Safeguarding public health

MHRA

Public Assessment Report

Decentralised Procedure

Oxaliplatin UKR 5 mg/ml, powder for solution for infusion

PL 11587/0048

UK/H/927/001/DC

Medac Gesellschaft für klinische Spezialpräparate GmbH

Medicines and Healthcare products Regulatory Agency

Lay summary

The Medicines and Healthcare products Regulatory Agency (MHRA) granted UKR Regulatory Affairs Limited a Marketing Authorisation (licence) for the medicinal products Oxaliplatin UKR 5 mg/ml, powder for solution for infusion (PL 19364/0016). Following successful completion of the Decentralised Procedure, a change of ownership was granted, licensing the product as PL 11587/0048 to Medac Gesellschaft für klinische Spezialpräparate GmbH on 17 December 2007.

This medicinal product contain the active ingredient oxaliplatin and is used, after complete surgical removal of the bowel tumour, to treat cancer of the large bowel (colon) that has spread beyond the bowel wall to nearby lymph glands but not to other tissues. It is also used to treat cancer of the colon and rectum that has spread beyond the bowel to other body tissues, such as the liver or lungs. In addition, this medicine can be used in combination with other anti-cancer medicinal products called 5-fluorouracil and folinic acid, with or without prior surgery to remove the cancer.

The data submitted in support of the application for Oxaliplatin UKR 5 mg/ml, powder for solution for infusion raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using this product outweigh the risks; hence a Marketing Authorisation has been granted.

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Module 1

Information about decentralised procedure

Name of the product in the Reference Member State	Oxaliplatin UKR 5 mg/ml, powder for solution for infusion
Type of application (Eudratrack details)	Level 1 Abridged Level 2 Initial Level 3 10.1 Level 4 Chemical substance Level 5 POM
Name of the active substance (INN)	Oxaliplatin
Pharmacotherapeutic classification (ATC code)	L01XA03
Pharmaceutical form and strength	Powder for solution for infusion, 5mg/ml
Reference numbers for the Mutual Recognition Procedure	UK/H/927/001/DC
Reference Member State	United Kingdom
Member States concerned	AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, LT, LV, NL, NO, PL, PT, SE, SI, SK
Date of start of the procedure	23 August 2006
End date of decentralised procedure	30 May 2007
Marketing Authorisation Number	PL 11587/0048
Name and address of the authorisation holder	Medac Gesellschaft für klinische Spezialpräparate GmbH, Fehlandtstraße 3, D-20354 Hamburg, Germany (PL 11587/0048)

Module 2

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Oxaliplatin UKR 5 mg/ml, powder for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of reconstituted solution contains 5 mg oxaliplatin.
50mg vial:
each vial contains 50mg of oxaliplatin for reconstitution in 10ml of solvent.
100mg vial:
each vial contains 100mg of oxaliplatin for reconstitution in 20ml of solvent.
150mg vial:
each vial contains 150mg of oxaliplatin for reconstitution in 30ml of solvent.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for infusion

White powder for solution for infusion.

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. During clinical development no specific dose adjustment for patients with abnormal liver function tests was performed.

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

In the event of extravasation, administration must be discontinued immediately.
Instructions for use:

Oxaliplatin must be reconstituted and further diluted before use. Only the recommended diluents should be used to reconstitute and then dilute the freeze-dried product. (See section 6.6).

4.3 Contraindications

Oxaliplatin is contra-indicated in patients who

- have a known history of hypersensitivity to oxaliplatin or to the excipient.
- are breast feeding.
- have 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.
- have a peripheral sensory neuropathy with functional impairment prior to first course.
- have a severely impaired renal function (creatinine clearance less than 30 ml/min).

4.4 Special warnings and precautions for use

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

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.

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/m^2 (metastatic setting) or 75 mg/m^2 (adjuvant setting).

- If paraesthesia without functional impairment persists until the next cycle, the subsequent oxaliplatin dose should be reduced from 85 to 65 mg/m^2 (metastatic setting) or 75 mg/m^2 (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/emesis particularly when combining oxaliplatin with 5-fluorouracil.

If haematological toxicity occurs (neutrophils < 1.5 x 10^9/l or platelets < 50 x 10^9/l), administration of the next course of therapy should be postponed until haemotological 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/emesis, 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 ≥ 1.5 x 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 (WHO), grade 3-4 neutropenia (neutrophils < 1.0 x 10^9/l), grade 3-4 thrombo-cytopenia (platelets < 50 x 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 or pulmonary fibrosis (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

In patients who have received a single dose of 85 mg/m^2 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 appraising 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 a 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 neurophathy). 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 FOLFOX arm) and from post marketing experience.
Frequencies in this table are defined using the following convention: very common (≥ 1/10) common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA Organ system classes	Very common	Common	Uncommon	Rare	Very rare
Infections and infestations *	- Infection	- Rhinitis - Upper respiratory tract infection - Febrile neutropenia/ Neutropenic sepsis			
Blood and the lymphatic system disorders*	- Anaemia - Neutropenia - Thrombocyto-penia - Leucopenia - Lymphopenia			- Immunoallergic thrombocytopenia - Haemolytic anaemia	
Immune system disorders*	- Allergy/ allergic reaction+				
Metabolism and nutrition disorders	- Anorexia - Glycaemia abnormalities - Hypokalaemia - Natraemia abnormalities	- Dehydration	- Metabolic acidosis		
Psychiatric disorders		- Depression - Insomnia	- Nervousness		
Nervous system disorders*	- Peripheral sensory neuropathy - Sensory disturbance - Dysgeusia - Headache	- Dizziness - Motor neuritis - Meningism		- Dysarthria	
Eye disorders		- Conjunctivitis - Visual disturbance		- Visual acuity reduced transiently - Visual field disturbances	- Optic neuritis
Ear and labyrinth disorders			- Ototoxicity	- Deafness	
Vascular disorders	- Epistaxis	- Haemorrhage - Flushing - Deep vein thrombosis - Pulmonary embolism			
Respiratory, thoracic and mediastinal disorders	- Dyspnoea - Cough	- Hiccups - Chest pain		- Interstitial lung disease - Pulmonary fibrosis**	

Gastrointestinal disorders*	- Nausea - Diarrhoea - Vomiting - Stomatitis/ Mucositis - Abdominal pain - Constipation	- Dyspepsia - Gastroesophageal reflux - Rectal haemorrhage	- Ileus - Intestinal obstruction	- Colitis including clostridium difficile diarrhoea	
Hepatobiliary disorders					Liver sinusoidal obstruction syndrome
Skin and subcutaneous tissue disorders	- Skin disorder - Alopecia	- Skin exfoliation (i.e. Hand & Foot syndrome) - Rash erythematous - Rash - Hyperhidrosis - Nail disorder			
Musculoskeletal, connective tissue and bone disorders	- Back pain	- Arthralgia - Bone pain			
Renal and urinary disorders		- Dysuria - Haematuria - Micturition frequency abnormal			Acute tubulo-interstitial nephropathy leading to acute renal failure
General disorders and administration site conditions	- Fatigue - Fever++ - Asthenia - Pain - Injection site reaction+++				
Investigations	- Hepatic enzyme increase - Blood alkaline phosphatase increase - Blood bilirubin increase - Blood lactate dehydrogenase increase - Weight increase (adjuvant setting)	- Blood creatinine increase - Weight decrease (metastatic setting)			

* See detailed section below.
** See section 4.4.

