

SUMMARY OF PRODUCT CHARACTERISTICS (English Version)

SUMMARY OF PRODUCT CHARACTERISTICS (English translation)

1. NAME OF THE MEDICINAL PRODUCT

Oxaliplatin medac 5 mg/ml powder for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with powder for solution for infusion contains 50 mg, 100 mg or 150 mg oxaliplatin.

One ml of reconstituted concentrate solution contains 5 mg oxaliplatin.

50 mg vial: Each vial contains 50 mg oxaliplatin for reconstitution in 10 ml of solvent.

100 mg vial: Each vial contains 100 mg oxaliplatin for reconstitution in 20 ml of solvent.

150 mg vial: Each vial contains 150 mg oxaliplatin for reconstitution in 30 ml of solvent.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for infusion

White to off-white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Oxaliplatin in combination with 5-fluorouracil (5-FU) and folinic acid (FA) is indicated for:

- Adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumour
- Treatment of metastatic colorectal cancer.

4.2 Posology and method of administration

Posology

FOR ADULTS ONLY

The recommended dose for oxaliplatin in adjuvant setting is 85 mg/m² intravenously repeated every two weeks for 12 cycles (6 months).

The recommended dose for oxaliplatin in treatment of metastatic colorectal cancer is 85 mg/m² intravenously repeated every 2 weeks.

Dosage given should be adjusted according to tolerability (see section 4.4).

Oxaliplatin should always be administered before fluoropyrimidines.

Oxaliplatin is administered as a 2- to 6-hour intravenous infusion in 250 to 500 ml of 5% glucose solution to give a concentration between 0.2 mg/ml and 0.70 mg/ml; 0.70 mg/ml is the highest concentration in clinical practice for an oxaliplatin dose of 85 mg/m².

Oxaliplatin was mainly used in combination with continuous infusion 5-fluorouracil based regimens. For the two-weekly treatment schedule 5-fluorouracil regimens combining bolus and continuous infusion were used.

Special Populations

- Renal impairment

Oxaliplatin has not been studied in patients with severe renal impairment (See section 4.3). In patients with moderate renal impairment, treatment may be initiated at the normally recommended dose (see section 4.4). There is no need for dose adjustment in patients with mild renal dysfunction.

- Hepatic impairment

In a phase I study including patients with several levels of hepatic impairment, frequency and severity of hepato-biliary disorders appeared to be related to progressive disease and impaired liver function tests at baseline. No specific dose adjustment for patients with abnormal liver function tests was performed during clinical development.

- Elderly patients

No increase in severe toxicities was observed when oxaliplatin was used as a single agent or in combination with 5-fluorouracil in patients over the age of 65. In consequence no specific dose adaptation is required for elderly patients.

Method of administration

Oxaliplatin is administered by intravenous infusion.

The administration of oxaliplatin does not require hyperhydration.

Oxaliplatin diluted via a central venous line or peripheral vein in 250 to 500 ml of 5% glucose solution to give a concentration not less than 0.2 mg/ml must be infused over 2 to 6 hours. Oxaliplatin infusion should always precede that of 5-fluorouracil.

In the event of extravasation, administration must be discontinued immediately.

The preparation of injectable solution of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicinal products used, in condition that guarantee the integrity of medical product, the protection of the environment and in the particular the protection of the personnel handling the medicinal products, in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Instructions for use:

See section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Breast-feeding
- Myelosuppression prior to starting first course, as evidenced by baseline neutrophils $< 2 \times 10^9/l$ and/or platelet count of $< 100 \times 10^9/l$
- Peripheral sensitive neuropathy with functional impairment prior to first course
- Severely impaired renal function (creatinine clearance less than 30 ml/min)

4.4 Special warnings and special precautions for use

Oxaliplatin should only be used in specialised departments of oncology and should be administered under the supervision of an experienced oncologist.

Due to limited information on safety in patients with moderately impaired renal function, administration should only be considered after suitable appraisal of the benefit/risk for the patient.

In this situation, renal function should be closely monitored and dose adjusted according to toxicity.

Patients with a history of allergic reaction to platinum compounds should be monitored for allergic symptoms. In case of an anaphylactic-like reaction to oxaliplatin, the infusion should be immediately discontinued and appropriate symptomatic treatment initiated. Oxaliplatin rechallenge is contra-indicated.

