Injection combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the Oxaliplatin for Injection plus 5-(creatinine clearance <30 mL/min), the initial recommended dose is 65 mg/m² (2.2)

Discontinue Oxaliplatin for Injection of Oxaliplatin for Injection to 75 mg/m² and infusional 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the initial recommended dose is 65 mg/m² (2.2)

Discontinue Oxaliplatin for Injection to 75 mg/m² and infusional 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the initial recommended for patients after recovery from grade 3/4 particular arm compared to 32% (any grade) and 5% (grade 3 and 4) in the initial recommended for patients after recovery from grade 3/4 particular arm compared to 32% (any grade) and 5% (grade 3 and 4) in the initial recommended for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive counts. Ausnnea cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, weight decrease, coughing. further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity as evidenced in the adjuvant study, by increase in transaminases (57% vs. 34%) and

alkaline phosphatase (42% vs. 20%) was observed more commonly in the Oxaliplatin for Injection For patients who experience 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 arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal

> 5.5 Use in Pregnancy Pregnancy Category D

Oxaliplatin for Injection 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 should be advised to avoid becoming pregnant while receiving treatment with Oxaliplatin for Injection, I see Use in Specific Populations (8.1)1.

5.6 Recommended Laboratory Tests Standard monitoring of the white blood cell count with differential, hemoglobin, platelet count, and blood chemistries (including ALT, AST, bilirubin and creatinine) is recommended before each Oxaliplatin for Injection cycle [see Dosage and Administration (2)].

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

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary xicities and hepatotoxicities can occur [See Warnings and Precautions (5.1)].

neutropenia, thrombocytopenia, anemia, Oxaliplatin for Injection is incompatible in solution with alkaline medications or media (such as basic Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. More than 1100 patients with stage II or III colon cancer and more than 4,000 patients with advanced Hypersensition

colorectal cancer have been treated in clinical studies 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, increase in transaminases and alkaline phosphatase, diarrhea, emesis, fatigue and stomatitis. The most common adverse reactions in previously untreated and treated patients were peripheral sensory neuropathies, fatique, neutropenia, ausea, emesis, and diarrhea [see Warnings 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 with stage II or III colon cancer, who had undergone

complete resection of the primary tumor, have been treated in a clinical study with Oxaliplatin 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 receiving Oxaliplatin for Injection and infusional 5-fluorouracil/leucovorin. Both 5-fluorouracil/ leucovorin and Oxaliplatin for Injection are associated with gastrointestinal or hematologic adverse reactions. When Oxaliplatin for Injection is administered in combination with infusional 5- fluorouracil/ leucovorin, the incidence of these events is increased.

The incidence of death within 28 days of last treatment, regardless of causality, was 0.5% (n=6) in both the Oxaliplatin for Injection combination and infusional 5- fluorouracil/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, respectively. On the Oxaliplatin for Injection combination arm, 3 deaths were due to sepsis/neutropenic sepsis, 2 from intracerebral bleeding and one from eosinophilic pneumonia. On the 5- fluorouracil/leucovorin 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 Isee Clinical Studies (14) by body system and decreasing order of frequency in the Oxaliplatin for jection and infusional 5- fluorouracil/leucovorin arm for events with overall incidences  $\geq$  5% and for NCI grade 3/4 events with incidences  $\geq 1\%$ .

Table 3 - Adverse Reactions Reported in Patients with Colon Cancer receiving Adjuvant Treatment

(≥5%	6 of all patients and	I with ≥1% NCI Grad	e 3/4 events)	
		jection + 5-FU/LV 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
	Allerg	gy/Immunology		
Allergic Reaction	10	3	2	<1
	Constitutio	nal Symptoms/Pain		
Fatigue	44	4	38	1
Abdominal Pain	18	1	17	2
	Derr	matology/Skin		
Skin Disorder	32	2	36	2
Injection Site Reaction <sup>1</sup>	11	3	10	3
	Gas	strointestinal		
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
	Fe	ver/Infection		
Fever	27	1	12	1
Infection	25	4	25	3
	i	Neurology		
Overall Peripheral				

<sup>1</sup> Includes thrombosis related to the catheter 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% 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 nationts, but with <1% NCI Grade 3/4 events) Ovalinlatin for Injection ± 5-FII/I V

5-FU/L All Grades (% Adverse reaction (WHO/Pref) Allergy/Immunolo onal Symptoms/Pain/ Headache Dermatology/Skin

Metabolic							
Phosphate Alkaline increased	42	20					
	Neurology						
Sensory Disturbance	8	1					

old, the incidence of grade 3/4 diarrhea and granulocytopenia was higher than in younger patients. Insufficient subgroup sizes prevented analysis of safety by race. The following additional adverse reactions, were reported in ≥2% and <5% of the patients in the Oxaliplatin for Injection and infusional The number of patients who developed secondary malignancies was similar; 62 in the Oxaliplatin for

Injection combination arm and 68 in the infusional 5- fluorouracil/leucovorin arm. An exploratory. Adverse reactions were similar in men and women and in patients -65 and >65 years, but older allysis showed that the number of deaths due to secondary malignancies was 1.96% in the patients may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia, fatigue Dxaliplatin for Injection combination arm and 0.98% in infusional 5- fluorouracil/leucovorin arm. In and syncope. The following additional adverse reactions, at least possibly related to treatment and addition, the number of cardiovascular deaths was 1.4% in the Oxaliplatin for Injection combination arm as compared to 0.7% in the infusional 5- fluorouracil/leucovorin arm. Clinical significance of these

Patients Previously Untreated for Advanced Colorectal Cancer

5-FU/LV

Myalgia

ebrile neutr

Hyperglyce

Urinary freq

Not otherwise specified

(WHO/Pref)

hinitis allergic

Neight loss

Tearing

Dysphasia

Alopecia

Taste perversion

Absolute neutrophil coun

The following table provides adverse reaction

colorectal cancer study [see Clinical Studies (14

in the Oxaliplatin for Injection and 5- fluoroura incidences ≥5% but with incidences <1% NCI G

Cancer Clinical Trial (≥5% of all pa

Oxaliplatin for Injection -

5-FU/LV N=259

All Grades (%

Two hundred and fifty-nine patients were treated in the Oxaliplatin for Injection and 5- fluorouracil A dose reduction of Oxaliplatin for Injection to 65 mg/m² and 5- fluorouracil by 20% (300 mg/m² or portal hypertension, which cannot be explained by liver metastases [see Clinical Trials Experience]

Previously Treated Patients with Advanced Colorectal Cancer

| Previously Treated Patients with Advanced Colorectal Cancer 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 in the tables below. Both 5- fluorouracil and Oxaliplatin for Injection are associated with gastrointestinal and hematologic colorectal cancer *[see Clinical Studies (14)]*. The adverse reaction profile in this study was similar to adverse reactions. When Oxaliplatin for Injection is administered in combination with 5- fluorouracil, the incidence of these events is increased.

neuropathies. Both 5- fluorouracil and Oxaliplatin for Injection are associated with gastrointestinal and hematologic adverse reactions. When Oxaliplatin for Injection is administered in combination with 5leucovorin combination, 5% with irinotecan plus 5- fluorouracil/leucovorin, and 3% with Oxaliplatin for njection plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the Oxaliplatin or Injection and 5- fluorouracil/leucovorin combination, 5.1% with irinotecan plus 5- fluorouracil/ leucovorin, and 3.1% with Oxaliplatin for Injection plus irinotecan.