+ Common allergic reactions such as skin rash (particularly urticaria), conjunctivitis, rhinitis. Common anaphylactic reactions, including bronchospasm, sensation of chest pain, angioedema, hypotension and anaphylactic shock.

++ Very common fever, rigors (tremors), either from infection (with or without febrile neutropenia) or possibly from immunological mechanism.

+++ Injection site reactions including local pain, redness, swelling and thrombosis have been reported. Extravasation may also result in local pain and inflammation which may be severe and lead to complications including necrosis, especially when oxaliplatin is infused through a peripheral vein (see section 4.4).

Haematological toxicity

Table 1: Incidence by patient (%), by grade

Oxaliplatin and 5-FU/FA 85 mg/m^2 every 2 weeks	**Metastatic Setting**			**Adjuvant Setting**		
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
Anaemia	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 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
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 dysaesthesia 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/m^2 (10 cycles) is approximately 10 % and 20 % for a cumulative dose of 1020 mg/m^2 (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 dysarthria, 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 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

Allergic reactions / Allergy	9.1	1	< 1	10.3	2.3	0.6

Hepatobiliary 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. Clinical manifestations may be portal hypertension and/or increased transaminases.

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
CYTOSTATIC AGENT
Pharmacotherapeutic group: other antineoplastic agents, 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-l-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/m^2 repeated every two weeks) combined with 5-fluorouracil/folinic acid (5-FU/FA) is reported in three clinical studies:

- In front-line treatment, the 2-arm comparative phase III EFC2962 study 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, the comparative three arms phase III study EFC4584 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, the uncontrolled phase II EFC2964 study 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, EFC2962 in front-line therapy and EFC4584 in pretreated patients, 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 EFC4584 performed in refractory pretreated patients, the difference in median overall survival (OS) between the combination of oxaliplatin and 5-FU/FA did not reach statistical significance.

Table 4: Response rate under FOLFOX4 versus LV5FU2

Response rate, % (95% CI) independent radiological review ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	22 (16-27)	49 (42-46)	NA*
Response assessment every 8 weeks	P value = 0.0001		
Pretreated patients EFC4584 (refractory to CPT-11 + 5-FU/FA)	0.7 (0.0-2.7)	11.1 (7.6-15.5)	1.1 (0.2-3.2)
Response assessment every 6 weeks	P value < 0.0001		
Pretreated patients EFC2964 (refractory to 5-FU/FA)	NA*	23 (13-36)	NA*
Response assessment every 12 weeks			

* NA: Not applicable.

Table 5: 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 EFC2962 (PFS)	6.0 (5.5-6.5)	8.2 (7.2-8.8)	NA*
	Log-rank P value = 0.0003		
Pretreated patients EFC4584 (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 EFC2964 (refractory to 5-FU/FA)	NA*	5.1 (3.1-5.7)	NA*

NA: Not applicable.

Table 6: Median Overall Survival (OS) under FOLFOX4 versus LV5FU2

Median OS, months (95% CI) ITT analysis	**LV5FU2**	**FOLFOX4**	**Oxaliplatin Single agent**
Front-line treatment EFC2962	14.7 (13.0-18.2)	16.2 (14.7-18.2)	NA*
	Log-rank P value = 0.12		
Pretreated patients EFC4584 (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 EFC2964 (refractory to 5-FU/FA)	NA*	10.8 (9.3-12.8)	NA*

* NA: Not applicable.

In pretreated patients (EFC4584), 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 (EFC2962), 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 MOSAÏC comparative phase III study (EFC3313) 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 7: EFC 3313 3-year disease free survival (ITT analysis)*

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 8: EFC 3313 3-year Disease Free Survival (ITT analysis)* according to Stage of Disease

Patient stage	Stage II (Duke's B2)		Stage III (Duke's C)	
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 MOSAÏC 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/m^2 every three weeks for 1 to 5 cycles and oxaliplatin at 85 mg/m^2 every two weeks for 1 to 3 cycles are as follows:

Table 9: Summary of Platinum Pharmacokinetic Parameter Estimates in Ultrafiltrate Following Multiple Doses of oxaliplatin at 85 mg/m^2 Every Two Weeks or at 130 mg/m^2 Every Three Weeks

Dose	**C_{max}**	**AUC_{0-48}**	**AUC**	**$t_{1/2\alpha}$**	**$t_{1/2\beta}$**	**$t_{1/2\gamma}$**	**V_{ss}**	**CL**
	µg/ml	µg * h /ml	µg * h /ml	h	h	h	l	l / h
85 mg/m^2 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/m^2 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 AUC_{0-48} and C_{max} values were determined on Cycle 3 (85 mg/m^2) or cycle 5 (130 mg/m^2).
Mean AUC, Vss , CL, and CL_{R0-48} values were determined on Cycle 1.
C_{end}, C_{max}, AUC, AUC_{0-48}, V_{ss} and CL values were determined by non-compartmental analysis.
$t_{1/2\alpha}$, $t_{1/2\beta}$, $t_{1/2\gamma}$ 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/m^2 every two weeks or 130 mg/m^2 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 preclinical 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/m^2) were well-tolerated by humans. Preclinical 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 folinic acid via a Y-line.

- DO NOT use in association with alkaline drugs or solutions, in particular 5-fluorouracil, basic solutions, trometamol and folinic acid products 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 reconstitute or 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 folinic acid).
- DO NOT use injection equipment containing aluminium.

6.3 Shelf life

Medicinal product as packaged for sale:
18 months

Reconstituted concentrate solution in the original vial:
From a microbiological and chemical point of view, the reconstituted concentrate solution should be diluted immediately.

Solution for infusion after dilution:
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 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.

