SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Lomustine medac 40 mg hard capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One capsule contains lomustine 40 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Hard capsules

The capsules are blue.

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)
- Small cell lung cancer
- Hodgkin's disease (resistant to conventional combination chemotherapy)
- Malignant melanoma (metastatic)
- Non-Hodgkin lymphoma

4.2 Posology and method of administration

Posology

Adults
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 6 to 8 weeks (or as a divided dose over 3 days, e.g. 40 mg/m²/day). The dose must not exceed 130 mg/m².

In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks.

Dosage is reduced
- if Lomustine medac is being given as part of a medication regimen which depresses the bone marrow function.
- in the presence of leucopenia below 3,000/mm³ or thrombocytopenia below 75,000/mm³.

Doses subsequent to the initial dose should be adjusted according to the haematological response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment.

Nadir after prior dose		Percentage of prior dose to be given
Leukocytes (/mm³)	**Platelets (/mm³)**	
≥4,000	≥100,000	100%
3,000–3,999	75,000–99,999	100%
2,000–2,999	24,000–74,999	70%
<2,000	<25,000	50%

Marrow depression after Lomustine medac is sustained longer than after nitrogen mustards and recovery of white cell and platelet counts may not occur for 6 weeks or more. Blood elements should be allowed to recover to 4,000/mm³ (white blood cells) and 100,000/mm³ (platelets) before repeating Lomustine medac dosage. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the haematological toxicity is delayed and cumulative.

The maximum cumulative dose of 1,000 mg/m² may not be exceeded due to the potential risk of lung fibrosis.

Paediatric population
The posology is the same in adults and children.

Renal impairment
Safety and efficacy of lomustine in patients with impaired renal function has not been established. Renal function tests should be monitored periodically (see sections 4.4 and 4.8).

Hepatic impairment
Safety and efficacy of lomustine in patients with impaired hepatic function has not been established. Liver function tests should be monitored periodically (see sections 4.4 and 4.8).

Method of administration
Lomustine medac is given orally. The capsules should preferably be taken at bedtime or 3 hours after meals.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Patients receiving Lomustine medac chemotherapy should be under the care of physicians experienced in cancer treatment. Blood counts should be carried out before starting the treatment and at frequent intervals during treatment (preferably weekly for at least 6 weeks after a dose; see section 4.8). At the recommended dosage, courses of lomustine should not be given more frequently than every 6 weeks.

Delayed bone marrow suppression, notably thrombocytopenia and leukopenia, which may contribute to bleeding and severe infections in an already compromised patient, is the most common and severe of the toxic effects of lomustine. Treatment and dosage is governed principally by the haemoglobin, white cell count and platelet count.

The haematological toxicity may be cumulative, leading to gradually lower white cell and platelet counts with repeated doses of the medicinal product. Therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see section 4.2) and caution should be used in administering lomustine to patients with decreased circulating platelets, leukocytes, or erythrocytes.

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).

Since lomustine may cause liver dysfunction, it is recommended that liver function should be assessed periodically (see section 4.8). Renal function tests should also be monitored periodically (see section 4.8), as renal insufficiency has been reported in isolated cases after long-term treatment with lomustine and high cumulative doses. The maximum cumulative dose should therefore not exceed 1,000 mg/m².

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.

Long term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies (e.g. secondary leukaemia) in treated patients.

Female and male patients of child-bearing age should use contraceptive precautions under treatment and at least 6 months after the end of therapy. Men should be informed of the risk of irreversible infertility associated with lomustine therapy (see section 4.6).

Patients with one of the following rare hereditary conditions should not use this medicine: galactose intolerance, total lactase deficiency or glucose-galactose malabsorption.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

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).

If theophylline or H²–antihistamine cimetidin are given together with Lomustine medac, increased bone marrow depression has been observed in rare cases.

Co-administration of antiepileptic and cytostatic medicinal products including lomustine can lead to complications secondary to pharmacokinetic interactions between the medicinal products. For example, pre-treatment with phenobarbital can cause a reduction of antitumour activity due to accelerated elimination of Lomustine medac caused by microsomal liver enzyme induction. Concomitant treatment with other cytostatics can increase the bone marrow depression of Lomustine medac.

4.6 Fertility, pregnancy and lactation

Pregnancy
Lomustine medac is contraindicated during pregnancy (see section 4.3). Safe use of lomustine during pregnancy has not been established. Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. If this medicinal product is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this medicinal product, the patient should be advised of the risks for the foetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Breast-feeding
Lomustine medac 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. There is a potential risk to the nursing child. A decision should be made whether to stop breast-feeding or to stop 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. 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, but Lomustine medac can impair the ability to drive and use machines, for instance 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)	Very rare	Secondary malignancies
	Not known	Acute leukaemia, myelodysplastic syndrome
Blood and lymphatic system disorders	Very common	Bone marrow depression, like thrombocytopenia, leukopenia, neutropenia, anaemia
Nervous system disorders	Uncommon	In combination therapy: Apathy, disorientation, confusion, stuttering
	Not known	Coordination abnormal, lethargy, dysarthria

Eye disorders	Very rare	After combined therapy with radiation: irreversible vision loss
Respiratory, thoracic and mediastinal disorders	Rare	Lung fibrosis, interstitial pneumonia
	Not known	Lung infiltration
Gastrointestinal disorders	Very common	Nausea, vomiting, anorexia
	Common	Stomatitis, diarrhoea
Hepatobiliary disorders	Common	Disorders of liver function (mostly mild), transient elevation of liver enzymes (ASAT, ALAT, LDH and alkaline phosphatase)
	Rare	Cholestatic jaundice
Skin and subcutaneous tissue disorders	Very rare	Alopecia
Renal and urinary disorders	Very rare	Renal failure
	Not known	Azotaemia, renal atrophy, renal injury
Investigations	Not known	Blood bilirubin increased

Blood and lymphatic system disorders
The most frequent and most serious toxicity of lomustine is delayed myelosuppression, consisting of thrombocytopenia, leukopenia with neutropenia, and anaemia. It usually occurs 4 to 6 weeks after administration of the medicinal product and is dose related. Frequency numbers between 15–54% exist in dependence of the combination regimen. The marrow toxicity is often of a prolonged nature. Thrombocytopenia appears about 4 weeks after a dose of Lomustine medac and lasts 1 or 2 weeks at a level around 80,000–100,000/mm³. Leukopenia appears after 5 to 6 weeks and lasts for 1 or 2 weeks.

Approximately 65% of patients receiving 130 mg/m² develop white blood 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.
Lomustine may produce cumulative myelosuppression, manifested by more depressed indices or longer duration of suppression after repeated doses.
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.

Respiratory, thoracic and mediastinal disorders
Pulmonary toxicity characterised by pulmonary infiltrates and/or fibrosis have 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.
Delayed onset 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
Gastrointestinal side effects occur with varying frequency (3–71%). Nausea and vomiting usually occur 3 to 6 hours after a full single dose of Lomustine medac and last less than 24 hours, followed by anorexia for 2 to 3 days. The effects are less troublesome if the six-weekly dose is divided into 3 doses and given on the first 3 days of each six-week period. Gastrointestinal tolerance is usually good if antiemetics (e.g. metoclopramide or chlorpromazine) are given prior to dosing and by the administration of lomustine to fasting patients. An effect on liver function is common (see general comment). In the majority of cases, this is mild. Cholestatic hepatitis has been reported in rare cases. Transient elevation of liver enzymes (ASAT, ALAT, LDH and alkaline phosphatase) is commonly observed.
Commonly patients develop stomatitis or diarrhoea.

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.

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. 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 national reporting system listed in Appendix V.

4.9 Overdose

Accidental overdose with lomustine has been reported, including fatal cases.

Symptoms
In case of accidental overdose bone marrow toxicity, abdominal pain, diarrhoea, nausea and vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath may occur.

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: antineoplastic agents, alkylating agents, nitrosoureas, ATC code: L01AD02

The mechanism of action is partly as an alkylating agent and partly by inhibition of several steps in the synthesis of nucleic acid as well as inhibition of the repair of strand breaks in DNA chains.
Cross-resistance with other nitrosoureas is usual, but cross-resistance with conventional alkylating agents is less usual.

5.2 Pharmacokinetic properties

The pharmacokinetics of lomustine are incompletely characterised.

Lomustine is rapidly absorbed from the gastrointestinal tract and undergoes complete “first pass” metabolism to monohydroxylated metabolites, namely trans-4-hydroxy-CCNU and cis-4-hydroxy-CCNU. Peak plasma concentrations are reached 3–4 hours after oral dosing. These metabolites show alkylating activity and are mainly eliminated by renal clearance with a plasma half-life of around 2 hours, showing large inter-individual variability. Highly reactive isocyanates are also formed, but their role for the pharmacological activity remains unclear.
After administration of radiolabelled lomustine, peak concentrations of the labelled products are reached about 3 hours after an oral dose of 30–100 mg/m². The radiolabelled products cross the blood-brain barrier after oral administration. Approximately 15 to 30 % of the radioactivity measured in the plasma can be detected in the cerebrospinal fluid.

5.3 Preclinical safety data

None available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule contents
Lactose, anhydrous
Wheat starch
Talc
Magnesium stearate

Capsule shell
Gelatin
Titanium dioxide E171
Indigo carmine E 132

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

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

6.5 Nature and contents of container

Plastic security containers containing 5°capsules.
Plastic security containers containing 20 capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

01/2024