The following 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 oxaliplatin for Injection alone, and 7% with 5- fluorouracil/leucovorin. Of the 7 deaths that occurred on ectal cancer study [see Clinical Studies (14)] by body system and decreasing order of frequency in the Oxaliplatin for Injection 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)

5-FU/LV

+ irinotecan

	N=	259	N=2	56	N=2	258	abiliorinancios, crioso		paratory boro	•••			
eaction	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4	Table 7 – Adverse R						cal Trial
Pref)	(%)	(%)	(%)	(%)	(%)	(%)		of all pat	ients and wi	th ≥1% NCI G	rade 3/4 eve	nts)	
	99	82 Allergy	98 /Immunology	70	99	76	Adverse reaction		J/LV 142)	Oxaliplatin (N=1	•	Oxaliplatin + 5-F	for Injec FU/LV
tivity	12	2	5	0	6	1	(WHO/Pref)	(N=	142)	(14=	133)	(N=	150)
		Card	iovascular				(WIIO/I ICI)	All Grades		All Grades	Grade	All Grades	Grade
S	6	5	6	6	3	3		(%)	(%)	(%)	3/4 (%)	(%)	(%
n	5	3	6	3	4	3	Any Event	98	41	100	46	99	73
	Const	itutional Symp	ptoms/Pain/O	cular/Visual						diovascular			
	70	7	58	11	66	16	Dyspnea	11	2	13	7	20	4
Pain	29	8	31	7	39	10	Coughing	9	0	11	0	19	1
	14	2	6	0	9	2	Edema	13	1	10	1	15	1
	7	1	5	1	6	1	Thromboembolism	4	2	2	1	9	8
ormal	5	0	2	1	6	1	Chest Pain	4	1	5	1	8	1
	5	0	0	0	2	1				nal Symptoms			
		Derma	tology/Skin				Fatigue	52	6	61	9	68	7
on -							Back Pain	16	4	11	0	19	3
	7	1	2	1	1	0	Pain	9	3	14	3	15	2
te	_			_					Dern	natology/Skin			
	6	0	1 1	0	4	1	Injection Site	5	1	9	0	10	3
			ointestinal			- 10	Reaction				"	10	
	71	6	67	15	83	19				trointestinal			
	56	12	65	29	76	25	Diarrhea	44	3	46	4	67	11
	41	4	43	13	64	23	Nausea	59	4	64	4	65	11
	38	0	25	1	19	1	Vomiting	27	4	37	4	40	9
_	35	2	25	4	27	5	Stomatitis	32	3	14	0	37	3
n	32	4	27	2	21	2	Abdominal Pain	31	5	31	7	33	4
	40	2	10	7	10	3	Anorexia	20	1	20	2	29	3
tinal	13		16	- /	16	<u> </u>	Gastroesophageal	3	0	1	0	5	2
stinal	_	_		_	_	_	Reflux						
	5	2	4	2	3	2				ology/Infectio			
		Hemato	logy/Infection				Fever	23	1	25	1	29	1
ormal		l .	_		_		Febrile Neutropenia	1	1	0	0	6	6
	10	4	5	1	7	2			epatic/Metal	olic/Laborato			
W			40				Hypokalemia	3	1	3	2	9	4
	8	8	12	11	9	8	Dehydration	6	4	5	3	8	3
nia	6 4	2	4 15	1	5	2				leurology			
tropenia		7		14	12	11	Neuropathy	17	0	76	7	74	7
mio	14	epatic/Metabo		у/ <b>непа</b> т З	12	3	Acute	10	0	65	5	56	2
mia		3	7	4	6	2	Persistent	9	0	43	3	48	6
ia	11 9	5	16	11	14	7	The following table	provides adve	rse reaction:	s reported in t	the previousl	y treated stud	ly [see C
n inomio	8	0	5	2	9	1	Studies (14)] by bod	ly system and	in decreasin	g order of free	quency in the	Oxaliplatin fo	r Injectio
ninemia		2	7				5- fluorouracil/leuco	vorin combina	tion arm for	events with ov	verall inciden	ces ≥5% but v	vith incid
nia	- 8 - 5	1	2	1	3	1	<1% NCI Grade 3/4 6	events.					
quency	] 0				_ J		Toble 0 Adverse D	locations P	artad In Pro-	rionalu Tre-t-	d Colorost-1	Concor Cli-:-	ol Tric!
ronath.	82	19	urology 18	2	69	7	Table 8 - Adverse R			viousiy i reate h < 1% NCI Gi			ai irial
ıropathy	77	18	16	2	62	6						,	
as	11	10	10		02	0			FU/LV	Oxaliplatin fo		Oxaliplatin t	
								(N	=142)	(N=15	53)	+ 5-F	U/LV

\* Absolute neutrophil coun

pigmentation changes, and urticaria.

fluorouracil, the incidence of these events is increased

rmalities; these are shown separately below.

pneumonitis, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nai

changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone pain

that seen in other studies and the adverse reactions in this trial are shown in the tables below.

Thirteen percent of patients in the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination

The incidence of death within 30 days of treatment in the previously treated study, regardless of

the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination arm within 30 days of stopping treatment, 3 may have been treatment related, associated with gastrointestinal bleeding or dehydration.