6.4 Special precautions for storage

Medicinal product as packaged for sale: This medicinal product does not require any special storage conditions. Do not freeze.
For storage conditions of the reconstituted medicinal product, see section 6.3.

Reconstituted concentrate solution: should be diluted immediately.

Solution for infusion after dilution: Store at 2°C to 8°C for not longer than 24 hours.
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.

6.5 Nature and contents of container

Clear glass vial (type I) with chlorobutyl rubber stopper.
Pack sizes: 1 vial containing 50 mg, 100 mg and 150 mg of oxaliplatin.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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 integrity of the product, 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 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, 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.

Instruction for use with folinic 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 folinic 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. Folinic 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.

Reconstitution of the powder

- Water for injections or 5 % glucose solution 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.

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 unless dilution has taken place in controlled and validated aseptic conditions.
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 should precede that 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
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 11587/0048

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

02/08/2007

10 DATE OF REVISION OF THE TEXT

02/08/2007

Module 3

Product Information Leaflet

Reconstitution of the powder

- Water for injections or 5 % glucose solution 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.

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 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 unless dilution has taken place in controlled and validated aseptic conditions.
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 should precede that 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.

This medicinal product is authorised in the Member States of the EEA under the following names:

Austria
Oxaliplatin UKR 5 mg/ml Pulver zur Herstellung einer Infusionslösung

Belgium
Oxaliplatin UKR 5 mg/ml poeder voor oplossing voor intraveneuze infusie

Cyprus
Oxaliplatin UKR 5 mg/ml powder for solution for infusion

Czech Republic
Oxaliplatin UKR 5 mg/ml Prášek pro přípravu infuzního roztoku

Denmark
Oxaliplatin UKR

Estonia
Oxaliplatin 5 mg/ml

Finland
Oxaliplatin UKR 5 mg/ml infuusiokuiva-aine, liuosta varten

France
Oxaliplatine UKR 5 mg/ml, poudre pour solution pour perfusion

Germany
Oxaliplatin 5mg/ml Pulver zur Herstellung einer Infusionslösung

Greece
Οξαλιπλατίνη UKR Regulatory Affairs Ltd 5 mg/ml Κόνις για διάλυμα προς έγχυση

Hungary
Oplin 5mg/ml, Por infúzióhoz

Ireland
Oxaliplatin UKR 5mg/ml powder for solution for infusion

Latvia
Oxaliplatin UKR 5 mg/ml pulveris infuziju šķīduma pagatavošanai

Lithuania
Oplin 5 mg/ml miltelial infuziniam tirpalui

Netherlands
Oxaliplatin UKR 5 mg/ml poeder voor oplossing voor intraveneuze infusie

Norway
Oxa 5mg/ml, Pulver til infusjonsvæske, oppløsning

Poland
Oxaliplatin 5mg/ml, Proszek do sporządzania roztworu do infuzji

Portugal
Oxaliplatino UKR 5 mg/ml pó para solução para perfusão

Slovak Republic
Oxaplat 5 mg/ml, Prášok na infúzny roztok

Slovenia
Oxaliplatin UKR 5 mg/ml prašek za raztopino za infundiranje

Spain
Oxaliplatino UKR Regulatory Affairs Ltd 5 mg/ml polvo para solución para perfusión

Sweden
Oxaliplatin UKR 5mg/ml, Pulver til infusionsvätska, lösning

United Kingdom
Oxaliplatin UKR 5 mg/ml Powder for Solution for Infusion

This leaflet was last approved on 25.05.2007.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Oxaliplatin UKR 5 mg/ml

powder for solution for infusion
Oxaliplatin

Read all of this leaflet carefully before you are given this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask your doctor or your pharmacist.
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT OXALIPLATIN UKR IS AND WHAT IT IS USED FOR

Oxaliplatin UKR is an anticancer drug and contains platinum.

Oxaliplatin UKR is used
- after complete surgical removal of the bowel tumour, to treat cancer of the large bowel (colon) that has spread beyond the bowel wall to nearby lymph glands but not to other tissues.
- to treat cancer of the colon and rectum (back passage) that has spread beyond the bowel to other body tissues, such as the liver or lungs.

Oxaliplatin UKR is used in combination with other anticancer medicinal products called 5-fluorouracil and folinic acid, with or without prior surgery to remove the cancer.

2. BEFORE YOU ARE GIVEN OXALIPLATIN UKR

You should not be given Oxaliplatin UKR if you
- are allergic (hypersensitive) to oxaliplatin or any of the other ingredients of Oxaliplatin UKR.
- are breast-feeding.
- already have a reduced number of blood cells.
- already have tingling and numbness in the fingers and/or toes, and have difficulty performing delicate tasks, such as buttoning clothes.
- have severe kidney problems.

Take special care with Oxaliplatin UKR:
- If you have ever suffered an allergic reaction to platinum-containing medicines such as carboplatin or cisplatin.
- If you have moderate kidney problems.
- If you have any liver problems.
- If blood cell counts are too low after previous oxaliplatin treatment. Your doctor will perform tests to check that you have sufficient blood cells before treatment.
- If you have symptoms of nerve damage such as weakness, numbness, disturbances of feeling or taste after previous oxaliplatin treatment. These effects are often triggered by exposure to cold. If you notice such symptoms tell your doctor, especially if they are troublesome and/or last longer than 7 days. Your doctor will carry out neurological examinations, before and regularly during treatment, especially if you are given other drugs which may cause nerve damage. Symptoms of nerve damage can persist after the end of the treatment.
- If you also receive 5-fluorouracil, because the risk of diarrhoea, vomiting, sore mouth and blood abnormalities is increased.

Before and/or during treatment with oxaliplatin you may be given special medicines to prevent and/or treat nausea and vomiting.
You should take appropriate contraceptive measures during and after cessation of therapy continuing for 4 months after treatment for women and for 6 months after treatment for men.
Oxaliplatin may have an anti-fertility effect, which could be irreversible. Male patients are therefore 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 (please refer to "pregnancy and breast-feeding").

Taking other medicines
Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine, including medicines obtained without a prescription.

Pregnancy and breast-feeding
It is not recommended that you become pregnant during treatment with oxaliplatin.
You should use appropriate contraception during treatment, and also for 4 months after treatment for women and also for 6 months after treatment for men.
If you get pregnant during your treatment, you must immediately inform your doctor.
You must not breast-feed while you are treated with oxaliplatin.
Oxaliplatin may have an anti-fertility effect, which could be irreversible. Male patients are therefore advised to seek advice on conservation of sperm prior to treatment.
Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines
It is unknown whether treatment with Oxaliplatin UKR affects the ability to drive and use machines. If you feel sleepy and/or dizzy following oxaliplatin infusion do not drive, operate potentially dangerous machinery, or engage in other activities that may be hazardous because of decreased alertness.

