SUMMARY OF PRODUCT CHARACTERISTICS

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
The capsules are blue with “medac” in white ink on the cap and with “LOM 40” in white ink on the body.

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. The capsules should not be opened and should be swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance, to other nitrosoureas or to any of the excipients listed in section 6.1,
- Previous failure of the tumour to respond to other nitrosoureas,
- Severe bone marrow depression,
- Severe renal impairment,
- Pregnancy, breast-feeding,
- Wheat allergy,
- Concomitant use of yellow fever vaccine or other live vaccines in immunosuppressed patients (see section 4.5).

4.4 Special warnings and precautions for use

Patients receiving lomustine chemotherapy should be under the care of physicians experienced in cancer treatment. Blood counts should be monitored before starting the treatment and at frequent intervals during treatment (preferably weekly for at least 6 weeks after a dose; see section 4.8). 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. Treatment and dosage are governed principally by the haemoglobin, white cell count and platelet count.

At the recommended dose, courses of lomustine must not be given more frequently than every 6 weeks.

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 (or as a divided dose over three days) and will not be repeated for at least 6 weeks (see section 4.2).

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

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 should be monitored periodically (see section 4.8).

Renal function tests should also be assessed periodically. The maximum cumulative dose should not exceed 1,000 mg/m² (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 the use of appropriate equipment, such as wearing gloves, and washing hands with soap and water after handling such products.

It is recommended that patients do not receive live vaccines until at least 3 months after the end of treatment with lomustine.

Excipients

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

Wheat starch
This medicine contains only very low levels of gluten (from wheat starch). It is regarded as ‘gluten-free’ and is very unlikely to cause problems in patients with coeliac disease. One capsule contains no more than 4 micrograms of gluten. Patients with wheat allergy must not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Lomustine use in combination with theophylline or with the H_2-receptor antagonist cimetidine may potentiate bone marrow toxicity.

Co-administration of antiepileptic and chemotherapeutic medicinal products including lomustine can lead to complications secondary to pharmacokinetic interactions between the medicinal products. For example, pre-treatment with phenobarbital can lead to a reduced antitumour effect of lomustine due to an accelerated elimination of lomustine caused by microsomal liver enzyme induction.

Concomitant treatment with other cytostatics or radiation therapy can increase the bone marrow depression of lomustine.

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).

Cross-resistance with other nitrosoureas is common while cross-resistance with conventional alkylating substances is uncommon.

4.6 Fertility, pregnancy and lactation

Contraception in men and women

Due to the genotoxic potential of lomustine (see section 5.3), women of childbearing potential should use effective contraceptive measures while being treated with lomustine and for 7 months following completion of treatment.

Men are recommended to use effective contraceptive measures and to not father a child while receiving lomustine and for 4 months following completion of treatment.

Pregnancy

Lomustine 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 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.

Breast-feeding

Lomustine is contraindicated during breast-feeding (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 should be made whether to discontinue breast-feeding or to discontinue lomustine therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the mother.

Fertility

Lomustine can have a mutagenic effect. Genetic consultation is recommended if a patient intends to have children after therapy with lomustine. Men treated with lomustine are therefore advised not to father children during treatment and for 4 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 can impair the ability to drive and use machines, e.g. because of nausea and vomiting.

4.8 Undesirable effects

Summary of the safety profile
Bone marrow toxicity and gastrointestinal symptoms are the most frequent and relevant undesirable effects of lomustine.

Tabulated list of adverse reactions
The list is presented by system organ class and frequency, using the following categories:

- 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
Infections and infestations	Common	Infection
	Not known	Herpes zoster
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Very rare	Second primary malignancy, acute leukaemia, myelodysplastic syndrome
Blood and lymphatic system disorders	Very common	Myelosuppression, pancytopenia, thrombocytopenia, leukopenia, neutropenia, anaemia
Immune system disorders	Common	Immunosuppression
Nervous system disorders	Common	Coordination abnormal, disorientation, lethargy, dysarthria, ataxia
	Uncommon	Apathy, confusional state, dysphemia
Eye disorders	Very rare	After combined therapy with radiation: blindness
Respiratory, thoracic and mediastinal disorders		
	Rare	Interstitial lung disease,