Studies (14) by body system and in decreasing order of frequency in the Oxalinlatin for Injection

and 5- fluorouracil/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

e following table provides adverse reactions reported in the previously treated study [see Clinical

u	lmonary				Allergic Reaction	1	3	10			
_	25	2	17	1	Rash	5	5	9			
	14	3	11	2		Ca	rdiovascular				
_	2	0	3	2	Peripheral Edema	11	5	10			
					Constitutional Symptoms/Pain/Ocular/Visual						
					Headache	8	13	17			
1	s reported in	the previous	elv untreated	for advanced	Arthralgia	10	7	10			
	4)] by body sys				Epistaxis	1	2	9			
	cil/leucovorin c				Abnormal Lacrimation	6	1	7			
	rade 3/4 events		uiiii ioi ovoiii	o with overall	Rigors	6	9	7			
					Dermatology/Skin						
tients Previously Untreated for Advanced Colorectal tients but with < 1% NCI Grade 3/4 events)					Hand-Foot Syndrome	13	1	11			
					Flushing	2	3	10			
T	Irinotecan +	E EII/I V	Oxaliplatin fo	r Injection +	Alopecia	3	3	7			
l	N=25	,	irinote	ecan	Gastrointestinal						
	N=20	10	N=2	58	Constipation	23	31	32			
T	All Grade	s (%)	All Grad	es (%)	Dyspepsia	10	7	14			
y	/Immunology				Taste Perversion	1	5	13			
Ì	4		7		Mucositis	10	2	7			
I	6		6		Flatulence	6	3	5			
d	iovascular					Hepatic/Metabolic/Laboratory/Renal					
I	13		10	)	Hematuria	4	0	6			
ı	ptoms/Pain/Oc	cular/Visual			Dysuria	1	1	6			
I	6		9				Neurology				
I	9		11	1	Dizziness	8	7	13			
I	2		2		Insomnia	4	11	9			
1 1 0					Dulmanam						

act Infection

Adverse reactions were similar in men and women and in patients <65 and ≥65 years, but older patients may have been more susceptible to dehydration, diarrhea, hypokalemia and fatigue. 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 Injection and 5- fluorouracil/leucovori ination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous ras increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, ahnormal micturition frequency dry skin, pruritus, hemophysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes

Hematologic Changes

ne following tables list the hematologic changes occurring in ≥5% of patients, based on laboratory values and NCI grade, with the exception of those events occurring in adjuvant patients and anemia in usly untreated for advanced colorectal cancer, respectively, which are based on AE

eporting and NCI grade alone. Table 9 - Adverse Hematologic Reactions in Patients with Colon Cancer Receiving Adjuvant Therapy (≥5% of patients)

		r Injection + 5-FU/LV N=1108)	5-FU/LV (N=1111)		
Hematology Parameter	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	

Oxaliplatin for Injection + 5-FU/LV (N=259)		Irinotecan	+ 5-FU/LV 256)	Oxaliplatin for Injection + irinotecan (N=258)		
Hematology	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Parameter	(%)	(%)	(%)	(%)	(%)	(%)
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

Oxaliplatin for Injection (N=142)(N=153)All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 (%) (%) Thrombocytopenia and Bleeding

abocytopenia 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 iously treated patients was higher on the Oxaliplatin for Injection combination arm compared to the infusional 5- fluorouracil/leucovorin arm. These events included gastrointestinal bleeding, hematuria,

and epistaxis. 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 atients treated for advanced colorectal cancer the incidence of Grade 3/4 thrombocytopenia was 3-5%, and the incidence of these events was greater for the combination of Oxaliplatin for Injection and 5fluorouracil/leucovorin over the irinotecan plus 5- fluorouracil/leucovorin or 5- fluorouracil/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%, respectively, in the irinotecan plus 5- fluorouracil/leucovorin or irinotecan plus Oxaliplatin for Injection arms.

Neutropenia was frequently observed with the combination of Oxaliplatin for Injection and 5orouracil/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, respectively. Grade 3 and 4 events were reported in 27% and 17% of previously treated patients, respectively. In adjuvant patients the incidence of either febrile neutropenia (0.7%) or documented infection with concomitant grade 3/4 neutropenia (1.1%) was 1.8% in the Oxaliplatin for Injection and 5- fluorouracil/leucovorin arm. The incidence of febrile neutropenia in the patients previously untreated for advanced colorectal cancer was 15% (3% of cycles) in the innotecan plus 5- fluorouracil/leucovorin arm and 4% (less than 1% of cycles) in the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination arm. Additionally, in this 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 incidence of febrile neutropenia in the iously 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/leucovorin combination arm.

In patients receiving the combination of Oxaliplatin for Injection plus infusional 5- fluorouracil/ leucovorin for adjuvant treatment for colon cancer the incidence of Grade 3/4 nausea and vomiting was greater than those receiving infusional 5- fluorouracil/leucovorin alone (see table). In patients previously untreated for advanced colorectal cancer receiving the combination 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- fluorouracil/leucovorin controls (see table). In previously treated patients receiving the combination of Oxaliplatin for Injection and 5- fluorouracil/leucovorin, the cidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5- fluorouracil/leucovorin controls (see table).

The incidence of gastrointestinal adverse reactions in the previously untreated and previously treated patients appears to be similar across cycles. Premedication with antiemetics, including 5-HT<sub>3</sub> blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of Oxaliplatin for Injection Clinical 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 cidences avoided during the infusion of Oxaliplatin for Injection.

Oxaliplatin for Injection did not increase the incidence of alopecia compared to 5- fluorouracil/ eucovorin alone. No complete alopecia was reported. The incidence of Grade 3/4 skin disorders was 2% in both the Oxaliplatin for Injection plus influsional 5- fluorouracil/leucovorin and the influsional 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 irinotecan plus 5- fluorouracil/leucovorin arm and 7% in the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination arm. The incidence of hand-foot syndrome in previously treated patients was 13% in the uracil/leucovorin arm and 11% in the Oxaliplatin for Injection and 5- fluorourac combination arm.

Intravenous Site Reactions

travasation, in some cases including necrosis, has been reported. Injection site reaction, including redness, swelling, and pain, has been reported

Anticoagulation and Hemorrhage

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

ut 5-10% 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 Oxaliplatin for Injection and 5- fluorouracil/leucovorin nation arm was 1% in the previously treated patients. Serum creatinine measurements were not reported in the adjuvant trial. Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to Oxaliplatin for Injection

nistry changes associated with hepatic toxicity 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 previously treated patients. Table 12 - Adverse Hepatic Reactions in Patients with Stage II or III Colon Cancer Receiving

combination therapy [see Warnings and Precautions (5.4)]. The following tables list the clinical

Adjuvant Therapy (≥5% of patients) 5-FII/I V Oxaliplatin for Injection + 5-FU/LV (N=1108)(N=11111)Grade 3/4 All Grades (%) (%) (%) (%) crease in

Table 13 - Adverse Hepatic - Clinical Chemistry Abnormalities in Patients Previously Untreated for

	Adv	anced Color	ectal Cancer (2	≥5% of patient	is)	
	Oxaliplatin for Injection + irinotecan (N=258)					
Clinical	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Chemistry	(%)	(%)	(%)	(%)	(%)	(%)
ALT	6	1	2	0	5	2
(SGPT-ALAT)						

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 treatmer 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

 Serious allergic reactions. Oxaliplatin for Injection can cause serious allergic reactions, including allergic eactions that may cause death. Oxaliplatin for Injectio is a platinum base medicine. Serious allergic reactions cluding death can occur in people who take Oxaliplatin or Injection and who have had previous allergic reactions to platinum medicines. Serious allergic reactions can appen 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: flushed face hives

swelling of your lips or tongue

sweating

See "What are the possible side effects of Oxaliplatin for Injection" for information about serious side effects What is Oxaliplatin for Injection? Oxaliplatin for Injection is an anti-cancer (chemotherapy

icine 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 vorin was shown to lower the chance of colon cance returning when given to patients with stage III colon cancer

after surgery to remove the tumor. Oxaliplatin for Injection

Oxaliplatin for Injection with infusional 5- fluorouracil and vorin was also shown to increase survival, shrin 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 platinum. See the end of this leaflet for a complete list of Ask your doctor if you are not sure if you take a medicine

What should I tell my doctor before treatment with Oxaliplatin for Injection Before receiving Oxaliplatin for Injection, tell your doctor

· 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.