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

Neurological toxicity of oxaliplatin should be carefully monitored, especially if co-administered with other medications with specific neurological toxicity. A neurological examination should be performed before each administration and periodically thereafter. For patients who develop acute laryngopharyngeal dysaesthesia (see section 4.8), during or within the hours following the 2-hour infusion, the next oxaliplatin infusion should be administered over 6 hours.

If neurological symptoms (paraesthesia, dysaesthesia) occur, the following recommended oxaliplatin dosage adjustment should be based on the duration and severity of these symptoms:

- If symptoms last longer than seven days and are troublesome, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).

- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m² (metastatic setting) or 75 mg/m² (adjuvant setting).

- If paraesthesia with functional impairment persists until the next cycle, oxaliplatin should be discontinued.

- If these symptoms improve following discontinuation of oxaliplatin therapy, resumption of therapy may be considered.

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

Gastrointestinal toxicity, which manifests as nausea and vomiting, warrants prophylactic and/or therapeutic anti-emetic therapy (see section 4.8).

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emetis particularly when combining oxaliplatin with 5-fluorouracil. In single cases pancreatitis is reported.

If haematological toxicity occurs (neutrophils $< 1.5 \times 10^9/l$ or platelets $< 50 \times 10^9/l$), administration of the next course of therapy should be postponed until haematological values return to acceptable levels. A full blood count with white cell differential should be performed prior to start of therapy and before each subsequent course.

Patients must be adequately informed of the risk of diarrhoea/emetis, mucositis/stomatitis and neutropenia after oxaliplatin and 5-fluorouracil administration so that they can urgently contact their treating physician for appropriate management.

If mucositis/stomatitis occurs with or without neutropenia, the next treatment should be delayed until recovery from mucositis/stomatitis to grade 1 or less and/or until the neutrophil count is $\geq 1.5 \times 10^9/l$.

For oxaliplatin combined with 5-fluorouracil (with or without folinic acid), the usual dose adjustments for 5-fluorouracil associated toxicities should apply.

If grade 4 diarrhoea, grade 3-4 neutropenia (neutrophils $< 1.0 \times 10^9/l$), grade 3-4 thrombocytopenia (platelets $< 50 \times 10^9/l$) occur, the dose of oxaliplatin should be reduced from 85 mg/m^2 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting), in addition to any 5-fluorouracil dose reductions required.

In case of abnormal liver function test results or portal hypertension which does not obviously result from liver metastases, very rare cases of drug-induced hepatic vascular disorders should be considered.

In the case of unexplained respiratory symptoms such as non-productive cough, dyspnoea, crackles or radiological pulmonary infiltrates, oxaliplatin should be discontinued until further pulmonary investigations exclude an interstitial lung disease (see section 4.8).

For use in pregnant women see section 4.6.

Genotoxic effects were observed with oxaliplatin in the preclinical studies. Therefore male patients treated with oxaliplatin are advised not to father a child during and up to 6 months after treatment and to seek advice on conservation of sperm prior to treatment because oxaliplatin may have an anti-fertility effect, which could be irreversible.

Women should not become pregnant during treatment with oxaliplatin and should use an effective method of contraception (see section 4.6).

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m² of oxaliplatin, immediately before administration of 5-fluorouracil, no change in the level of exposure to 5-fluorouracil has been observed.

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

4.6 Pregnancy and lactation

To date there is no available information on safety of use in pregnant women. In animal studies, reproductive toxicity was observed. Consequently, oxaliplatin is not recommended during pregnancy and in women of childbearing potential not using contraceptive measures. The use of oxaliplatin should only be considered after suitably apprising the patient of the risk to the foetus and with the patient's consent.

Appropriate contraceptive measures must be taken during and after cessation of therapy during 4 months for women and 6 months for men.

Excretion in breast milk has not been studied. Breast-feeding is contra-indicated during oxaliplatin therapy.

Oxaliplatin may have an anti-fertility effect (see section 4.4).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, nausea, vomiting and mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

The frequencies reported in the table below are derived from clinical trials in the metastatic and adjuvant settings (having included 416 and 1108 patients respectively in the oxaliplatin + 5-FU/FA treatment arms) and from post marketing experience.

Frequencies in this table are defined using the following convention: very common (> 1/10) common (> 1/100, ≤ 1/10), uncommon (> 1/1000, ≤ 1/100), rare (> 1/10000, ≤ 1/1000), very rare (≤ 1/10000) including isolated report.

Further details are given after the table.

Table 1: Adverse effects by system organ class

| System Organ Class | Very common | Common | Uncommon | Rare | Very rare |
|--|--|---|--------------------|--|------------------|
| Infections and infestations | Infection | Febrile neutropenia / neutropenic sepsis (i.e. neutropenia grade 3,4 and documented infections)* Rhinitis, upper respiratory tract infection | | | |
| Blood and lymphatic system disorders | Anemia, neutropenia, thrombocytopenia* Leukopenia, lymphopenia* | | | Immunoallergic thrombocytopenia, haemolytic anemia | |
| Immune system disorders | Allergy/ allergic reaction ² | | | | |
| Metabolism and nutrition disorders | Anorexia Glycemia abnormalities, hypokalaemia, natriaemia abnormalities | Dehydration | Metabolic acidosis | | |
| Psychiatric disorders | | Depression, insomnia | Nervousness | | |
| Nervous system disorders | Peripheral sensory neuropathy, headache Sensory disturbance Taste perversion | Dizziness, Neuritis motor, Meningism | | Dysarthria | |
| Eye disorders | | Conjunctivitis, vision abnormal | | Transient fall in visual acuity, visual field disturbances, optic neuritis | |
| Ear and labyrinth disorders | | | Ototoxicity | Deafness | |
| Vascular disorders | Epistaxis | Haemorrhage, thrombophlebitis deep, embolism pulmonary, haemorrhage rectum Flushing | | | |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea, coughing | Chest pain, hiccup | | Interstitial lung disease, pulmonary fibrosis** | |

| | | | | | |
|---|--|--|-------------------------------|--|---------------------------------------|
| Gastrointestinal disorders | Diarrhea, nausea, vomiting, stomatitis / mucositis, abdominal pain, constipation | Dyspepsia, gastroesophageal reflux | Ileus, intestinal obstruction | Colitis including Clostridium difficile diarrhea | Pancreatitis |
| Hepatobiliary disorders | Alkaline phosphatase increase, bilirubin increase, LDH increase, hepatic enzymes (SGPT/ALAT, SGOT/ASAT) increase | | | | Liver sinusoidal obstruction syndrome |
| Skin and subcutaneous tissue disorders | Skin disorder, alopecia | Skin exfoliation (i.e. hand and foot syndrome), rash erythematous, rash, sweating increased, nail disorder | | | |
| Musculoskeletal and connective tissue disorders | Back pain | Arthralgia, skeletal pain | | | |
| Renal and urinary disorders | | Dysuria, micturition frequency abnormal, creatinine increase, haematuria | | | Acute tubulo-interstitial nephropathy |
| General disorders and administration site conditions | Fever ³ , fatigue, asthenia, pain, weight increase (adjuvant setting) Injection site reaction ¹ | Weight decrease (metastatic setting) | | | |

¹ Extravasation may result in local pain and inflammation which may be severe and lead to complications, especially when oxaliplatin is infused through a peripheral vein (see section 4.4).

² Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis. Common anaphylactic reactions, including bronchospasm, angioedema, hypotension and anaphylactic shock

³ Very common fever, either from infection (with or without febrile neutropenia) or isolated fever from immunological mechanism.

* See detailed section below

** See section 4.4.

Haematological toxicity

Table 2: Incidence by patient (%), by grade

| Oxaliplatin and 5-FU/FA 85 mg/m ² every 2 weeks | Metastatic Setting | | | Adjuvant Setting | | |
|---|--------------------|------|------|------------------|------|------|
| | All grades | Gr 3 | Gr 4 | All grades | Gr 3 | Gr 4 |
| Anemia | 82.2 | 3 | < 1 | 75.6 | 0.7 | 0.1 |
| Neutropenia | 71.4 | 28 | 14 | 78.9 | 28.8 | 12.3 |
| Thrombocytopenia | 71.6 | 4 | < 1 | 77.4 | 1.5 | 0.2 |
| Febrile neutropenia | 5.0 | 3.6 | 1.4 | 0.7 | 0.7 | 0.0 |
| Neutropenic sepsis | 1.1 | 0.7 | 0.4 | 1.1 | 0.6 | 0.4 |

Digestive toxicity

Table 3: Incidence by patient (%), by grade

| Oxaliplatin and 5-FU/FA 85 mg/m ² every 2 weeks | Metastatic Setting | | | Adjuvant Setting | | |
|---|--------------------|------|------|------------------|------|------|
| | All grades | Gr 3 | Gr 4 | All grades | Gr 3 | Gr 4 |
| Nausea | 69.9 | 8 | < 1 | 73.7 | 4.8 | 0.3 |
| Diarrhoea | 60.8 | 9 | 2 | 56.3 | 8.3 | 2.5 |
| Vomiting | 49.0 | 6 | 1 | 47.2 | 5.3 | 0.5 |
| Mucositis / Stomatitis | 39.9 | 4 | < 1 | 42.1 | 2.8 | 0.1 |

Prophylaxis and/or treatment with potent antiemetic agents is indicated.

Dehydration, paralytic ileus, intestinal obstruction, hypokalemia, metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when combining oxaliplatin with 5-fluorouracil (see section 4.4). In single cases pancreatitis is reported.

Nervous system:

The dose limiting toxicity of oxaliplatin is neurological. It involves a sensory peripheral neuropathy characterised by dyaesthesia and/or paraesthesia of the extremities with or without cramps, often triggered by the cold. These symptoms occur in up to 95 % of patients treated. The duration of these symptoms, which usually regress between courses of treatment, increases with the number of treatment cycles.

The onset of pain and/or a functional disorder are indications, depending on the duration of the symptoms, for dose adjustment, or even treatment discontinuation (see section 4.4).

This functional disorder includes difficulties in executing delicate movements and is a possible consequence of sensory impairment. The risk of occurrence of persistent symptoms for a cumulative dose of 850 mg/m² (10 cycles) is approximately 10 % and 20 % for a cumulative dose of 1020 mg/m² (12 cycles).

In the majority of the cases, the neurological signs and symptoms improve or totally recover when treatment is discontinued. In the adjuvant setting of colon cancer, 6 months after treatment cessation, 87 % of patients had no or mild symptoms. After up to 3 years of follow up, about 3 % of patients presented either with persisting localised paraesthesias of moderate intensity (2.3 %) or with paraesthesias that may interfere with functional activities (0.5 %).

Acute neurosensory manifestations (see section 5.3) have been reported. They start within hours of administration and often occur on exposure to cold. They usually present as transient paraesthesia, dysaesthesia and hypoesthesia. An acute syndrome of pharyngolaryngeal dysaesthesia occurs in 1 % - 2 % of patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation, without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or bronchospasm (no stridor or wheezing). Although antihistamines and bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome (see section 4.4). Occasionally other symptoms that have been observed include jaw spasm/muscle spasms/muscle contractions-involuntary/muscle twitching/myoclonus, coordination abnormal/gait abnormal/ataxia/balance disorders, throat or chest tightness/pressure/discomfort/pain. In addition, cranial nerve dysfunctions may be associated, or also occur as an isolated event such as ptosis, diplopia, aphonia/dysphonia/hoarseness, sometimes described as vocal cord paralysis, abnormal tongue sensation or dysarthria, sometimes described as aphasia, trigeminal neuralgia/facial pain/eye pain, decrease in visual acuity, visual field disorders.

Other neurological symptoms such as loss of deep tendon reflex and Lhermitte's sign were reported during treatment with oxaliplatin. Isolated cases of optic neuritis have been reported.

Allergic reactions:

Table 4: Incidence by patient (%), by grade

| Oxaliplatin and 5-FU/FA 85 mg/m ² every 2 weeks | Metastatic Setting | | | Adjuvant Setting | | |
|---|--------------------|------|------|------------------|------|------|
| | All grades | Gr 3 | Gr 4 | All grades | Gr 3 | Gr 4 |
| Allergic reactions / Allergy | 9.1 | 1 | < 1 | 10.3 | 2.3 | 0.6 |

Hepato-biliary disorders:

Liver sinusoidal obstruction syndrome, also known as veno-occlusive disease of liver, or pathological manifestations related to such liver disorder, including peliosis hepatis, nodular regenerative hyperplasia, perisinusoidal fibrosis has been reported. Clinical manifestations may be portal hypertension and/or increased transaminases.

Renal and urinary disorders:

Acute tubulo-interstitial nephropathy leading to acute renal failure has been reported.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platinum compounds, ATC code: L01XA 03

Oxaliplatin is an antineoplastic drug belonging to a new class of platinum-based compounds in which the platinum atom is complexed with 1,2-diaminocyclohexane (“DACH”) and an oxalate group.

Oxaliplatin is a single enantiomer, the Cis-[oxalato(trans-1,2- DACH)platinum].

Oxaliplatin exhibits a wide spectrum of both *in vitro* cytotoxicity and *in vivo* antitumour activity in a variety of tumour model systems including human colorectal cancer models. Oxaliplatin also demonstrates *in vitro* and *in vivo* activity in various cisplatin resistant models. A synergistic cytotoxic action has been observed in combination with 5-fluorouracil both *in vitro* and *in vivo*.

Studies on the mechanism of action of oxaliplatin, although not completely elucidated, show that the aqua-derivatives resulting from the biotransformation of oxaliplatin, interact with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and antitumour effects.

In patients with metastatic colorectal cancer, the efficacy of oxaliplatin (85 mg/m² repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in three clinical studies:

- In front-line treatment, a 2-arm comparative phase III study (de Gramont, A et al., 2000) randomised 420 patients either to 5-FU/FA alone (LV5FU2, N=210) or the combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=210).
- In pretreated patients, a comparative three arms phase III study (Rothenberg, ML et al., 2003) randomised 821 patients refractory to an irinotecan (CPT-11) + 5-FU/FA combination either to 5-FU/FA alone (LV5FU2, N=275), oxaliplatin single agent (N=275), or combination of oxaliplatin with 5-FU/FA (FOLFOX4, N=271).
- Finally, an uncontrolled phase II study (André, T et al., 1999) included patients refractory to 5-FU/FA alone, that were treated with the oxaliplatin and 5-FU/FA combination (FOLFOX4, N=57)

The two randomised clinical trials in front-line therapy (de Gramont, A et al.) and in pretreated patients (Rothenberg ML et al.), demonstrated a significantly higher response rate and a prolonged progression free survival (PFS) / time to progression (TTP) as compared to treatment with 5-FU/FA alone. In the study of Rothenberg et al. performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA versus 5-FU/FA did not reach statistical significance.

Table 5: Response rate under FOLFOX4 versus LV5FU2

| Response rate, % (95% CI) independent radiological review ITT analysis | LV5FU2 | FOLFOX4 | Oxaliplatin Single agent |
|--|------------------|--------------------|-------------------------------------|
| Front-line treatment (de Gramont, A et al., 2000) <i>Response assessment every 8 weeks</i> | 22 (16-27) | 49 (42-46) | NA* |
| | P value = 0.0001 | | |
| Pretreated patients (Rothenberg, ML et al., 2003) (refractory to CPT-11 + 5-FU/FA) <i>Response assessment every 6 weeks</i> | 0.7 (0.0-2.7) | 11.1 (7.6-15.5) | 1.1 (0.2-3.2) |
| | P value = 0.0001 | | |
| Pretreated patients (André, T et al., 1999) (refractory to 5-FU/FA) <i>Response assessment every 12 weeks</i> | NA* | 23 (13-36) | NA* |

* NA: Not applicable.

**Table 6: Median Progression Free Survival (PFS) / Median Time to Progression (TTP)
FOLFOX4 versus LV5FU2**

| Median PFS/TTP, Months (95% CI) independent radiological review ITT analysis | LV5FU2 | FOLFOX4 | Oxaliplatin Single agent |
|--|---------------------------|------------------|-------------------------------------|
| Front-line treatment (de Gramont, A et al., 2000) (PFS) | 6.0 (5.5-6.5) | 8.2 (7.2-8.8) | NA* |
| | Log-rank P value = 0.0003 | | |
| Pretreated patients (Rothenberg, ML et al., 2003) (TTP) (refractory to CPT-11 + 5-FU/FA) | 2.6 (1.8-2.9) | 5.3 (4.7-6.1) | 2.1 (1.6-2.7) |
| | Log-rank P value = 0.0001 | | |
| (Pretreated patients (André, T et al., 1999) (refractory to 5-FU/FA) | NA* | 5.1 (3.1-5.7) | NA* |

* NA: Not applicable.

Table 7: Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

| Median OS, months (95% CI) ITT analysis | LV5FU2 | FOLFOX4 | Oxaliplatin Single agent |
|--|-------------------------|---------------------|-------------------------------------|
| Front-line treatment (de Gramont, A et al., 2000) | 14.7 (13.0-18.2) | 16.2 (14.7-18.2) | NA* |
| | Log-rank P value = 0.12 | | |
| Pretreated patients (Rothenberg, ML et al., 2003) (TTP) (refractory to CPT-11 + 5-FU/FA) | 8.8 (7.3-9.3) | 9.9 (9.1-10.5) | 8.1 (7.2-8.7) |
| | Log-rank P value = 0.09 | | |
| Pretreated patients (André, T et al., 1999) (refractory to 5-FU/FA) | NA* | 10.8 (9.3-12.8) | NA* |

* NA: Not applicable.

In pretreated patients (Rothenberg, ML et al., 2003), who were symptomatic at baseline, a higher proportion of those treated with oxaliplatin and 5-FU/FA experienced a significant improvement of their disease-related symptoms compared to those treated with 5-FU/FA alone (27.7 % vs. 14.6 %, $p = 0.0033$).

In non pretreated patients (de Gramont, A et al., 2000), no statistically significant difference between the two treatment groups was found for any of the quality of life dimensions. However, the quality of life scores were generally better in the control arm for measurement of global health status and pain and worse in the oxaliplatin arm for nausea and vomiting.

In the adjuvant setting, the MOSAIC comparative phase III study randomised 2246 patients (899 stage II / Duke's B2 and 1347 stage III / Duke's C) further to complete resection of the primary tumour of colon cancer either to 5-FU/FA alone (LV5FU2, N=1123 (B2 / C = 448 / 675) or to combination of oxaliplatin and 5-FU/FA (FOLFOX4, N=1123 (B2 / C) = 451 / 672).

Table 8: MOSAIC-3-year disease free survival (ITT analysis)* for the overall population

| Treatment arm | LV5FU2 | FOLFOX4 |
|---|---------------------|---------------------|
| Percent 3-year disease free survival (95% CI) | 73.3 (70.6-75.6) | 78.7 (76.2-81.1) |
| Hazard ratio (95% CI) | 0.76 (0.64-0.89) | |
| Stratified log rank test | P = 0.0008 | |

* median follow up 44.2 months (all patients followed for at least 3 years)

The study demonstrated an overall significant advantage in 3-year disease free survival for the oxaliplatin and 5-FU/FA combination (FOLFOX4) over 5-FU/FA alone (LV5FU2).

Table 9: MOSAIC-3-year Disease Free Survival (ITT analysis)* according to Stage of Disease

| Patient stage | Stage II (Duke's B2) | | Stage III (Duke's C) | |
|---|-------------------------|---------------------|-------------------------|---------------------|
| | LV5FU2 | FOLFOX4 | LV5FU2 | FOLFOX4 |
| Treatment arm | LV5FU2 | FOLFOX4 | LV5FU2 | FOLFOX4 |
| Percent 3-year disease free survival (95% CI) | 84.3 (80.9-87.7) | 87.4 (84.3-90.5) | 65.8 (62.1-69.5) | 72.8 (69.4-76.2) |
| Hazard ratio (95% CI) | 0.79 (0.57-1.09) | | 0.75 (0.62-0.90) | |
| Stratified log rank test | P = 0.151 | | P = 0.002 | |

* median follow up 44.2 months (all patients followed for at least 3 years)

Overall Survival (ITT analysis):

At time of the analysis of the 3-year disease free survival, which was the primary endpoint of the MOSAIC trial, 85.1 % of the patients were still alive in the FOLFOX4 arm versus 83.8 % in the LV5FU2 arm. This translated into an overall reduction in mortality risk of 10 % in favour of FOLFOX4 not reaching statistical significance (hazard ratio = 0.90). The figures were 92.2 % versus 92.4 % in the stage II (Duke's B2) sub-population (hazard ratio = 1.01) and 80.4 % versus 78.1 % in the stage III (Duke's C) sub-population (hazard ratio = 0.87), for FOLFOX4 and LV5FU2, respectively.

5.2 Pharmacokinetic properties

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

Table 10: Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate following Multiple Doses of Oxaliplatin at 85 mg/m² Every Two Weeks or at 130 mg/m² Every Three Weeks

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

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

Mean AUC, V_{ss}, CL, and CL_{R0-48} values were determined on Cycle 1.

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

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

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

Biotransformation *in vitro* is considered to be the result of non-enzymatic degradation and there is no evidence of cytochrome P450-mediated metabolism of the diaminocyclohexane (DACH) ring.

Oxaliplatin undergoes extensive biotransformation in patients, and no intact drug was detectable in plasma ultrafiltrate at the end of a 2h-infusion. Several cytotoxic biotransformation products including the monochloro-, dichloro- and diaquo-DACH platinum species have been identified in the systemic circulation together with a number of inactive conjugates at later time points.

Platinum is predominantly excreted in urine, with clearance mainly in the 48 hours following administration.

By day 5, approximately 54 % of the total dose was recovered in the urine and < 3 % in the faeces.

A significant decrease in clearance from 17.6 ± 2.18 l/h to 9.95 ± 1.91 l/h in renal impairment was observed together with a statistically significant decrease in distribution volume from 330 ± 40.9 to 241 ± 36.1 l. The effect of severe renal impairment on platinum clearance has not been evaluated.

5.3 Preclinical safety data

The target organs identified in non-clinical species (mice, rats, dogs, and/or monkeys) in single- and multiple-dose studies included the bone marrow, the gastrointestinal system, the kidney, the testes, the nervous system, and the heart. The target organ toxicities observed in animals are consistent with those produced by other platinum-containing drugs and DNA-damaging, cytotoxic drugs used in the treatment of human cancers with the exception of the effects produced on the heart. Effects on the heart were observed only in the dog and included electrophysiological disturbances with lethal ventricular fibrillation.

Cardiotoxicity is considered specific to the dog not only because it was observed in the dog alone but also because doses similar to those producing lethal cardiotoxicity in dogs (150 mg/m²) were well-tolerated by humans. Non-clinical studies using rat sensory neurons suggest that the acute neurosensory symptoms related to oxaliplatin may involve an interaction with voltage-gated Na⁺ channels.

Oxaliplatin was mutagenic and clastogenic in mammalian test systems and produced embryo-fetal toxicity in rats. Oxaliplatin is considered a probable carcinogen, although carcinogenic studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate.

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 described in section 6.6, oxaliplatin can be co-administered with folic acid via a Y-line.

- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin (see section 6.6).
- DO NOT dilute oxaliplatin with saline or other solutions containing chloride ions (including calcium, potassium or sodium chlorides).
- DO NOT mix with other drugs in the same infusion bag or infusion line (see section 6.6 for instructions concerning simultaneous administration with folic acid).
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

Medicinal product as packaged for sale:

4 years

Reconstituted concentrate solution in the original vial:

The reconstituted concentrate solution should be diluted immediately.

Solution for infusion after dilution:

After dilution of the reconstituted solution in 5 % glucose solution, chemical and physical in-use stability has been demonstrated for 24 hours at 2°C to 8°C.

From a microbiological point of view, the solution for infusion should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

6.4 Special precautions for storage

Medicinal product as packaged for sale:

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted and diluted product, see section 6.3.

6.5 Nature and contents of container

Type I glass vials with stoppers of chlorobutyl elastomer.

Supplied in packs of 1 vial containing oxaliplatin 50 mg, 100 mg or 150 mg.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

As with other potentially toxic compounds caution should be exercised when handling and preparing oxaliplatin solutions.

Instructions for Handling

The handling of this cytotoxic agent by nursing or medical personnel requires every precaution to guarantee the protection of the handler and his surroundings.

The preparation of injectable solutions of cytotoxic agents must be carried out by trained specialist personnel with knowledge of the medicines used, in conditions that guarantee the protection of the environment and in particular the protection of the personnel handling the medicines in accordance with the hospital policy. It requires a preparation area reserved for this purpose. It is forbidden to smoke, eat or drink in this area.

Personnel must be provided with appropriate handling materials, notably long sleeved gowns, protection masks, caps, protective goggles, sterile single-use gloves, protective covers for the work area, containers and collection bags for waste.

Excreta and vomit must be handled with care.

Pregnant women must be warned to avoid handling cytotoxic agents.

Any broken container must be treated with the same precautions and considered as contaminated waste. Contaminated waste should be incinerated in suitably labelled rigid containers. See below section "Disposal".

If oxaliplatin powder, reconstituted solution or infusion solution should come into contact with skin, wash immediately and thoroughly with water.

If oxaliplatin powder, reconstituted solution or infusion solution should come into contact with mucous membranes, wash immediately and thoroughly with water.

Special precautions for administration

- DO NOT use injection material containing aluminium.
- DO NOT administer undiluted.
- Only glucose 5% infusion solution (50 mg/ml) is to be used as a diluent.
- DO NOT reconstitute or dilute for infusion with sodium chloride or chloride containing solutions.
- DO NOT administer extravascularly.
- DO NOT mix with any other medication in the same infusion bag or administer simultaneously by the same infusion line.
- DO NOT mix with alkaline drugs or solutions, in particular 5-fluorouracil, folic acid preparations containing trometamol as an excipient and trometamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Instruction for use with folic acid (as calcium folinate or disodium folinate)

Oxaliplatin 85mg/m² IV infusion in 250 to 500 ml of 5% glucose solution (50 mg/ml) is given at the same time as folic acid IV infusion in 5% glucose solution, over 2 to 6 hours, using a Y-line placed immediately before the site of infusion.

These two drugs should **not** be combined in the same infusion bag. Folic acid must not contain trometamol as an excipient and must only be diluted using isotonic 5% glucose solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

Instruction for use with 5-fluorouracil

Oxaliplatin should always be administered before fluoropyrimidines – i.e. 5-fluorouracil.

After oxaliplatin administration, flush the line and then administer 5-fluorouracil.

For additional information on drugs combined with oxaliplatin, see the corresponding manufacturer's summary of product characteristics.

Any reconstituted solution that shows evidence of precipitation should not be used and should be destroyed with due regard to legal requirements for disposal of hazardous waste (see below).

Reconstitution of the powder

- Water for injections or 5 % glucose solution (50 mg/ml) should be used to reconstitute the solution.
- For a vial of 50 mg: add 10 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.
- For a vial of 100 mg: add 20 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.
- For a vial of 150 mg: add 30 ml of solvent to obtain a concentration of 5 mg oxaliplatin/ml.

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused solution should be discarded (see below "Disposal").

Dilution before infusion

Withdraw the required amount of reconstituted concentrate solution from the vial(s) and then dilute with 250 ml to 500 ml of a 5 % glucose solution to give an oxaliplatin concentration between not less than 0.2 mg/ml and 0.7 mg/ml, concentration range for which the physico-chemical stability of oxaliplatin has been demonstrated.

Administer by IV infusion.

After dilution in 5% glucose, chemical and physical in-use stability has been demonstrated for 24 hours at +2°C to +8°C.

From a microbiological point of view, this infusion preparation should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C.

Inspect visually prior to use. Only clear solutions without particles should be used.

The medicinal product is for single use only. Any unused solution should be discarded.

NEVER use sodium chloride solution for either reconstitution or dilution.

The compatibility of Oxaliplatin solution for infusion has been tested with representative, PVC-based, administration sets.

Infusion

The administration of oxaliplatin does not require prehydration.

Oxaliplatin diluted in 250 to 500 ml of a 5% glucose solution to give a concentration not less than 0.2 mg/ml **must** be infused either by peripheral vein or central venous line over 2 to 6 hours. When oxaliplatin is administered with 5-fluorouracil, the oxaliplatin infusion must precede the administration of 5-fluorouracil.

Disposal

Remnants of the medicinal product as well as all materials that have been used for reconstitution, for dilution and administration must be destroyed according to hospital standard procedures applicable to cytotoxic agents with due regard to current laws related to the disposal of hazardous waste.

7. MARKETING AUTHORISATION HOLDER

medac

Gesellschaft für klinische Spezialpräparate mbH

Fehlandtstraße 3

D-20354 Hamburg

Telephone: +49 4103 8006-0

Telefax: +49 4103 8006-100

8. MARKETING AUTHORISATION NUMBER(S)

PA 623/8/1

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd February 2007

10. DATE OF REVISION OF THE TEXT

July 2010