3. HOW OXALIPLATIN UKR IS GIVEN

Oxaliplatin UKR should only be used in specialised departments of cancer treatment and should be administered under the supervision of an experienced specialist in cancer treatment.
Oxaliplatin UKR is given by injection into a vein (an intravenous infusion) over a 2 to 6 hour period. The injection is first made by mixing the powder with a small amount of water or glucose solution. This is then diluted further in approximately 250 to 500 ml of glucose solution.
The needle must remain in the vein while the drug is being given. If the needle comes out or becomes loose, or the solution is going into the tissue outside the vein (you may feel discomfort or pain) - **tell the doctor or nurse immediately.**
Oxaliplatin UKR will be made up in a special area before the doctor or nurse gives it to you.
The dose of Oxaliplatin UKR is based on your body surface area. This is calculated from your height and weight.
The usual dose for adults including the elderly is 85 mg/m² of body surface area once every 2 weeks before the infusion of the other anticancer medicines.
The dose you receive will also depend on results of blood tests and whether you have previously experienced side effects with Oxaliplatin UKR.
The duration of treatment will be determined by your doctor. Treatment for 6 months is recommended when Oxaliplatin is used after surgery to remove your cancer.
Oxaliplatin is only to be given to adults.

If you use more Oxaliplatin 5 mg/ml than you should
Your doctor will ensure that the correct dose for your condition is given. In case of an overdose, you may experience increased side effects. Your doctor will monitor your blood counts carefully and will treat your symptoms.

If you forget to use Oxaliplatin 5 mg/ml
Oxaliplatin 5 mg/ml needs to be given on a fixed schedule. Be sure to keep all appointments. If you miss a dose, you should discuss this with your doctor. Your doctor will decide when you should be given your next dose of Oxaliplatin 5 mg/ml.

If you stop treatment with Oxaliplatin 5 mg/ml
Stopping your treatment with Oxaliplatin 5 mg/ml may stop the effect on tumour growth. Do not stop treatment with Oxaliplatin 5 mg/ml unless you have discussed this with your doctor.
If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Oxaliplatin UKR can cause side effects, although not everybody gets them. If you experience any side effect it is important that you inform your doctor before your next treatment.

Tell your doctor immediately, if you notice any of the following:
- Persistent or severe diarrhoea or vomiting.
- Stomatitis/mucositis (sore lips or mouth ulcers).
- Swelling of the face, lips, mouth or throat.
- Unexplained respiratory symptoms such as dry cough, difficulty in breathing or crackles.
- Difficulty in swallowing.
- Numbness or tingling in your fingers or toes.
- Extreme tiredness.
- Abnormal bruising or bleeding.
- Signs of infection, such as sore throat and high temperature.
- Sensation of discomfort close to or at the injection site during the infusion.

Very common side effects (in more than or equal 1 in 10 patients) are:
- A disorder of the nerves which can cause weakness, tingling or numbness in the fingers, toes, around the mouth or in the throat that may sometimes occur in association with cramps. This is often triggered by exposure to cold e.g. opening a refrigerator or holding a cold drink. You may also have difficulty in performing delicate tasks, such as buttoning clothes. Although in the majority of cases these symptoms resolve completely there is a possibility of persistent symptoms after the end of the treatment.
- Some people have experienced a tingling shock-like sensation passing down the arms or trunk when the neck is flexed.
- Oxaliplatin can sometimes cause an unpleasant sensation in the throat, in particular when swallowing, and give the sensation of shortness of breath. This sensation, if it happens, usually occurs during or within hours of the infusion and may be triggered by exposure to the cold. Although unpleasant, it will not last long and usually subsides without the need for any treatment. Jaw spasm, muscle spasms and twitching, abnormal coordination and gait, balance disorders and a feeling of chest pressure have also been reported.
In addition, eye disorders such as drooping of upper eye lid (ptosis) or double vision (diplopia), voice loss (aphonia), impairment of voice (dysphonia), roughness of voice (hoarseness), abnormal tongue sensation or speech disturbance (dysarthria) as well as facial pain and eye pain have been observed.
Your doctor may decide to alter your treatment as a result.
- Taste disorder.
- Headache.
- Signs of infection such as a sore throat and high temperature.
- Reduction in the number of white blood cells, which make infections more likely.
- Reduction in red blood cells, which can make the skin pale and cause weakness or breathlessness.
- Reduction in blood platelets, which increases risk of bleeding or bruising.

Your doctor will take blood to check that you have sufficient blood cells before you start treatment and before each subsequent course.
- Nosebleeds.
- Allergic reactions - skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing) and you may feel you are going to faint.
- Shortness of breath, coughing.
- Loss or lack of appetite.
- Nausea (feeling sick), vomiting (being sick) - medication to prevent sickness is usually given to you by your doctor before treatment and may be continued after treatment.
- Diarrhoea. If you suffer from persistent or severe diarrhoea or vomiting contact your doctor immediately for advice.
- Sore mouth or lips, mouth ulcers.
- Stomach pain, constipation.
- Skin disorder.
- Hair loss.
- Back pain.
- Tiredness, loss of strength/weakness, body pain.
- Pain or redness close to or at the injection site during the infusion.
- Fever.
- Weight gain.
- Abnormal levels of glucose (sugar) in your blood.
- Low blood levels of potassium which can cause abnormal heart rhythm.
- Abnormal levels of sodium blood levels e.g. low sodium levels which can cause tiredness and confusion, muscle twitching, fits or coma.
- Abnormal blood tests which show changes of liver function (increase of alkaline phosphatase, bilirubin, LDH and hepatic enzymes).

Common side effects (in less than 1 in 10 but more than or equal 1 in 100 patients) are:
- Fever and/or infection due to a reduction in the number of white blood cells.
- Dehydration.
- Depression.
- Difficulty sleeping.
- Dizziness.
- Inflammation of nerves leading to muscle spasms, cramps, loss of certain reflexes.
- Neck stiffness, intolerance/dislike of bright light and headache.
- Conjunctivitis, visual problems.
- Abnormal bleeding, blood in the urine and stools.
- Blood clot, usually in a leg, which causes pain, swelling or redness.
- Blood clot in the lungs which causes chest pain and breathlessness.
- Runny nose.
- Nose and throat infection.
- Flushing.
- Chest pain, hiccups.
- Indigestion and heartburn.
- Loss of weight.
- Peeling skin, skin rash, increased sweating and nail disorder.
- Joint pain and bone pain.
- Pain on passing urine or a change in frequency when passing urine.
- Abnormal blood tests which show changes of kidney function (e.g. increase of creatinine).