You and your doctor should decide whether you will stop breastfeeding or not take Oxalinlatin for Injection Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and

are breastfeeding or plan to breastfeed. It is not know

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

· It is very important that you do exactly what your doctor

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

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 nedicines, 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. Treatment Day 1: Oxaliplatin for Injection and leucovorin are given through a thin plastic tube put into a vein (intravenous infusion or LV.) and given for 2 hours. You will be watched by a healthcare

Right after the Oxaliplatin for Injection and Jeucovorin 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 You will not get Oxaliplatin for Injection on Day 2. Leucovor and 5- fluorouracil will be given the same way as on Day 1.

provider during this time.

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

During your treatment with Oxaliplatin for Injection:

It is important for you to keep all appointments. Call your

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 nsible 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 skir 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.

temperatures?" for more information.

Talk with your doctor and nurse about your level of activity during treatment with Oxaliplatin for Injection. Follow the What are the possible side effects of Oxaliplatin for

Oxaliplatin for Injection can cause serious side effects:

see "How can I reduce the side effects caused by cold

Dimension: 600 x 380 mm Rev.: 0; Ver.: 1; Dt.: 08.01.13

Front Side

- . 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 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:
- confusion or a change in the way you think
- 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
- 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?
- Lung problems (interstitial fibrosis). Tell your doctor right away if you get a dry cough and have  $\sqrt{\text{Liver and Gastrointestinal system disorders:}}$ next treatment. These may be signs of a serious lung
- · 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

The most common side effects with Oxaliplatin for Injection

 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 · 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)
- cough that brings up mucus
- · chills or shivering
- burning or pain on urination pain on swallowing
- redness or swelling at intravenous site . Bleeding or bruising. Tell your doctor about any signs or
- symptoms of bleeding or bruising.

sore throat

- Nausea Vomiting
- Constipation
- Mouth sores · Stomach pair Decreased appetite
- · Injection site reactions. Reactions may include redness, swelling, pain, tissue damage at the site of injection.
- · Hair loss (alopecia)
- Dehvdration (too much water loss). Call you doctor if you have signs of dehydration including:
- tiredness
- · 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 vour doctor or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088 or Pfizer, nc. at 1-800-438-1985

## How can I reduce the side effects caused by cold

- 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
- 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
- Do not run the air-conditioning at high levels in the house
- or in the car in hot weather
- -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. 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. ou can ask your doctor or pharmacist for information about Oxaliplatin for Injection that is written for health

## What are the ingredients in Oxaliplatin for Injection?

Powder for solution for infusion inactive ingredients: lactose



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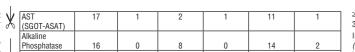


Table 14 - Adverse Hepatic - Clinical Chemistry Abnormalities in Previously Treated Patients

(20 /0 of patients)								
		J/LV 142)		for Injection 153)	Oxaliplatin for Injection + 5-FU/LV (N=150)			
Clinical Chemistry	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)		
ALT (SGPT-ALAT)	28	3	36	1	31	0		
AST (SGOT-ASAT)	39	2	54	4	47	0		
Total Bilirubin	22	6	13	5	13	1		

The incidence of thromboembolic events in adjuvant patients with 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 Oxaliplatin for Injection and infusional 5- fluorouracil/leucovorin combined arm, respectively. The incidence was 6 and clearance < 30 mL/min) [see Dosage and Administration (2.2)]. 9% of the patients previously untreated for advanced colorectal cancer and previously treated patients n the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination arm, respectively.

The following adverse reactions have been identified during post-approval use of Oxaliplatin for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not

Several cases of overdoses have been reported with Oxaliplatin for Injection. Adverse reactions observed always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

### angioedema, anaphylactic shock

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

trouble breathing (shortness of breath) before your severe diarrhea/vomiting resulting in hypokalemia, colitis (including *Clostridium difficile* diarrhea), 11 DESCRIPTION metabolic acidosis; ileus; intestinal obstruction, pancreatitis; veno-occlusive disease of liver also known as sinusoidal obstruction syndrome, and perisinusoidal fibrosis which rarely may progress. Hearing and vestibular system disorders:

Platelet, bleeding, and clotting disorders: immuno-allergic thrombocytopenia

prolongation of prothrombin time and of INR in patients receiving anticoagulants Red Blood Cell disorders: molytic uremic syndrome, immuno-allergic hemolytic anemia

### Renal disorders: Acute tubular necrosis, acute interstitial nephritis and acute renal failure.

Respiratory system disorders: pulmonary fibrosis, and other interstitial lung diseases (sometimes fatal)

Vision disorders: decrease of visual acuity, visual field disturbance, optic neuritis and transient vision loss (reversible ingredient at 450 mg and 900 mg in the 50 mg and 100 mg dosage strengths, respectively.

### following therapy discontinuation 7 DRUG INTERACTIONS

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m<sup>2</sup> Oxaliplatin for Injection and 5-fluorouracil/leucovorin 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 eliminated primarily 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

Pregnancy Category D

Based on direct interaction with DNA, Oxaliplatin for Injection 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. Reproductive 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 embryo-fetal development at maternal doses that were below the recommended human dose based on the reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafiliterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases (t<sub>1,20</sub>, 0.43 hours and t<sub>1,20</sub>, 16.8 hours) and the total development at maternal doses that were below the recommended human dose based on the commendation of the unbound platinum in plasma to the productive 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 the productive toxicity studies are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafiltrates are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafiltrates are present as a fraction of the unbound platinum in plasma ultrafiltrates.

Pregnant rats were administered oxaliplatin at less than one-tenth the recommended human dose based on body surface area during gestation days 1-5 (pre-implantation), 6-10, or 11-16 (during organogenesis). Oxaliplatin caused developmental mortality (increased early resorptions) when administered on days 6-10 and 11-16 and adversely affected fetal growth (decreased fetal weight, delayed ossification) when administered on days 6-10. Administration of oxaliplatin to male and female rats prior to mating resulted in 97% post implantation loss in animals that received approximately one seventh the recommended human dose based on the body surface area.