System Organ Class	Frequency	MedDRA Term
		pulmonary fibrosis, dyspnoea, cough
	Not known	Lung infiltration
Gastrointestinal disorders	Very common	Nausea, vomiting, decreased appetite
	Common	Stomatitis, diarrhoea
Hepatobiliary disorders	Common	Hepatic function abnormal
	Rare	Jaundice cholestatic, hepatic failure
Skin and subcutaneous tissue disorders	Rare	Alopecia, rash, pruritus
Renal and urinary disorders	Uncommon	Renal failure, renal injury
	Not known	Azotaemia, renal atrophy
Reproductive system and breast disorders	Rare	Spermatogenesis abnormal, ovulation disorder
General disorders and administration site conditions	Common	Pyrexia, chills, swelling (especially feet and lower legs)
Investigations	Common	Hepatic enzymes increased (ASAT, ALAT, LDH and alkaline phosphatase)
	Not known	Blood bilirubin increased

Description of selected adverse reactions

Blood and lymphatic system disorders

The most frequent and most serious toxicity of lomustine is delayed or prolonged myelosuppression. It usually occurs 4 to 6 weeks after administration of the medicinal product and is dose related. Thrombocytopenia occurs at about 4 weeks post-administration and lasts 1 or 2 weeks at a level around 80 - 100,000/mm³. Leukopenia occurs 5 to 6 weeks after a dose of lomustine and persists for 1 to 2 weeks. Approximately 65 % of patients receiving 130 mg/m² develop white blood cell counts below 5,000 WBC/mm³. Thirty-six percent develop white blood cell counts below 3,000/mm³.

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

Lomustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.

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

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

Respiratory, thoracic and mediastinal disorders

Pulmonary toxicity characterised by pulmonary infiltrates, interstitial pneumonia and/or fibrosis has been rarely reported with lomustine. Onset of toxicity has occurred after an interval of 6 months or longer from the start of therapy with cumulative doses of lomustine usually greater than 1,100 mg/m². There is one report of pulmonary toxicity at a cumulative dose of only 600 mg/m².

Delayed pulmonary fibrosis occurring up to 17 years after treatment has been reported in patients with intracranial tumours who received related nitrosoureas during their childhood and early adolescence.

Gastrointestinal disorders

Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually last for less than 24 hours, followed by anorexia for 2 to 3 days. The effects are less troublesome if the 6-weekly dose is divided into three doses and given on the first 3 days of each 6-week period. The frequency and duration may be reduced by the use of antiemetics prior to dosing and by the administration of lomustine to fasting patients.

Hepatobiliary disorders

A reversible type of hepatic toxicity, manifested by increased transaminase, alkaline phosphatase, and bilirubin levels, has been reported in a small percentage of patients receiving lomustine.

An effect on liver function manifested by transient elevation of liver enzymes (ASAT, ALAT, LDH and alkaline phosphatase) is commonly observed. In the majority of cases, this is mild. Cholestatic jaundice has been reported in rare cases.

Renal and urinary disorders

Renal abnormalities consisting of decrease in kidney size, progressive azotaemia, and renal failure have been reported in patients who receive large cumulative doses after prolonged therapy with lomustine and related nitrosoureas. The cumulative dose in these cases was higher than 1,500 mg/m². Kidney damage has also been reported occasionally in patients receiving lower total doses.

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

Overdose with lomustine has been reported, including fatal cases.

Symptoms

Overdose can lead to increases in side effects. It has been associated with bone marrow suppression, abdominal pain, diarrhoea, nausea, vomiting, anorexia,

lethargy, dizziness, abnormal hepatic function, cough and shortness of breath. In very severe cases, multiple organ failure may occur.

Emergency procedures

Overdose should be treated immediately by gastric lavage.

Antidote

There is no specific antidote for overdose with lomustine. In case of overdose, appropriate supportive measures should be taken e.g., infection prophylaxis. 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) and 50 hours (t ½). 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

Printing ink:
Shellac
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(S)

PL 11587/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 August 2006

10 DATE OF REVISION OF THE TEXT

24/04/2026