

Summary of Product Characteristics

Lomustine "medac" 40 mg PL 11587/0003

1. NAME OF THE MEDICINAL PRODUCT

Lomustine "medac" 40 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lomustine (CCNU) 40 mg per capsule

3. PHARMACEUTICAL FORM

Hard capsule

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

As palliative or supplementary treatment, usually in combination with radiotherapy and/or surgery as part of multiple drug regimens in:

Brain tumours (primary or metastatic)
Lung tumours (especially oat-cell carcinoma)
Hodgkin's disease (resistant to conventional combination chemotherapy)
Malignant melanoma (metastatic)

Lomustine "medac" may also be of value as second-line treatment in Non-Hodgkin's lymphoma, myelomatosis, gastrointestinal tumours, carcinoma of the kidney, the testis, the ovary, the cervix uteri and the breast.

4.2 Posology and Method of Administration

Dosage

Adults:

Lomustine "medac" is given by mouth. The recommended dose in patients with normally functioning bone marrow receiving Lomustine "medac" as their only chemotherapy is 120-130 mg/m² as a single dose every six to eight weeks (or as a divided dose over 3 days, e.g. 40 mg/m²/day).

Dosage is reduced if:

- (i) Lomustine "medac" is being given as part of a drug regimen which includes other marrow-depressant drugs, and
- (ii) In the presence of leucopenia below 3,000/mm³ or thrombocytopenia below 75,000/mm³.

Marrow depression after Lomustine "medac" is sustained longer than after nitrogen mustards and recovery of white cell and platelet counts may not occur for six weeks or more. Blood elements depressed below the above levels should be allowed to recover to 4,000/mm³ (WBC) and 100,000/mm³ (platelets) before repeating Lomustine "medac" dosage.

Children:

Until further data is available, administration of Lomustine "medac" to children with malignancies other than brain tumours should be restricted to specialised centres and exceptional situations. Dosage in children, like that in adults, is based on body surface area (120 – 130 mg/m² every six to eight weeks, with the same qualifications as apply to adults).

Route of Administration:

Lomustine "medac" is given by mouth.

4.3 Contra-indications

Lomustine can cause birth defects. Men and women are recommended to take contraceptive precautions during therapy with lomustine and for 6 months after treatment. Men should be informed about the risk for an irreversible infertility due to treatment with lomustine.

Lomustine "medac" should not be administered to patients who are pregnant or to mothers who are breast feeding.

Other contraindications are:

- (i) Previous hypersensitivity to nitrosoureas;
- (ii) Previous failure of the tumor to respond to other nitrosoureas;
- (iii) Severe bone-marrow depression;
- (iv) Severe renal impairment;
- (v) Coeliac disease or wheat allergy.

4.4 Special Warnings and Precautions for Use

Patients receiving LOMUSTINE "MEDAC" chemotherapy should be under the care of doctors experienced in cancer treatment. Blood counts should be carried out before starting the drug and at frequent intervals (preferably weekly) during treatment. Treatment and dosage is governed principally by the haemoglobin, white cell count and platelet count. Liver and kidney function should also be assessed periodically.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

Lomustine "medac" use in combination with theophylline or with the H₂-receptor antagonist cimetidine may potentiate bone marrow toxicity. Cross resistance with other nitrosoureas is usual, but cross resistance with conventional alkylating agents is unusual.

Pre-treatment with phenobarbital can lead to a reduced antitumour effect of lomustine due to an accelerated elimination caused by induction of microsomal liver enzymes.

4.6 Pregnancy and Lactation

Lomustine is contraindicated in women who are pregnant and mothers who are breast feeding.

4.7 Effects on Ability to Drive and Use Machines

Lomustine "medac" capsules can impair the ability to drive and use machines, e.g. because of nausea and vomiting.

4.8 Undesirable Effects

Haematological

The principal adverse effect is marrow toxicity of a delayed or prolonged nature. Thrombocytopenia appears about four weeks after a dose of Lomustine "medac" and lasts one or two weeks at a level around 80-100,000/mm³. Leucopenia appears after six weeks and persists for one or two weeks at about 4 – 5,000/mm³.

The haematological toxicity may be cumulative, leading to successively lower white cell and platelet counts with successive doses of the drug.

Gastrointestinal

Nausea and vomiting usually occur four to six hours after a full single dose of Lomustine "medac" and last for 24-48 hours, followed by anorexia for two or three days. The effects are less troublesome if the 6 weekly dose is divided into three doses given on each of the first three days of the six week period. Gastrointestinal tolerance is usually good, however, if prophylactic antiemetics are given (e. g. metoclopramide or chlorpromazine). Disorders of liver function have been reported commonly. They are mild in most cases. In rare cases a cholestatic jaundice occurs. Transient elevation of liver enzymes (SGOT, SGPT, LDH or alkaline phosphatase) are occasionally observed.

More rarely patients are troubled by stomatitis and diarrhoea.

Neurologic system

Mild neurologic symptoms, like e.g. apathy, disorientation, confusion and stuttering can occur uncommonly in combination therapy with other antineoplastic drugs or radiation.

Pulmonary system

Interstitial pneumonia or lung fibrosis have been reported rarely.

Renal system

Renal failure has been reported in single cases after prolonged treatment with lomustine reaching a high cumulative total dose. Therefore it is recommended not to exceed a maximum cumulative total lomustine dose of 1000 mg/m².

Other Side Effects

Loss of scalp hair has been reported rarely.

In single cases an irreversible vision loss has been reported after a combined therapy of lomustine with radiation.

4.9 Overdose

Symptoms

Symptoms of overdosage with Lomustine "medac" will probably include bone-marrow toxicity, haematological toxicity, nausea and vomiting.

Emergency Procedures

Overdosage should be treated immediately by gastric lavage.

Antidote

There is no specific antidote to overdosage with Lomustine "medac". Treatment should be symptomatic and supportive. Appropriate blood product replacement should be given as clinically required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

The mode of action is believed to be partly as an alkylating agent and partly by inhibition of several steps in the synthesis of nucleic acid and inhibition of the repair of single strand breaks in DNA chains.

5.2 Pharmacokinetic Properties

Lomustine "medac" is readily absorbed from the intestinal tract. A maximum plasma concentration of 0.5-2 ng/ml is reached after 3 hours following an oral dose of 30-100 mg/m².

The plasma-disappearance of the chloroethyl-group follows by a single phased course with a half-life of 72 hours. The cyclohexyl-group disappears according to a twofold plasma-disappearance with half-lives of 4 hours ($t_{1/2\alpha}$) and 50 hours ($t_{1/2\beta}$). After oral application of radioactive marked lomustine the blood-brain-barrier is passed. Approximately 15 to 30 % of the measured radioactivity in the plasma can be detected in the cerebrospinal fluid.

Lomustine "medac" is rapidly metabolised and metabolites are excreted mainly via the kidneys. Lomustine "medac" cannot be detected in its active form in the urine at any time.

5.3 Pre-clinical Safety Data

None available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Capsule Contents:

Lactose
Wheat Starch
Talc
Magnesium Stearate

Capsule Shell:

Gelatin
Indigo carmine E132
Titanium Dioxide E171

6.2 Incompatibilities

None stated.

6.3 Shelf-Life

3 years as packaged for sale.

6.4 Special Precautions for Storage

Do not store above 25 °C.
Store in the original container protected from light and moisture.

6.5 Nature and Content of Container

Securitainers containing 20 capsules.

6.6 Instructions for Use, Handling and Disposal

None.

ADMINISTRATIVE DATA

7. MARKETING AUTHORIZATION HOLDER

medac - Gesellschaft fuer klinische Spezialpraeparate mbH
Fehlandtstraße 3
20354 Hamburg, Germany

8. MARKETING AUTHORISATION NUMBER

PL 11587/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/08/2006

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25/08/2006