It is 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

Metabolism in nursing infants from Oxaliplatin for Injection, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

ne effectiveness of oxaliplatin in children has not been established. Oxaliplatin has been tested in 2 patients, including several cytotoxic species (monochloro DACH platinum, dichloro DACH platinum, Phase 1 and 2 Phase 2 trials in 235 patients ages 7 months to 22 years with solid tumors (see below)

And monoaquo and diaquo DACH platinum) and a number of noncytotoxic, conjugated species.

received 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 present of t the main adverse reactions. No responses were observed.

In a second Phase 1 study, oxaliplatin was administered 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 Renal Impairment the winter. These include your car door and mailbox. Wear gloves to touch cold objects.

The following table and figures summarize the disease-free survival (DFS) results in the overall tumors mainly neuroblastoma and ganglioneuroblastoma. No responses were observed. The DLT was been not run the air-conditioning at high levels in the house on the cold objects.

The following table and figures summarize the disease-free survival (DFS) results in the overall tumors mainly neuroblastoma and ganglioneuroblastoma. 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 sensory neuropathy at the 160 mg/m² dose. Based on these studies, oxaliplatin 130 mg/m² as a 2-hour median duration of follow-up was approximately 77 months.

> platinum appeared to be similar among the normal, mild and moderate renal function groups, but ox amplatin 130 mg/m² every 3 weeks for a maximum of 12 months in absence of progressive disease are 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.
>
> By description of the distribution of the common adverse reactions reported were leukopenia (65%, G3/4: 12%), neutropenia (58%, G3/4: 16%) and sensory neuropathy (40%, G3/4: 5%). One partial response was observed.
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> osteosarcoma, Eving sarcoma or peripheral PNET, ependymoma, rhabdomyosarcoma, hepatoblastoma, high grade astrocytoma, Brain stem glioma, low grade astrocytoma, malignant germ cell tumor and other tumors of interest received oxaliplatin 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: 63/4: 9%), vomiting (26%, G3/4: 2%). Now partial responses were observed. G3/4: 17%), anemia (37%, G3/4: 97%), volinting (20%, G3/4: 97%), repartial responses were observed.
>
> AST increased (24%, G3/4: 2%), and nausea (23%, G3/4: 3%). Two partial responses were observed.
>
> Since platinum-containing species are eliminated primarily through the kidney, clearance of these The pharmacokinetic parameters of ultrafiltrable platinum have been evaluated in 105 pediatric patients during the first cycle. The mean clearance in pediatric patients estimated by the population has not been specifically studied. pharmacokinetic analysis was 4.7 L/h. The inter-patient variability of platinum clearance in pediatric cancer patients was 41%. Mean platinum pharmacokinetic parameters in ultrafiltrate were  $C_{max}$  of 0.75 ± 0.24 mcg/mL, AUC<sub>0-40</sub> of 7.52 ± 5.07 mcg-h/mL and AUC<sub>m</sub> of 8.83 ± 1.57 mcg-h/mL at 85 mg/m<sup>2</sup> of 3.11 Carcinogenesis, Mutagenesis, Impairment of Fertility  $\pm$  0.24 mcg/mL, AUC<sub>0-48</sub> or 7.52  $\pm$  5.07 micy finite and AUC<sub>inf</sub> or 0.05  $\pm$  1.57 meg finite at 65 mg. a coaliplatin and C<sub>max</sub> of 1.10  $\pm$  0.43 mcg/mL, AUC<sub>0-48</sub> of 9.74  $\pm$  2.52 mcg•h/mL and AUC<sub>inf</sub> of 17.3  $\pm$  5.34 Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin and C<sub>max</sub> of 1.10  $\pm$  0.43 mcg/mL, AUC<sub>0-48</sub> of 9.74  $\pm$  2.52 mcg•h/mL and AUC<sub>inf</sub> of 17.3  $\pm$  5.34 Long-term animal studies have not been performed to evaluate the carcinogenic potential of oxaliplatin and C<sub>max</sub> of 1.10  $\pm$  0.43 mcg/mL, AUC<sub>0-48</sub> of 9.74  $\pm$  2.52 mcg•h/mL and AUC<sub>inf</sub> of 17.3  $\pm$  5.34 mcg•h/mL at 130 mg/m² of oxaliplatin.

## 8.5 Geriatric Use

No significant effect of age on the clearance of ultrafilterable platinum has been observed.

In the adjuvant therapy colon cancer randomized clinical trial, [see Clinical Studies (14)] /23 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/leucovorin alone arm appeared to be maintained across genders. The effect of Oxaliplatin for Injection in patients ≥65 years of age was not conclusive. Insufficient subgroup sizes prevented analysis by race. Patients weight).

55 years of age receiving the Oxaliplatin for Injection combination therapy experienced more grade Testicular damage, characterized by degeneration, hypoplasia, and atrophy, was observed in dogs \* Disease-free survival at 5 years 3-4 granulocytopenia than patients < 65 years of age (45% yersus 39%).

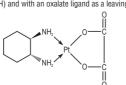
In the previously untreated for advanced colorectal cancer randomized clinical trial [see Clinical Studies] was not identified. This daily dose is approximately one-sixth of the record (14)) of Oxaliplatin for Injection. 160 patients treated with Oxaliplatin for Injection and 5- fluorouracil/ ucovorin 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 Oxaliplatin for Injection and 5- fluorouracil/leucovorin were <65 years and 55 patients were ≥65 years. The rates of overall adverse reactions, including grade 3 and 4 events, were similar across and within eukopenia, fatigue and syncope were higher in patients ≥65 years old. No adjustment to starting dose was required in patients ≥65 years old.

caliplatin for Injection is administered to patients with renal impairment. The starting Oxaliplatin for Injection dose does not need to be reduced in patients with mild (creatinine clearance=50-80 mL/ anal margin) and undergone (within 7 weeks prior to randomization) complete resection of the primary min) or moderate (creatinine clearance=30-49 mL/min) renal impairment. However, the starting dose of Oxaliplatin for Injection should be reduced in patients with severe renal impairment (creatinine clearance). The starting dose chemotherapy immunotherapy or radiotherapy, and have an ECOG performance status of 0, 1, or 2

There is no known antidote for Oxaliplatin for Injection overdose. In addition to thrombocytopenia, the anticipated complications of an Oxaliplatin for Injection overdose include hypersensitivity reaction, myelosuppression, nausea, vomiting, diarrhea and neurotoxicity.

were Grade 4 thrombocytopenia (<25,000/mm<sup>3</sup>) without any bleeding, anemia, sensory neuropathy such as paresthesia, dysesthesia, laryngospasm and facial muscle spasms, gastrointestinal disorders such as nausea, vomiting, stomatitis, flatulence, abdomen enlarged and Grade 4 intestinal obstruction, Grade 4 dehydration, dyspnea, wheezing, chest pain, respiratory failure, severe bradycardia and death. Patients suspected of receiving an overdose should be monitored, and supportive treatment should nistered. The maximum dose of oxaliplatin that has been administered in a single infusion is

Oxaliplatin for Injection, USP is an antineoplastic agent with the molecular formula C8H14N2O4Pt and the chemical name of cis-[(1 R,2 R)-1,2-cyclohexanediamine-N,N] [oxalato(2-)- 0,0] platinum. Oxaliplatin is an organoplatinum complex in which the platinum atom is complexed with 1,2-diaminocyclohexane(DACH) and with an oxalate ligand as a leaving group.