Uncommon side effects (in less than 1 in 100 but more than or equal 1 in 1,000 patients) are:
- Nervousness.
- Hearing problems.
- Impaired or blocked bowel passage.
- Disturbance in the body's acid-base balance.

Rare side effects (in less than 1 in 1,000 but more than or equal 1 in 10,000 patients) are:
- Reduction in blood platelets due to an allergic reaction.
- Reduction in red blood cells caused by cell destruction.
- Slurred speech.
- Temporary deterioration in eyesight.
- Deafness.
- Unexplained respiratory symptoms, difficulties in breathing, scarring of the lungs which causes shortness of breath.
- Bowel inflammation causing abdominal pain or diarrhoea, including severe bacterial infection (Clostridium difficile).

Very rare effects (in less than 1 in 10,000 patients) are:
- Liver disease.
- Kidney inflammation and kidney failure.
- Inflammation of the optic nerve.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

Oxaliplatin UKR should not come into contact with the eyes or skin. If there is any accidental spillage, tell the doctor or nurse immediately.

5. HOW TO STORE OXALIPLATIN UKR

Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.
Do not use this medicine after the expiry date which is stated on the carton. The expiry date refers to the last day of that month.
Do not freeze.
The reconstituted concentrated solution in the vial should be diluted immediately before use in glucose 5 % solution. The solution for infusion should then 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. FURTHER INFORMATION

What Oxaliplatin UKR contains
The active substance is 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.
One ml of the reconstituted concentrate solution contains 5 mg oxaliplatin.
The other ingredient is lactose monohydrate.

What Oxaliplatin UKR looks like and contents of the pack
Each vial contains a white powder for solution for infusion containing 50 mg, 100 mg or 150 mg oxaliplatin with lactose monohydrate. The vials are supplied in cartons of one (1).

Marketing Authorisation Holder and Manufacturer

Marketing authorisation holder:
medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstr. 3
D-20354 Hamburg, Germany
Tel.: +49 / 4103 / 8006-0
Fax: +49 / 4103 / 8006-100

Manufacturer:
medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstr. 3
D-20354 Hamburg, Germany
Production Site:
Theaterstr. 6
D-22880 Wedel, Germany

90400-VPGB-M
AA

The following information is intended for medical or healthcare professionals only:

Instructions for use and 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 integrity of the product, 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 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, folinic acid preparations containing tromethamol as an excipient and tromethamol salts of other drugs. Alkaline drugs or solutions will adversely affect the stability of oxaliplatin.

Instruction for use with folinic acid (as calcium folinate or disodium folinate)
Oxaliplatin 85 mg/m² IV infusion in 250 to 500 ml of 5% glucose solution (50 mg/ml) is given at the same time as folinic 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. Folinic acid must not contain tromethamol as an excipient and must only be diluted using isotonic 5% glucose solution, never in alkaline solutions or sodium chloride or chloride containing solutions.

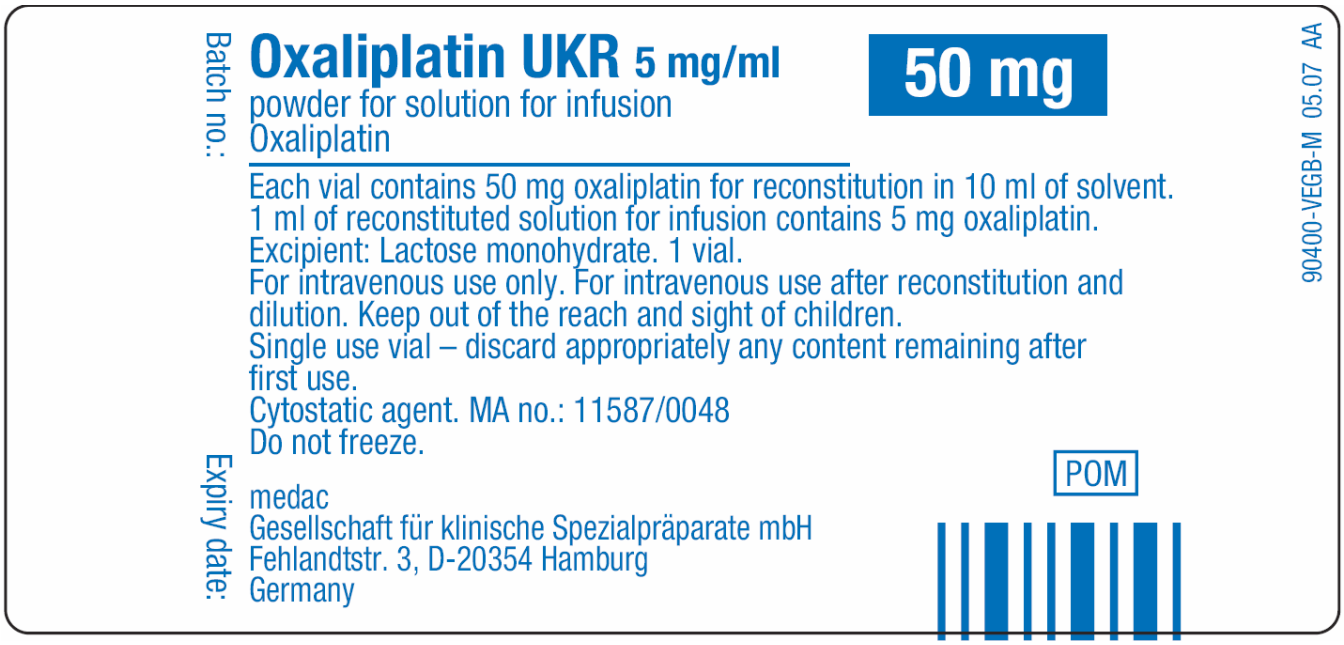
Instruction for use with 5-fluorouracil

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.

