Summary of product Characteristics

1. Name of the medicinal product

XPLATIN (Oxaliplatin Injection USP 50mg/25 ml)

Strength: 50mg/25 ml

2. Qualitative and quantitative composition

Each ml contains:

Oxaliplatin USP……2 mg

For full list of excipients, see Section 6.1

3. Pharmaceutical form

Description: A Clear colorless solution

Pharmaceutical form: Concentrate for solution for Infusion

4. Clinical particulars

4.1 Therapeutic indications

Oxaliplatin 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 the primary tumor.
- treatment of advanced colorectal cancer.

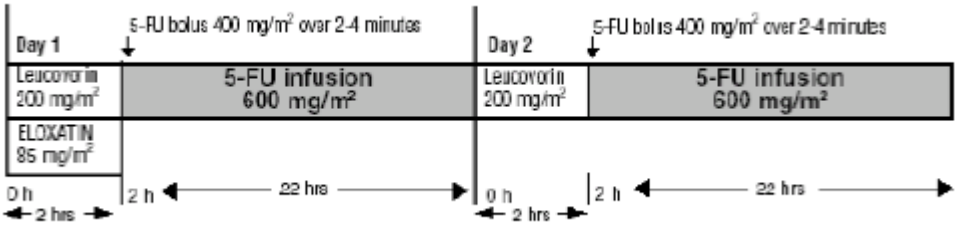
4.2 Posology and method of administration

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

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

Day 1: Oxaliplatin Injection 85 mg/m^2 intravenous infusion in 250-500 mL 5% Dextrose injection, USP and leucovorin 200 mg/m^2 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^2 intravenous bolus given over 2-4 minutes, followed by 5-fluorouracil 600 mg/m^2 intravenous infusion in 500 mL 5% Dextrose Injection, USP (recommended) as a 22-hour continuous infusion.

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



The administration of Oxaliplatin Injection does not require prehydration. Premedication with antiemetics, including 5-HT_3 blockers with or without dexamethasone, is recommended. For information on 5-fluorouracil and leucovorin, see the respective package inserts.

Dose Modification Recommendation

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

Adjuvant Therapy in Patients with Stage III Colon Cancer

Neuropathy and other toxicities were graded using the NCI CTC scale version 1.

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

A dose reduction of Oxaliplatin Injection to 75 mg/m^2 and infusional 5-fluorouracil to 300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5 x 10^9/L and platelets ≥75 x 10^9/L.

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

Neuropathy was graded using a study-specific neurotoxicity scale. Other toxicities were graded by the NCI CTC, Version 2.0.

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

A dose reduction of Oxaliplatin Injection to 65 mg/m^2 and 5-fluorouracil by 20% (300 mg/m^2 bolus and 500 mg/m^2 22-hour infusion) is recommended for patients after recovery from grade 3/4 gastrointestinal (despite prophylactic treatment) or grade 4 neutropenia or grade 3/4 thrombocytopenia. The next dose should be delayed until: neutrophils ≥1.5 x 10^9/L and platelets ≥75 x 10^9/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 Injection is 85 mg/m^2. In patients with severe renal impairment, the initial recommended Oxaliplatin Injection dose should be reduced to 65 mg/m^2.

Preparation of Infusion Solution

Powder for solution for infusion

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 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 is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

Oxaliplatin Injection is not light sensitive.

Concentrate for solution for infusion

Do not freeze and protect from light the concentrated solution.

A final dilution must never be performed with a sodium chloride solution or other chloride-containing solutions.

The solution must be further diluted in an infusion solution of 250-500 mL of 5% Dextrose Injection, USP.

After dilution with 250-500 mL of 5% Dextrose Injection, USP, the shelf life is 6 hours at room temperature [20-25°C (68-77°F)] or up to 24 hours under refrigeration [2-8°C (36-46°F)].

After final dilution, protection from light is not required.

Oxaliplatin 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 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 Injection should not be used for the preparation or mixing of the drug. Aluminum has been reported to cause degradation of platinum compounds.

4.3 Contraindications

Oxaliplatin Injection should not be administered to patients with a history of known allergy to Oxaliplatin or other platinum compounds.