The molecular weight is 397.3. Oxaliplatin is slightly soluble in water at 6 mg/mL, very slightly soluble in methanol, and practically insoluble in ethanol and acetone. Oxaliplatin for Injection, USP is supplied in vials containing 50 mg or 100 mg of oxaliplatin as a sterile,

### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action Oxaliplatin undergoes nonenzymatic conversion in physiologic solutions to active derivatives via displacement of the labile oxalate ligand. Several transient reactive species are formed, including monoaguo and diaguo DACH platinum, which covalently bind with macromolecules, Both inter- and intrastrand Pt-DNA crosslinks are formed. Crosslinks are formed between the *NT* 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. Cytotoxicity is cell-cycle nonspecific. In vivo studies have shown antitumor activity of oxaliplatin against colon carcinoma. In combination with 5-fluorouracil, oxaliplatin exhibits in vitro and in vivo antiproliferative activity greate than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210

embryo-letal development at material doses that were below the recommended manifer development at material doses that were below the recommended manifer dose below the properties of the potential should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant and use effective contraception while receiving Interpatient and intrapatient variability in ultrafilterable platinum exposure (AUC<sub>0-48hr</sub>) assessed over

> 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 irrevers 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/m<sup>2</sup> every two weeks

> 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

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 Oxaliplatin for Injection, urinary elimination accounted for about 54% of the platinum eliminated, with malignant solid tumors, mainly neuroblastoma and osteosarcoma. Twenty eight pediatris 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. Fifteen patients

intravenous infusion on day 1 every 2 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 tolerable.

Tor 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 In one Phase 2 study, 43 pediatric patients with recurrent or refractory embryonal CNS tumors received the mild, moderate, and severe groups, respectively, than in the normal group. Mean C<sub>max</sub> of unbound

Drug - Drug Interactions In a second Phase 2 study, 123 pediatric patients with recurrent solid tumors, including neuroblastoma, No pharmacokinetic interaction between 85 mg/m² of Oxaliplatin for Injection and infusional 5-

Oxaliplatin was not mutagenic to bacteria (Ames test) but was mutagenic to mammalian cells in vitro (L5178Y mouse lymphoma assay). Oxaliplatin was clastogenic both *in vitro* (chromosome aberration in human lymphocytes) and *in vivo* (mouse bone marrow micronucleus assay).

In the adjuvant therapy colon cancer randomized clinical trial, [see Clinical Studies (14)] 723 patients

In a fertility study, male rats were given oxaliplatin at 0, 0.5, 1, or 2 mg/kg/day for five days every 21

administered oxaliplatin at 0.75 mg/kg/day x 5 days every 28 days for three cycles. A no effect level \*\* A hazard ratio of less than 1.00 favors Oxaliplatin for Injection + Infusional 5- fluorouracil/

## 14 CLINICAL STUDIES

body surface area basis.

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

An international, multicenter, randomized study compared the efficacy and evaluated the safety Daaiphain for Injection in Combination with an infusional schedule of 5-fluorouracii/leucovorin arms in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, in the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and within the different age groups in all studies. The incidence of diarrhea, dehydration, hypokalemia, and hypo colon cancer who had undergone complete resection of the primary tumor. The primary objective of the study was to compare the 3-year disease-free survival (DFS) in patients receiving Oxaliplatin for Stage III patients. Injection and infusional 5- fluorouracil/leucovorin to those receiving 5- fluorouracil/leucovorin alone. 8.6 Patients with Renal Impairment
The exposure (AUC) of unbound platinum in plasma ultrafiltrate tends to increase in renally impaired patients [see Pharmacokinetics (12.3)]. Caution and close monitoring should be exercised when carcinoma (with the inferior pole of the tumor above the peritoneal reflection, i.e., ≥15 cm from the (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 carcinoembyrogenic antigen (CEA) <10 ng/mL. Patients with preexisting peripheral neuropathy (NCI grade ≥ 1) were ineligible for this trial.

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

Table 15 - Dosing Regimens in Adjuvant Therapy Study									
reatment Arm	Dose	Regimen							
Oxaliplatin 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 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 12 cycles							
5-FU/LV (N=1123)	Day 1: 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 12 cycles							

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

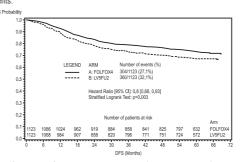
### Table 16 - Patient Characteristics in Adjuvant Therapy Study liplatin for Injection + infusional 5-FU/LV

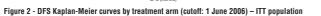
	Uxaliplatin for Injection + infusional 5-FU/LV	
	N=1123	Infusional 5-FU/LV N=1123
Sex: Male (%)	56.1	52.4
Female (%)	43.9	47.6
Median age (years)	61.0	60.0
<65 years of age (%)	64.4	66.2
≥65 years of age (%)	35.6	33.8
	Karnofsky Performance Status (KPS) (%)	
100	29.7	30.5
90	52.2	53.9
80	4.4	3.3
70	13.2	11.9
≤60	0.6	0.4
	Primary site (%)	
Colon including 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 Randomization (%)	
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	76.0	75.9
T4	19.0	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

M1		0.4	0.8					
Table 17 - Dosing in Adjuvant Therapy Study								
		Oxaliplatin for Injection + infusiona 5-FU/LV N=1108	I Infusional 5-FU/LV N=1111					
Median Relative Dose Inte	nsity (%)							
5-FU		84.4	97.7					
Oxaliplatin for Injection		80.5	N/A					
Median Number of Cycles		12	12					
Median Number of cycles with		11	N/A					

	Oxaliplatin for Injection + infusional 5-FU/LV	Infusional 5-FU/LV
Parameter		
	Overall	1
N	1123	1123
Number of events – relapse or death (%)	304 (27.1)	360 (32.1)
Disease-free survival % [95% CI] *	73.3 [70.7, 76.0]	67.4 [64.6, 70.2]
Hazard ratio [95% CI] ** 0.80 [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, 70.0]	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)
	83.7 [80.2, 87.1]	79.9 [76.2, 83.7]
Disease-free survival % [95% CI] *	03.7 [00.2, 07.1]	10.0 [10.2, 00.1]
Disease-free survival % [95% CI] * Hazard ratio [95% CI] **	0.84 [0.62,	

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.





