

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 (/mm ³)	Platelets (/mm ³)	
≥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 not be opened and should be swallowed whole. The capsules should preferably be taken at bedtime or 3 hours after meals.

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 dosage, 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 (see dose adjustment table under section 4.2).

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 H₂-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 an 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).

4.6 Fertility, pregnancy and lactation

Contraception in men and women

Due to the genotoxic potential of lomustine, 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 medac is contraindicated during pregnancy (see section 4.3). Safe use of lomustine during 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 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. 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 up to 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 medac 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 ($\geq 1/10$)
- Common ($\geq 1/100$ to $< 1/10$)
- Uncommon ($\geq 1/1,000$ to $< 1/100$)
- Rare ($\geq 1/10,000$ to $< 1/1,000$)
- Very rare ($< 1/10,000$)
- Not known (cannot be estimated from the available data).

System Organ Class	Frequency	MedDRA Term
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Infections and infestations	Common	Infection, including opportunistic infection (e.g. herpes zoster)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Very rare	Secondary malignancies including acute leukaemia and myelodysplastic syndrome
Blood and lymphatic system disorders	Very common	Myelosuppression, pancytopenia, thrombocytopenia, leukopenia, neutropenia, anaemia
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, pulmonary fibrosis
	Not known	Lung infiltration
Gastrointestinal disorders	Very common	Nausea, vomiting, decreased appetite
	Common	Stomatitis, diarrhoea
Hepatobiliary disorders	Common	Hepatic function abnormal
	Rare	Jaundice cholestatic
Skin and subcutaneous tissue disorders	Rare	Alopecia
Renal and urinary disorders	Uncommon	Renal failure, renal injury
	Not known	Azotaemia, renal atrophy
Reproductive system and breast disorders	Rare	Spermatogenesis abnormal, ovulation disorder
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 80,000–100,000/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 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 decreased appetite for 2 to 3 days. The effects are less troublesome if the 6-weekly dose is divided into 3 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. Therefore, it is recommended not to exceed a maximum cumulative total lomustine dose of 1,000 mg/m².

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

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, decreased appetite, lethargy, dizziness, abnormal hepatic function, cough, shortness of breath, and neurological disorders. 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: 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 oral administration of radiolabelled lomustine, no unchanged lomustine was detected. Peak concentrations of the labelled degradation products are reached about 3 hours after an oral dose of 30–100 mg/m². A metabolite containing the chloroethyl-group had a half-life of 72 hours, whereas a metabolite containing the cyclohexyl-group had a terminal half-life of 50 hours. 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

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, 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

2025-03-14