4.4 Special warnings and precautions for use

Allergic Reactions:

Grade 3/4 hypersensitivity, including anaphylactic/anaphylactoid reactions, to Oxaliplatin Injection has been observed in 2-3% of colon cancer patients. These allergic reactions which can be fatal, 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, 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. Drug-related deaths associated with platinum compounds from anaphylaxis have been reported.

Neurologic Toxicity:

Neuropathy: Oxaliplatin 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 recurs with further dosing. The symptoms may be precipitated or exacerbated by exposure to cold temperature or cold objects and they usually present as transient paresthesia, dysesthesia and hypoesthesia in the hands, feet, perioral area, or throat. Jaw spasm, abnormal tongue sensation, dysarthria, eye pain, and a feeling of chest pressure have also been observed. The acute, reversible pattern of sensory neuropathy was observed in about 56% of study patients who received Oxaliplatin Injection with 5-fluorouracil/leucovorin. In any individual cycle acute neurotoxicity was observed in approximately 30% of patients. In adjuvant patients the median cycle of onset for grade 3 peripheral sensory neuropathy was 9 in the previously treated patients the median number of cycles administered on the Oxaliplatin Injection with 5-fluorouracil/leucovorin combination arm was 6.

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

A persistent (>14 days), primarily peripheral, sensory neuropathy that is usually characterized by paresthesias, dysesthesias, hypoesthesias, but may also include

deficits in proprioception that can interfere with daily activities (e.g., writing, buttoning, swallowing, and difficulty walking from impaired proprioception). These forms of neuropathy occurred in 48% of the study patients receiving Oxaliplatin Injection with 5-fluorouracil/leucovorin. Persistent neuropathy can occur without any prior acute neuropathy event. The majority of the patients (80%) who developed grade 3 persistent neuropathy progressed from prior Grade 1 or 2 events. These symptoms may improve in some patients upon discontinuation of Oxaliplatin Injection.

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

Table 1 - NCI CTC Grading for Neuropathy in Adjuvant Patients

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

Peripheral sensory neuropathy was reported in adjuvant patients treated with the Oxaliplatin 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

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

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

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 experience. Signs and symptoms of RPLS could be headache, altered mental functioning, seizures, abnormal vision from blurriness to blindness, associated or not with hypertension. Diagnosis of RPLS is based upon confirmation by brain imaging.

Pulmonary Toxicity

Oxaliplatin Injection has been associated with pulmonary fibrosis (<1% of study patients), which may be fatal. The combined incidence of cough and dyspnea was 7.4% (any grade) and <1% (grade 3) with no grade 4 events in the Oxaliplatin Injection plus infusional 5-fluorouracil/leucovorin arm compared to 4.5% (any grade) and no grade 3 and 0.1% grade 4 events in the infusional 5fluorouracil/leucovorin alone arm in adjuvant colon cancer patients. In this study, one patient died from eosinophilic pneumonia in the Oxaliplatin Injection combination arm. The combined incidence of cough, dyspnea and hypoxia was 43% (any grade) and 7% (grade 3 and 4) in the Oxaliplatin Injection plus 5-fluorouracil/leucovorin arm compared to 32% (any grade) and 5% (grade 3 and 4) in the irinotecan plus 5-fluorouracil/ leucovorin arm of unknown duration for patients with previously untreated colorectal cancer. In case of unexplained respiratory symptoms such as non-productive cough, dyspnea, crackles, or radiological pulmonary infiltrates, Oxaliplatin Injection should be discontinued until further pulmonary investigation excludes interstitial lung disease or pulmonary fibrosis.

Hepatotoxicity

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 Injection combination arm than in the control arm. The incidence of increased bilirubin was similar on both arms. Changes noted on liver biopsies include: peliosis, nodular regenerative hyperplasia or sinusoidal alterations, perisinusoidal fibrosis, and veno-occlusive lesions. Hepatic vascular disorders should be considered, and if appropriate, should be investigated in case of abnormal liver function test results or portal hypertension, which cannot be explained by liver metastases.