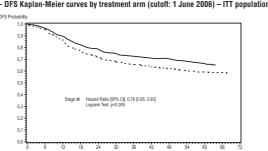


Figure 3 - DFS Kaplan-Meier curves by treatment arm in Stage III patients (cutoff:1 June 2006) -ITT population The following table summarizes the overall survival (OS) results in the overall randomized population

# and in patients with stage II and III disease, based on the ITT analysis

Parameter	Oxaliplatin for Injection +	Infusional 5-FU/LV	
	infusional 5-FU/LV		
	Overall		
	1123	1123	
umber of death events (%)	245 (21.8)	283 (25.2)	
azard ratio* [95% CI]	0.84 [0.71 , 1.00]		
	Stage III (Dukes' C)		
	672	675	
umber of death events (%)	182 (27.1)	220 (32.6)	
azard ratio* [95% CI]	0.80 [0.65 , 0.97]		
	Stage II (Dukes' B2)		
	451	448	
umber of death events (%)	63 (14.0)	63 (14.1)	
azard ratio* [95% CI]	1.00 [0.70 . 1.41]		

A hazard ratio of less than 1.00 favors Oxaliplatin for Injection + Infusional 5-fluorouracil/leucovorin Data cut off for overall survival 16 January 2007

A North American, multicenter, open-label, randomized controlled study was sponsored by the National Cancer Institute (NCI) as an intergroup study led by the North Central Cancer Treatment irrinotecan plus 5- fluorouracil/leucovorin was seen in both genders; however it was greater among Group (NCCTG). The study had 7 arms at different times during its conduct, four of which were closed due to either changes in the standard of care, toxicity, or simplification. During the study, the control arm was changed to irrinotecan plus 5- fluorouracil/leucovorin. The results reported below compared of patients received additional post study criteriounicapy after study dearning discontinuation of a rms. Fifty-eight percent of patients on the Oxaliplatin for Injection plus 5- fluorouracil/leucovorin arm received an irinotecan-containing regimen and 23% of patients on the irinotecan plus 5- fluorouracil/. The dosing regimens of the study are presented in the table below leucovorin arm received oxaliplatin-containing regimens. Oxaliplatin was not commercially available

## 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 Cance

Clinical Trial		
Treatment Arm	Dose	Regimen
Oxaliplatin 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-hourinfusion), 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 intravenous (2-hour infusion) + irinotecan 200 mg/m² intravenous over 30 minutes	Every 3 weeks

### 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 The demographics of the patient population entered into this study are shown in the table below

	Oxaliplatin for Injection + 5-FU/LV (N=267)	Irinotecan + 5-FU/LV (N=264)	Oxaliplatin for Injection Irinotecan (N=264)
Sex: Male (%)	58.8	65.2	61.0
Female (%)	41.2	34.8	39.0
Median age (years)	61.0	61.0	61.0
<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	39.0
Liver + other	41.2	38.6	40.9
Lung only	6.4	3.8	5.3
Other (including lymph nodes)	11.6	11.0	12.9
Not reported	0.7	1.5	1.5
Prior radiation (%)	3.0	1.5	3.0

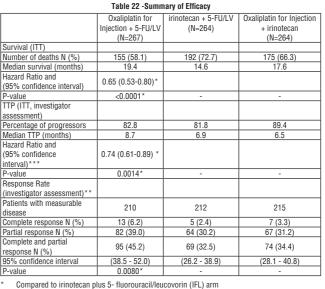
However, a statistically significant improvement in DFS was not noted in Stage II patients.

Figure 2 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin for Injection and 7 (21.0 weeks) for the irinotecan plus 5- fluorouracil/leucovorin regimen, and 7 (21.0 weeks) for the Injection alone. infusional 5-fluorouracil/leucovorin combination and infusional 5-fluorouracil/leucovorin alone for the overall population (ITT analysis).

Oxaliplatin for Injection plus irinotecan regimen. Patients treated with the Oxaliplatin for Injection and 5- fluorouracil/leucovorin combination had a significantly longer time to tumor progression based

Figure 3 shows the DFS Kaplan-Meier curves for the comparison of Oxaliplatin for Injection and on investigator assessment, longer overall survival, and a significantly higher confirmed response infusional 5- fluorouracil/leucovorin combination and infusional 5- fluorouracil/leucovorin alone in Stage III patients.

Take based on investigator assessment compared to patients given irinotecan plus 5- fluorouracil/leucovorin. The following table summarizes the efficacy results.

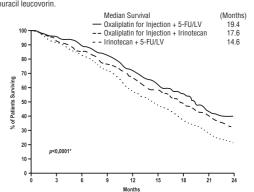


The length of a treatment cycle was 2 weeks for the Oxaliplatin for Injection and 5- fluorouracil/

ucovorin regimen; 6 weeks for the irinotecan plus 5- fluorouracil/leucovorin regimen; and 3 weeks

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 1.00 favors Oxaliplatin for Injection + Infusional 5-fluorouracil/

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



 $^* Log\ rank\ test\ comparing\ Oxaliplatin\ for\ Injection\ plus\ 5-FU/LV\ to\ irinotecan\ plus\ 5-FU/LV.$ Figure 4 - Kaplan-Meier Overall Survival by treatment arm

A descriptive subgroup analysis demonstrated that the improvement in survival for Oxaliplatin for 14.2 Combination Therapy with Oxaliplatin for Injection and 5-fluorouracil leucovorin in Patients

Previously Untreated for Advanced Colorectal Cancer

A descriptive Subgroup analysis definitionated and the improvement in Survival for Oxaliplatin for Injection and 5-fluorouracil/leucovorin oxaliplatin for Injection plus 5- fluorouracil/leucovorin oxaliplatin for Injection plus 5- fluorouracil/leucovorin appeared to be maintained across age groups, prior adjuvant therapy, and number of organs involved.

the efficacy and safety of two experimental regimens, Oxaliplatin for Injection in combination with infusional 5-fluorouracil/leucovorin and a combination of Oxaliplatin for Injection plus irinotecan, to an approved control regimen of irinotecan plus 5- fluorouracil/leucovorin in 795 concurrently randomized patients previously untreated for locally advanced or metastatic colorectal cancer. After completion schedule of 5- fluorouracil/leucovorin to the same dose and schedule of 5- fluorouracil/leucovorin of enrollment, the dose of irinotecan plus 5- fluorouracii/leucovorin was decreased due to toxicity. alone and to single agent oxaliplatin in patients with advanced colorectal cancer who had relapsed/ Patients and patients' caregivers should be informed of the expected side effects of Oxaliplatin for Patients had to be at least 18 years of age, have known locally advanced, locally recurrent, or metastatic progressed during or within 6 months of first-line therapy with bolus 5- fluorozin and colorectal adenocarcinoma not curable by surgery or amenable to radiation therapy with curative intent, irinotecan. The study was intended to be analyzed for response rate after 450 patients were enrolled. 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 10<sup>9</sup>/L, platelets ≥ 100 x study is complete, with 821 patients enrolled. Patients in the study had to be at least 18 years of age, cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposed skin prior to exposure to cold drinks, use of ice, and should cover exposure to cold drinks, use of ice, and should cover exposure to cold drinks, use of ice, and should cover exposure to cold drinks, use of ice, and should cover exposure to cold drinks, use of ice, and should cover exposure to cold drinks. 10<sup>9</sup>/L, hemoglobin ≥9.0 gm/dL, creatinine ≤ 1.5 x ULN, total bilirubin ≤ 1.5 mg/dL, AST ≤ 5 x ULN, and have unresectable, measurable, histologically proven colorectal adenocarcinoma, with a Karnofsky alkaline phosphatase  $\leq 5 \times ULN$ . Patients may have received adjuvant therapy for resected Stage II or III disease without 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. 265 years). Although no post study treatment was specified in the protocol, 65 to 72% 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, Patients should be instructed to contact their physician if persistent vomiting, diarrhea, signs of of patients received additional post study chemotherapy after study treatment discontinuation on all in which cases <5x ULN was permitted. Prior radiotherapy was permitted if it had been completed at

Table 23 – Dosing Regimens in Refractory and Relapsed Colorectal Cancer Clinical Trial			
Treatment Arm	Dose	Regimen	
Oxaliplatin for Injection + 5-FU/LV	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)	Every 2 weeks	
(N=152)	Day 2: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion)	WOORG	
5-FU/LV	Day 1: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion)	Every 2	
(N=151)	Day 2: LV 200 mg/m² (2-hour infusion), followed by 5-FU: 400 mg/m² (bolus), 600 mg/m² (22-hour infusion)	weeks	
Oxaliplatin for Injection (N=156)	Day 1: Oxaliplatin for Injection: 85 mg/m² (2-hour infusion)	Every 2 weeks	

Tumor response and progression were assessed every 3 cycles (6 weeks) using the Response 1021988 Evaluation Criteria in Solid Tumors (RECIST) until radiological documentation of progression or for 13 months following the first dose of study drug(s), whichever came first. Confirmed responses were based on two tumor assessments separated by at least 4 weeks.

esion measuring ≥20 mm using conventional CT or MRI scans, or ≥10mm using a spiral CT scan.

	5-FU/LV	Oxaliplatin for	Oxaliplatin for Injection + 5-FU/L\
	(N=151)	Injection (N=156)	(N=152)
Sex: Male (%)	54.3	60.9	57.2
Female (%)	45.7	39.1	42.8
Median age (years)	60.0	61.0	59.0
Range	21-80	27-79	22-88
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 - 100	94.7	92.3	95.4
50 - 60	2.6	4.5	2.0
Not reported	2.6	3.2	2.6
Prior radiotherapy (%)	25.2	19.2	25.0
Prior pelvic radiation (%)	18.5	13.5	21.1
Number of metastatic sites (9	%)		
1	27.2	31.4	25.7

Liver only Liver + other for the Oxaliplatin for Injection plus irinotecan regimen. The median number of cycles administered per The median number of cycles administered per patient was 6 for the Oxaliplatin for Injection and 5-

> Patients treated with the combination of Oxaliplatin for Injection and 5- fluorouracil/leucovorin had an increased response rate compared to patients given 5- fluorouracil/leucovorin or oxaliplatin alone. The efficacy results are summarized in the tables below.

### Table 25 - Response Rates (ITT Analysis)

est Response	5-FU/LV (N=151)	Oxaliplatin 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. Oxaliplatin for Injection + 5-FU/LV				
95%CI	0-2.4%	0.2-4.6%	4.6-14.2%		
Table 26 - Summary of Badiographic Time to Progression*					

patients were excluded from the analysis based on unavailability of the radiographs for independent At the time of the interim analysis 49% of the radiographic progression events had occurred. In this

observed compared to 5- fluorouracil/leucovorin alone. Of the 13 patients who had tumor response to the combination of Oxaliplatin for Injection and 5-fluorouracil/leucovorin, 5 were female and 8 were male, and responders included patients <65 years old and >65 years old. The small number of non-Caucasian participants made efficacy analyses in these

interim analysis an estimated 2-month increase in median time to radiographic progression was

Centers for Disease Control and Prevention, National Institute for Occupational Safety and Health OHHS (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

# and recommendations for practice (2nd. ed.) Pittsburgh, PA: Oncology Nursing Society

and aluminum flip-off seals containing 50 mg or 100 mg of oxaliplatin as a sterile, preservative-free lyophilized powder for reconstitution. Lactose monohydrate is also present as an inactive ingredient. NDC 0069-0067-01: 50 mg single-use vial with flip-off seal individually packaged in a carton. NDC 0069-1010-01: 100 mg single-use vial with flip-off seal individually packaged in a carton.

As with other potentially toxic anticancer agents, care should be exercised in the handling 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 Procedures for the handling and disposal of anticancer drugs should be considered. Several guidelines

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

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.

neurologic symptoms that affect gait and balance may lead to a minor or moderate influence on the Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation



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est Response	5-FU/LV (N=151)	Oxaliplatin 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. Oxaliplatin for Injection + 5-FU/LV				
95%CI	0-2.4%	0.2-4.6%	4.6-14.2%		

Table 26 - Summary of Radiographic Time to Progression*			
5-FU/LV (N=151)	Oxaliplatin for Injection (N=156)	Oxaliplatin for Injection + 5-FU/LV (N=152)	
74	101	50	
22 (15%)	16 (10%)	17 (11%)	
2.7	1.6	4.6	
1.8-3.0	1.4-2.7	4.2-6.1	
	5-FU/LV (N=151) 74 22 (15%) 2.7	5-FU/LV (N=151) Oxaliplatin for Injection (N=156) 74 101 22 16 (15%) (10%) 2.7 1.6	

\*This is not an ITT analysis. Events were limited to radiographic disease progression documented by independent review of radiographs. Clinical progression was not included in this analysis, and 18% of

# NIOSH Alert: Preventing occupational exposures to antineoplastic and other hazardous drugs in healthcare settings. 2004. U.S. Department of Health and Human Services, Public Health Service,

4. Polovich, M., White, J. M., & Kelleher, L.O. (eds.) 2005. Chemotherapy and biotherapy guidelines

16.1 How Supplied Oxaliplatin for Injection, USP is supplied in clear, glass, single-use vials with gray elastomeric stoppers

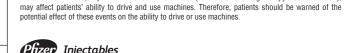
# **16.2 Storage**Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

16.3 Handling and Disposal

16 HOW SUPPLIED/STORAGE AND HANDLING

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

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 increase risk of dizziness, nausea and vomiting, and other



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