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

Posology

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 Lomustine "medac" is given as part of a drug regimen which includes other marrow-depressant medicinal products.
- 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.

Paediatric population
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).

Method of administration
Lomustine "medac" is given by mouth.

4.3 Contraindications

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 (see section 4.6).

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

Other contraindications are:

- Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1;
- Previous hypersensitivity to nitrosoureas;
- Previous failure of the tumour to respond to other nitrosoureas;
- Severe bone marrow depression;
- Severe renal impairment;
- Coeliac disease or wheat allergy;
- Concomitant use of yellow fever vaccine or other live vaccines is contraindicated in immunosuppressed patients (see section 4.5).

4.4 Special warnings and precautions for use

Patients receiving Lomustine "medac" chemotherapy should be under the care of doctors experienced in cancer treatment. Delayed bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and overwhelming infections in an already compromised patient, is the most common and severe of the toxic effects of lomustine.
Therefore, blood counts should be carried out before starting the medicinal product and at frequent intervals (preferably weekly for at least 6 weeks after a dose; see section 4.8) 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.

Patients must be strictly instructed not to use higher doses of lomustine than recommended by a physician and should be told that lomustine is taken as a single oral dose and will not be repeated for at least 6 weeks.

The bone marrow toxicity of lomustine is cumulative and therefore dose adjustments must be considered on the basis of nadir blood counts from prior dose.

Caution should be used in administering lomustine to patients with decreased circulating platelets, leukocytes, or erythrocytes.

Pulmonary toxicity from lomustine appears to be dose-related (see section 4.8). Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline below 70 % of the

predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLco) are particularly at risk.

Since lomustine may cause liver dysfunction, it is recommended that liver function tests be monitored periodically (see section 4.8).

Renal function tests should also be monitored periodically (see section 4.8).

Long term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies.

Care must be taken whenever handling anticancer products. Steps should be taken to avoid exposure. This includes appropriate equipment, such as wearing gloves, and washing hands with soap and water after handling such products.

Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucosegalactose malabsorption should not take this medicine.

This medicinal product contains less than 1 mmol sodium (23 mg) per hard capsule, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Lomustine "medac" use in combination with theophylline or with the H_2 receptor antagonist cimetidine may potentiate bone marrow toxicity. Cross-resistance with other nitrosoureas is usual, but cross-resistance with conventional alkylating agents is unusual.
Pretreatment with phenobarbital can lead to a reduced antitumour effect of lomustine due to an accelerated elimination caused by induction of microsomal liver enzymes.

There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients (see section 4.3)

Co-administration of antiepileptic medicinal products and chemotherapeutic medicinal products including lomustine can lead to complications secondary to pharmacokinetic interaction between the medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
Lomustine "medac" is contraindicated during pregnancy (see section 4.3). Safe use in pregnancy has not been established. Animal studies have shown reproductive toxicity (see section 5.3). If this medicinal product is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this medicinal product, the patient should be apprised of the potential hazard to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Breastfeeding
Lomustine "medac" is contraindicated during breastfeeding (see section 4.3). Due to the lipophilic nature of lomustine, it is likely to be excreted in human milk. As a risk to the nursing child potentially exists, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from Lomustine "medac" therapy taking into account the benefit of breastfeeding for the child and the benefit of therapy for the woman.

Fertility
Lomustine can have a mutagenic effect. Men treated with lomustine are therefore advised not to father children during treatment and for up to 6 months afterwards, and

to seek advice regarding sperm conservation before the start of treatment given the possibility of irreversible infertility caused by lomustine therapy.

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.

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

4.8 Undesirable Effects

The list is presented by system organ class and frequency

- 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).

System Organ Class	Frequency	MedDRA Term
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	Acute leukaemia, myelodysplastic syndrome
Blood and lymphatic system disorders	Very common	Leukopenia
	Not known	Bone marrow failure, thrombocytopenia, anaemia
Nervous system disorders	Not known	Coordination abnormal, disorientation, lethargy, dysarthria
Respiratory, thoracic and mediastinal disorders	Not known	Pulmonary fibrosis, lung infiltration
Gastrointestinal disorders	Not known	Nausea, vomiting, stomatitis
Hepatobiliary disorders	Not known	Transaminases increased, blood bilirubin increased
Skin and subcutaneous tissue disorders	Not known	Alopecia
Renal and urinary disorders	Not known	Renal failure, azotaemia, renal atrophy, renal injury
Investigations	Not known	Blood alkaline phosphatase increased

Blood and lymphatic system disorders
The principal adverse effect is marrow toxicity of a delayed or prolonged nature. It usually occurs four to six weeks after administration of the medicinal product and is dose-related. 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 five to 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 medicinal product. Approximately 65 % of patients receiving 130 mg/m² develop white blood cell counts below 5,000 WBC/mm³. Thirty-six percent developed white blood cell counts below

3,000/mm³. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

The occurrence of acute leukaemia and bone marrow dysplasia have been reported in patients following long-term nitrosourea therapy.

Anaemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

Gastrointestinal disorders
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.

Nervous system disorders
Mild neurological symptoms, like e.g. apathy, disorientation, confusion and stuttering can occur uncommonly in combination therapy with other antineoplastic medicinal products or radiation.

Respiratory, thoracic and mediastinal disorders
Interstitial pneumonia or lung fibrosis have been reported rarely.

Renal and urinary disorders
Renal failure, decrease in kidney size, and progressive azotaemia have been reported in single cases after prolonged treatment with lomustine and related nitrosoureas reaching a high cumulative total dose. Therefore it is recommended not to exceed a maximum cumulative total lomustine dose of 1,000 mg/m².
Kidney damage has also been reported occasionally in patients receiving lower total doses.

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms
Accidental overdose with lomustine has been reported, including fatal cases. Symptoms of overdose with Lomustine "medac" will probably include bone marrow toxicity, haematological toxicity, abdominal pain, nausea and vomiting, diarrhoea, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

Emergency procedures
Overdose should be treated immediately by gastric lavage.

Antidote
There is no specific antidote to overdose 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

Pharmacotherapeutic group: cytostatics, alkylating agents, ATC code: L01A D02

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 ($t_{½\ \alpha}$) and 50 hours ($t_{½\ \beta}$). 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 Preclinical safety data

Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents:
Lactose
Wheat Starch
Talc
Magnesium Stearate

Capsule shell:
Gelatine
Indigo carmine E132
Titanium Dioxide E171

6.2 Incompatibilities

Not applicable.

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 in order to protect from light and moisture.

6.5 Nature and contents of container

Securitainers containing 20 capsules.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

8. MARKETING AUTHORISATION NUMBER

PL 11587/0003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 August 2006

10. DATE OF REVISION OF THE TEXT

04/2020