4.5 Interaction with other medicinal products and other forms of Interaction

No specific cytochrome P-450-based drug interaction studies have been conducted. No pharmacokinetic interaction between 85 mg/m^2 Oxaliplatin 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/m^2 Oxaliplatin 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.

4.6 Pregnancy and lactation

Pregnancy

Based on direct interaction with DNA, Oxaliplatin Injection may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of Oxaliplatin Injection in pregnant women. 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 body surface area. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient 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 treatment with Oxaliplatin Injection.

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.

Nursing Mothers

It is not known whether Oxaliplatin Injection or its derivatives are excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Oxaliplatin 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.

4.7 Effects on ability to drive and use machines

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

Vision abnormalities, in particular transient vision loss (reversible following therapy discontinuation), may affect patient's ability to drive and use machines. Therefore, patients should be warned of the potential effect of these events on the ability to drive or use machines.

4.8 Undesirable effects

Clinical Trials Experience

Serious adverse reactions including anaphylaxis and allergic reactions, neuropathy, pulmonary toxicities and hepatotoxicities can occur because clinical trials are conducted

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

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

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

One thousand one hundred and eight patients with stage II or III colon cancer, who had undergone complete resection of the primary tumor, have been treated in a clinical study with Oxaliplatin Injection in combination with infusional 5-fluorouracil/leucovorin The incidence of grade 3 or 4 adverse reactions was 70% on the Oxaliplatin 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 Injection and infusional 5-fluorouracil/leucovorin. Both 5fluorouracil/leucovorin and Oxaliplatin Injection are associated with gastrointestinal or hematologic adverse reactions. When Oxaliplatin Injection is administered in combination with infusional 5fluorouracil/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 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 Injection combination and infusional 5-fluorouracil/leucovorin arms, respectively. On the Oxaliplatin 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 by body system and decreasing order of frequency in the Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥ 5% and for NCI grade 3/4 events with incidences ≥ 1%.

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

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

[1] Includes thrombosis related to the catheter

The following table provides adverse reactions reported in the adjuvant therapy colon cancer clinical trial by body system and decreasing order of frequency in the Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin arm for events with overall incidences ≥ 5% but with incidences <1% NCI grade 3/4 events.

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

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

Although specific events can vary, the overall frequency of adverse reactions was similar in men and women and in patients <65 and ≥65 years. However, the following grade 3/4 events were more common in females: diarrhea, fatigue, granulocytopenia, nausea and vomiting. In patients ≥65 years 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 Injection and infusional 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): pain, leukopenia, weight decrease, coughing.

The number of patients who developed secondary malignancies was similar; 62 in the Oxaliplatin Injection combination arm and 68 in the infusional 5-fluorouracil/leucovorin arm. An exploratory analysis showed that the number of deaths due to secondary malignancies was 1.96% in the Oxaliplatin Injection combination arm and 0.98% in infusional 5-

fluorouracil/leucovorin arm. In addition, the number of cardiovascular deaths was 1.4% in the Oxaliplatin Injection combination arm as compared to 0.7% in the infusional 5-fluorouracil/leucovorin arm. Clinical significance of these findings is unknown.

Patients Previously Untreated for Advanced Colorectal Cancer

Two hundred and fifty-nine patients were treated in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm of the randomized trial in patients previously untreated for advanced colorectal cancer. 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 Injection are associated with gastrointestinal and hematologic adverse reactions. When Oxaliplatin Injection is administered in combination with 5-fluorouracil, the incidence of these events is increased.

The incidence of death within 30 days of treatment in the previously untreated for advanced colorectal cancer study, regardless of causality, was 3% with the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination, 5% with irinotecan plus 5-fluorouracil/leucovorin, and 3% with Oxaliplatin Injection plus irinotecan. Deaths within 60 days from initiation of therapy were 2.3% with the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination, 5.1% with irinotecan plus 5-fluorouracil/leucovorin, and 3.1% with Oxaliplatin Injection plus irinotecan.

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study by body system and decreasing order of frequency in the Oxaliplatin 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)

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

* Not otherwise specified
** Absolute neutrophil count

The following table provides adverse reactions reported in the previously untreated for advanced colorectal cancer study by body system and decreasing order of frequency in the

Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥5% but with incidences <1% NCI Grade 3/4 events.

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

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

* Absolute neutrophil count

Adverse reactions were similar in men and women and in patients <65 and ≥65 years, but older patients may have been more susceptible to diarrhea, dehydration, hypokalemia, leukopenia, fatigue and syncope. The following additional adverse reactions, at least possibly related to treatment and potentially important, were reported in ≥2% and <5% of the patients in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): metabolic, pneumonitis, catheter infection, vertigo, prothrombin time, pulmonary, rectal bleeding, dysuria, nail

changes, chest pain, rectal pain, syncope, hypertension, hypoxia, unknown infection, bone pain, pigmentation changes, and urticaria.

Previously Treated Patients with Advanced Colorectal Cancer

Four hundred and fifty patients (about 150 receiving the combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin) were studied in a randomized trial in patients with refractory and relapsed colorectal cancer. 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.

Thirteen percent of patients in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm and 18% in the 5-fluorouracil/leucovorin arm of the previously treated study had to discontinue treatment because of adverse effects related to gastrointestinal, or hematologic adverse reactions, or neuropathies. Both 5-fluorouracil and Oxaliplatin Injection are associated with gastrointestinal and hematologic adverse reactions. When Oxaliplatin Injection is administered in combination with 5-fluorouracil, the incidence of these events is increased.

The incidence of death within 30 days of treatment in the previously treated study, regardless of causality, was 5% with the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination, 8% with Oxaliplatin Injection alone, and 7% with 5-fluorouracil/leucovorin. Of the 7 deaths that occurred on the Oxaliplatin 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.

The following table provides adverse reactions reported in the previously treated study by body system and in decreasing order of frequency in the Oxaliplatin 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 abnormalities; these are shown separately below.

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

	5-FU/LV (N = 142)		ELOXATIN (N = 153)		ELOXATIN + 5-FU/LV (N = 150)	
Adverse reaction (WHO/Pref)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Any Event	98	41	100	46	99	73
Cardiovascular						

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

The following table provides adverse reactions reported in the previously treated study by body system and in decreasing order of frequency in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm for events with overall incidences ≥5% but with incidences <1% NCI Grade 3/4 events.

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

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

Adverse reactions were similar in men and women and in patients <65 and ≥65 years, but older 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 Injection and 5-fluorouracil/leucovorin combination arm (listed in decreasing order of frequency): anxiety, myalgia, erythematous rash, increased sweating, conjunctivitis, weight decrease, dry mouth, rectal hemorrhage, depression, ataxia, ascites, hemorrhoids, muscle weakness, nervousness, tachycardia, abnormal micturition frequency, dry skin, pruritus,

hemoptysis, purpura, vaginal hemorrhage, melena, somnolence, pneumonia, proctitis, involuntary muscle contractions, intestinal obstruction, gingivitis, tenesmus, hot flashes, enlarged abdomen, urinary incontinence.

Hematologic Changes

The 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 the patients previously untreated for advanced colorectal cancer, respectively, which are based on AE reporting and NCI grade alone.

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

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

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

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

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

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

Thrombocytopenia and Bleeding

Thrombocytopenia was frequently reported with the combination of Oxaliplatin Injection and infusional 5-fluorouracil/leucovorin. The incidence of all hemorrhagic events in the adjuvant

and previously treated patients was higher on the Oxaliplatin 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 patients 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 Injection and 5-fluorouracil/leucovorin over the irinotecan plus 5-fluorouracil/leucovorin or 5fluorouracil/leucovorin control groups. Grade 3/4 gastrointestinal bleeding was reported in 0.2% of adjuvant patients receiving Oxaliplatin Injection and 5-fluorouracil/leucovorin. In the previously untreated patients, the incidence of epistaxis was 10% in the Oxaliplatin Injection and 5-fluorouracil/leucovorin arm, and 2% and 1%, respectively, in the irinotecan plus 5-fluorouracil/leucovorin or irinotecan plus Oxaliplatin Injection arms.

Neutropenia

Neutropenia was frequently observed with the combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin, with Grade 3 and 4 events reported in 29% and 12% of adjuvant patients with colon cancer, respectively. In the adjuvant trial, 3 patients died from sepsis/ neutropenic sepsis. Grade 3 and 4 events were reported in 35% and 18% of the patients previously untreated for advanced colorectal cancer, 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 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 irinotecan plus 5-fluorouracil/leucovorin arm and 4% (less than 1% of cycles) in the Oxaliplatin 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 Injection and 5-fluorouracil/leucovorin combination. The incidence of febrile neutropenia in the previously treated patients was 1% in the 5-fluorouracil/leucovorin arm and 6% (less than 1% of cycles) in the Oxaliplatin Injection and 5-fluorouracil/ leucovorin combination arm.

Gastrointestinal

In patients receiving the combination of Oxaliplatin 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. In patients previously untreated for advanced colorectal cancer receiving the combination of Oxaliplatin 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. In

previously treated patients receiving the combination of Oxaliplatin Injection and 5-fluorouracil/leucovorin, the incidence of Grade 3 and 4 nausea, vomiting, diarrhea, and mucositis/stomatitis increased compared to 5fluorouracil/leucovorin controls.
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-HT3 blockers, is recommended. Diarrhea and mucositis may be exacerbated by the addition of Oxaliplatin Injection to 5-fluorouracil/leucovorin, and should be managed with appropriate supportive care. Since cold temperature can exacerbate acute neurological symptoms, ice (mucositis prophylaxis) should be avoided during the infusion of Oxaliplatin Injection.

Dermatologic
Oxaliplatin Injection did not increase the incidence of alopecia compared to 5-fluorouracil/ leucovorin alone. No complete alopecia was reported. The incidence of Grade 3/4 skin disorders was 2% in both the Oxaliplatin Injection plus infusional 5-fluorouracil/leucovorin and the infusional 5-fluorouracil/leucovorin alone arms in the adjuvant colon cancer patients. The incidence of hand-foot syndrome in patients previously untreated for advanced colorectal cancer was 2% in the irinotecan plus 5-fluorouracil/leucovorin arm and 7% in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm. The incidence of hand-foot syndrome in previous ly treated patients was 13% in the 5-fluorouracil/leucovorin arm and 11% in the Oxaliplatin Injection and 5-fluorouracil/leucovorin combination arm.

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

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

Renal
About 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 Injection and 5-fluorouracil/leucovorin combination arm was 1% in the previously treated patients. Serum creatinine measurements were not reported in the adjuvant trial.

Hepatic
Hepatotoxicity (defined as elevation of liver enzymes) appears to be related to Oxaliplatin Injection combination therapy. The following tables list the clinical chemistry 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 Adjuvant Therapy (≥5% of patients)

Hepatic Parameter	ELOXATIN + 5-FU/LV (N=1108)		5-FU/LV (N=1111)	
	All Grades (%)	Grade 3/4 (%)	All Grades (%)	Grade 3/4 (%)
Increase in transaminases	57	2	34	1
ALP increased	42	<1	20	<1
Bilirubinaemia	20	4	20	5

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

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

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

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

Thromboembolism

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 Injection and infusional 5-fluorouracil/leucovorin combined arm, respectively. The incidence was 6 and 9% of the patients previously untreated for advanced colorectal cancer and previously treated patients in the Oxaliplatin Injection and 5-fluorouracil/ leucovorin combination arm, respectively.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Oxaliplatin Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a whole:

angioedema, anaphylactic shock

Central and peripheral nervous system disorders:

loss of deep tendon reflexes, dysarthria, Lhermitte's sign, cranial nerve palsies, fasciculations, convulsion, Reversible Posterior Leukoencephalopathy Syndrome (RPLS, also known as PRES).

Liver and Gastrointestinal system disorders:

severe diarrhea/vomiting resulting in hypokalemia, colitis (including *Clostridium difficile* diarrhea), 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:

deafnessimmuno-allergic thrombocytopenia prolongation of prothrombin time and of INR in patients receiving anticoagulants

Red Blood Cell disorders:

hemolytic uremic syndrome, immuno-allergic hemolytic anemia

Renal disorders:

Acute tubular necrosis, acute interstitial 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 following therapy discontinuation)

4.9 Overdose

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

Several cases of overdoses have been reported with Oxaliplatin Injection. Adverse reactions observed were Grade 4 thrombocytopenia (<25,000/mm3) without any bleeding, anemia,

sensory neuropathy such as paresthesia, 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 be administered. The maximum dose of oxaliplatin that has been administered in a single infusion is 825 mg.

5. Pharmacological Characteristics

5.1 Pharmacodynamic properties:

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 monoaquo and diaquo DACH platinum, which covalently bind with macromolecules. Both inter-and intrastrandPt-DNA crosslinks are formed. Crosslinks are formed between the N7 positions of two adjacent guanines (GG), adjacent adenine-guanines (AG), and guanines separated by an intervening nucleotide (GNG). These crosslinks inhibit DNA replication and transcription. 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 greater than either compound alone in several tumor models [HT29 (colon), GR (mammary), and L1210 (leukemia)].

5.2 Pharmacokinetics:

The reactive oxaliplatin derivatives are present as a fraction of the unbound platinum in plasma ultrafiltrate. The decline of ultrafilterable platinum levels following oxaliplatin administration is triphasic, characterized by two relatively short distribution phases ($t_{1/2\alpha}$; 0.43 hours and $t_{1/2\beta}$; 16.8 hours) and a long terminal elimination phase ($t_{1/2\gamma}$; 391 hours). Pharmacokinetic parameters obtained after a single 2- hour intravenous infusion of Oxaliplatin at a dose of 85 mg/m^2 expressed as ultrafilterable platinum were C_{max} of 0.814 mcg /mL and volume of distribution of 440 L. Interpatient and intrapatient variability in ultrafilterable platinum exposure ($AUC_{0\text{-}48hr}$) assessed over 3 cycles was moderate to low (23% and 6%, respectively). A pharmacodynamic relationship between platinum ultrafiltrate levels and clinical safety and effectiveness has not been established.

Distribution

At the end of a 2-hour infusion of Oxaliplatin, approximately 15% of the administered platinum is present in the systemic circulation. The remaining 85% is rapidly distributed into tissues or eliminated in the urine. In patients, plasma protein binding of platinum is irreversible and is greater than 90%. The main binding proteins are albumin and gamma-globulins. Platinum also binds irreversibly and accumulates (approximately 2-fold) in

erythrocytes, where it appears to have no relevant activity. No platinum accumulation was observed in plasma ultrafiltrate following 85 mg/m^2 every two weeks.

Metabolism

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

Elimination

The major route of platinum elimination is renal excretion. At five days after a single 2-hour infusion of Oxaliplatin for Injection, USP, urinary elimination accounted for about 54% of the platinum eliminated, with fecal excretion accounting for only about 2%. Platinum was cleared from plasma at a rate (10 to 17 L/h) that was similar to or exceeded the average human glomerular filtration rate (GFR; 7.5 L/h). There was no significant effect of gender on the clearance of ultrafilterable platinum. The renal clearance of ultrafilterable platinum is significantly correlated with GFR.

5.3 Preclinical safety data

Not data Available.

6. Pharmaceutical Particulars

6.1 List of Excipients Used:

Water for Injection USP

6.2 Incompatibilities

The diluted medicinal product should not be mixed with other medications in the same infusion bag or infusion line. Under instructions for use, oxaliplatin can be co-administered with folinic acid (FA) via a Y-line.

Do not mix with alkaline medicinal products or solutions, in particular 5-fluorouracil, folinic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Do not dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chloride).

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30^0C. Protect from light. Do not freeze.

6.5 Nature and contents of container

30ml amber molded USP Type I glass vials stoppered with 20 mm rubber plugs sealed with 20 mm aluminium seal with flip off is placed in a carton along with pack insert.

6.6 Instruction for use and handling

Any unused product or waste material should be disposed of in accordance with local requirements.

7. Marketing Autorization Holder

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8. Marketing Authorization Number(s)

TAN 22 HM 0291

9. Date of first registration/renewal of the registration

04th May, 2022

10. Date of the revision of the text