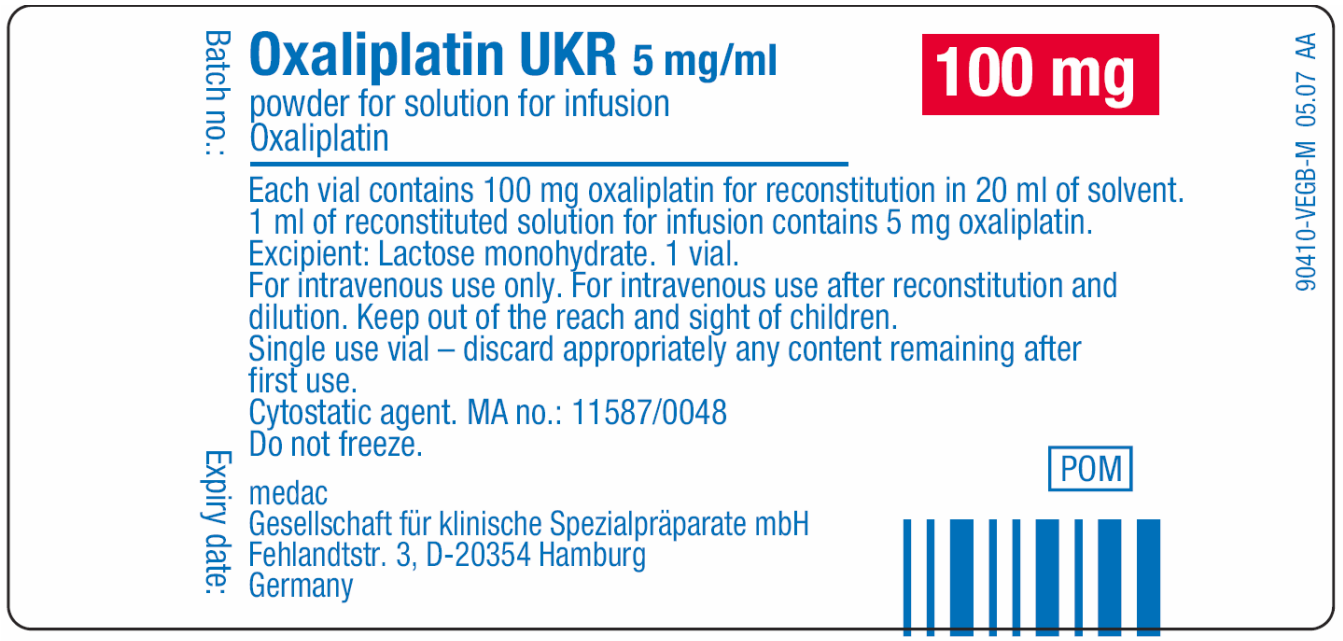
Module 4

Labelling

50 mg label:



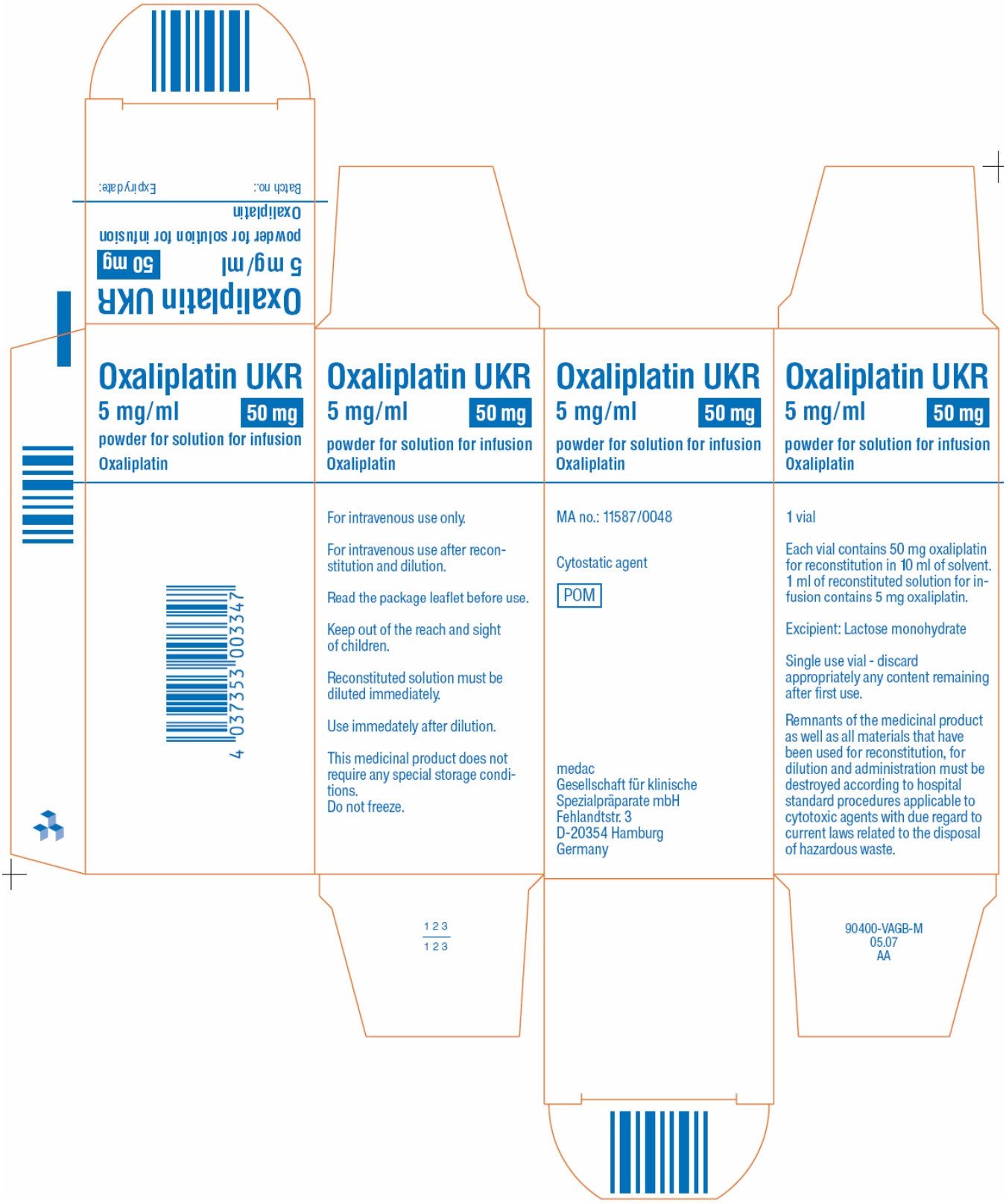
100 mg label:



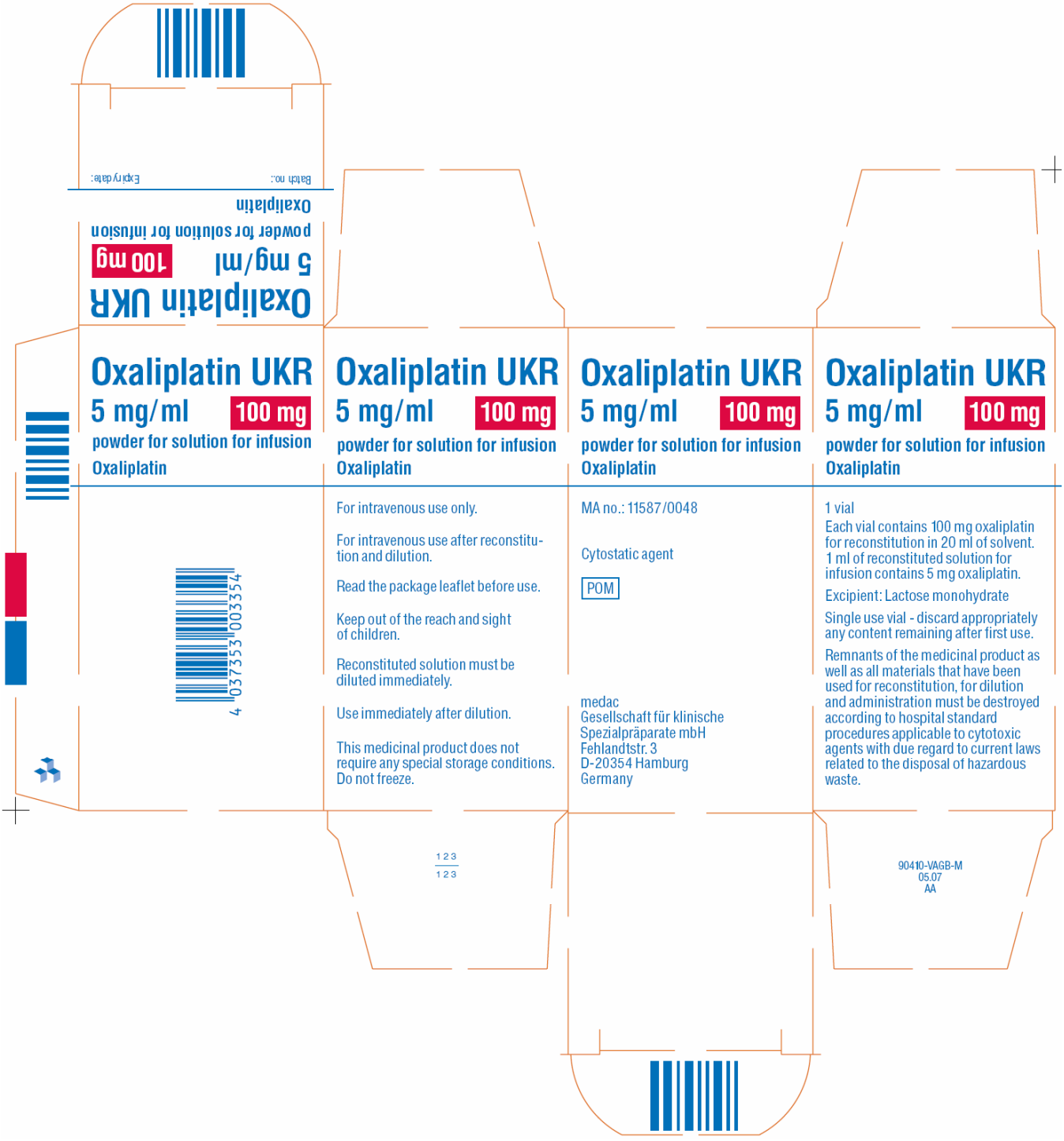
150 mg label:


Batch no.:
Oxaliplatin UKR 5 mg/ml
150 mg
powder for solution for infusion Oxaliplatin
Each vial contains 150 mg oxaliplatin for reconstitution in 30 ml of solvent.
1 ml of reconstituted solution for infusion contains 5 mg oxaliplatin.
Excipient: Lactose monohydrate. 1 vial.
For intravenous use after reconstitution and dilution. For intravenous use only.
Keep out of the reach and sight of children.
Do not freeze.
Cytostatic agent.
Single use vial – discard appropriately any content remaining after first use.
MA no.: 11587/0048
POM
Expiry date:
medac Gesellschaft für klinische Spezialpräparate mbH
Fehlandtstraße 3 - D-20354 Hamburg
Germany
90420-VEGB-M 06.07 AA

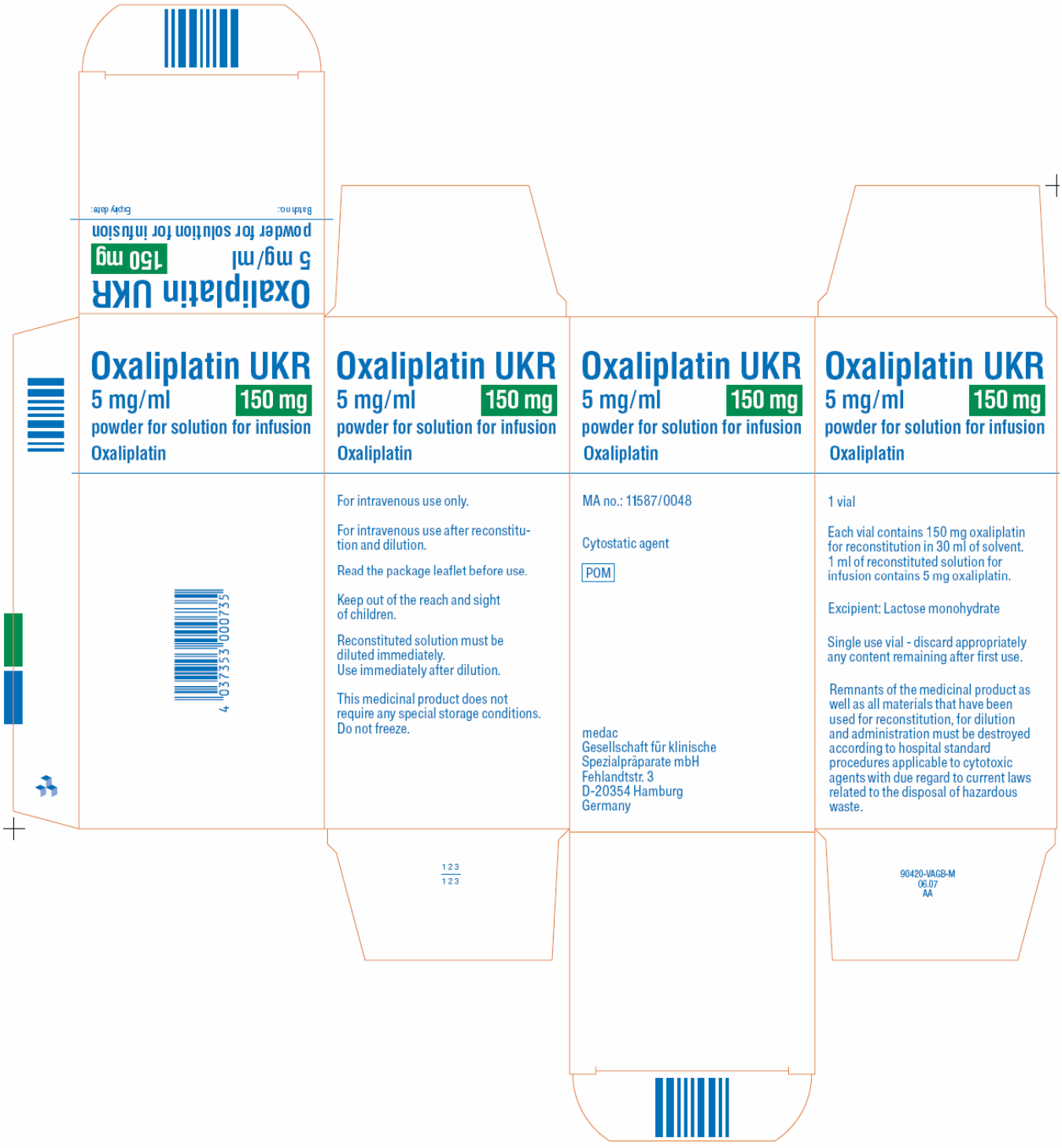
50 mg carton:


Oxaliplatin UKR
5 mg/ml
50 mg
powder for solution for infusion
Oxaliplatin
Batch no.:
Expiry date:
Oxaliplatin UKR
5 mg/ml
50 mg
powder for solution for infusion
Oxaliplatin
4 037353 003347
Oxaliplatin UKR
5 mg/ml
50 mg
powder for solution for infusion
Oxaliplatin
For intravenous use only.
For intravenous use after reconstitution and dilution.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Reconstituted solution must be diluted immediately.
Use immedately after dilution.
This medicinal product does not require any special storage conditions.
Do not freeze.
1 2 3
1 2 3
Oxaliplatin UKR
5 mg/ml
50 mg
powder for solution for infusion
Oxaliplatin
MA no.: 11587/0048
Cytostatic agent
POM
medac
Gesellschaft für klinische
Spezialpräparate mbH
Fehlandtstr. 3
D-20354 Hamburg
Germany
Oxaliplatin UKR
5 mg/ml
50 mg
powder for solution for infusion
Oxaliplatin
1 vial
Each vial contains 50 mg oxaliplatin for reconstitution in 10 ml of solvent. 1 ml of reconstituted solution for infusion contains 5 mg oxaliplatin.
Excipient: Lactose monohydrate
Single use vial - discard appropriately any content remaining after first use.
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.
90400-VAGB-M
05.07
AA

100 mg carton:



150 mg carton:



Module 5

Scientific discussion during initial procedure

RECOMMENDATION
Based on the review of the data on quality, safety and efficacy, the RMS considers that the application for Oxaliplatin UKR 5 mg/ml, powder for solution for infusion (UK/H/927/001/DC), in the treatment of metastatic colorectal cancer, could be approved.

EXECUTIVE SUMMARY
Problem statement
This abridged decentralised application concerns a generic version of oxaliplatin submitted under Article 10.1. The originator product is Eloxatin 5mg/ml Powder for Solution for Infusion, authorised to Sanofi-Aventis in France on 12 April 1996. The legal basis is satisfactory.

With the UK as the Reference Member State in this Decentralised Procedure, UKR Regulatory Affairs Limited applied for Marketing Authorisations for Oxaliplatin UKR 5 mg/ml, powder for solution for infusion in AT, BE, CY, CZ, DE, DK, EE, EL, ES, FI, FR, HU, IE, LT, LV, NL, NO, PL, PT, SE, SI and SK.

About the product
Oxaliplatin is a platinium based compound used in combination with fluorouracil and folinic acid, for the treatment of metastatic colorectal cancer and as adjuvant treatment of colon cancer after resection of the primary tumour.

General comments on the submitted dossier
The submitted dossier is of adequate standard.

General comments on compliance with GMP, GLP, GCP and agreed ethical principles.
The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, 'close-out letters' or 'exchange of information' issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

SCIENTIFIC OVERVIEW AND DISCUSSION

Quality aspects

Drug substance
The chemical-pharmaceutical documentation and Expert Report in relation to Oxaliplatin UKR 5 mg/ml, powder for solution for infusion are of sufficient quality in view of the present European regulatory

requirements. The active substance, oxaliplatin, is described in the European Pharmacopoeia. The drug substance specification is acceptable. Stability studies have been performed with the drug substance. No significant changes in any parameters were observed.

Drug Product
The development of the product has been described, the choice of excipients is justified and their functions explained. The product specifications cover appropriate parameters for this dosage form. Validations of the analytical methods have been presented. Batch analysis has been performed and the results show that the finished product meet the specifications proposed. The conditions used in the stability studies are according to the ICH stability guideline. The control tests and specifications for the drug product are adequately drawn up. The stability data support the shelf life and conditions.

Non clinical aspects
The pharmacodynamic, pharmacokinetic and toxicological properties of oxaliplatin are well known. As oxaliplatin is a well known active substance, no further new non-clinical data are required and the applicant has not provided any.

Clinical aspects

Pharmacokinetics
No novel PK data are supplied. The PK claims within the SPC are appropriately consistent with the innovator label.

Pharmacodynamics
No novel efficacy or safety data are supplied or required for this application. The PD claims within the SPC are appropriately consistent with the UK innovator label.

Clinical efficacy
No novel efficacy data are supplied or required for this generic application, thus the efficacy claims within the SPC are appropriately consistent with the UK innovator label.

Clinical safety
No new safety data have been submitted and none are required for this application, hence the SPC claims are appropriate.

BENEFIT RISK ASSESSMENT
Overall the risk:benefit for this medicinal product considered favourable and approval is recommended.

Overall conclusion

QUALITY

The important quality characteristics of Oxaliplatin UKR 5 mg/ml, powder for solution for infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No preclinical data is needed for these applications.

No new or unexpected safety concerns arise from these applications.

EFFICACY

Clinical studies have demonstrated the efficacy of Oxaliplatin UKR 5 mg/ml, powder for solution for infusion in the treatment of metastatic colorectal cancer and adjuvant treatment of stage III (Duke's C) colon cancer after complete resection of primary tumor.

The product literature is satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified.