SISTEMA SANITARIO REGIONALE
AZIENDA OSPEDALIERA
SAN CAMILLO FORLANINI

REGIONE LAZIO

**DELIBERAZIONE N.** 1404 **DEL** 07 OTT. 2021

Struttura proponente: AREA GOVERNO DELLE RISORSE STRUMENTALI– U.O.C. ACQUISIZIONE BENI E SERVIZI

Codice settore proponente: **BSDG 366 del 01/10/2021**

Centro di Costo: A0RZ21JC1S

Oggetto: Acquisto all'estero del principio attivo Lomustina compresse 40 mg. privo di A.I.C., non in commercio in Italia, indispensabile alle esigenze di un paziente in cura presso l'Azienda Ospedaliera San Camillo- Forlanini.

L'estensore
D.ssa M. Tantarli

**IL DIRETTORE GENERALE f.f.**
**(D.ssa Francesca Milito)**

***Parere del Direttore Amministrativo:*** **D.ssa Francesca Milito**

☒ FAVOREVOLE ☐ NON FAVOREVOLE (*con motivazioni allegate al presente atto*)

*Firma* _____ *Data* 6/10/2021

***Parere del Direttore Sanitario:*** **D.ssa Daniela Orazi**

☒ FAVOREVOLE ☐ NON FAVOREVOLE (*con motivazioni allegate al presente atto*)

*Firma* _____ *Data* 06.10.2021

Il Dirigente addetto al controllo del budget, con la sottoscrizione del presente atto, attesta che lo stesso non comporta scostamenti sfavorevoli rispetto al budget economico/investimenti generale aziendale.

Voce del conto Economico/Patrimoniale su cui si imputa l'importo: Vedere "Allegato Assunzione Autorizzazione"

Visto del Dirigente addetto al controllo del budget economico aziendale:
Direttore U.O.C. Programmazione e Controllo di Gestione - **D.ssa Miriam Piccini**

Firma _____ Data 05/10/21 2021 2022

*Il Dirigente e/o il Responsabile del procedimento con la sottoscrizione del presente atto, a seguito dell'istruttoria effettuata, attestano che l'atto è legittimo nella forma e nella sostanza.*

Responsabile del Procedimento: **Dott. Paolo Farfusola**

Firma _____ Data 01.10.2021

Il Dirigente: **Dott. Paolo Farfusola**

Firma _____ Data 01.10.2021

**IL DIRETTORE U.O.C. ACQUISIZIONE BENI E SERVIZI**

**VISTI**

il D. Leg.vo n. 502 del 30/12/92 e successive modifiche ed integrazioni, recante norme sul "Riordino della disciplina in materia sanitaria, a norma dell'art.1 della L. n. 421 del 23/10/92";

la L.R. n. 18 del 16/06/94 e successive modifiche ed integrazioni recante "Disposizioni per il riordino del Servizio Sanitario Regionale ai sensi del D. Leg.vo n. 502/92 e successive modifiche ed integrazioni – Istituzione delle Aziende Unità Sanitarie Locali e delle Aziende Ospedaliere";

la L.R. n. 45 del 31/10/96 recante "Norme sulla gestione contabile e patrimoniale delle Aziende Unità Sanitarie Locali e delle Aziende Ospedaliere";

la L. n. 178 del 30/12/2020: Legge di stabilità dello Stato per l'anno finanziario 2021;

la L.R. n. 25 del 30/12/2020: Legge di stabilità regionale 2021;

la L.R. n. 26 del 30/12/2020: Bilancio di previsione finanziario della Regione Lazio 2021-2023;

il D. Leg.vo n. 50 del 18/04/2016: Attuazione delle direttive 2014/23/UE, 2014/24/UE e 2014/25/UE sull'aggiudicazione dei contratti di concessione, sugli appalti pubblici e sulle procedure d'appalto degli enti erogatori nei settori dell'acqua, dell'energia, dei trasporti e dei servizi postali, nonché per il riordino della disciplina vigente in materia di contratti pubblici relativi a lavori, servizi e forniture;

il D. Leg.vo n. 56 del 19/04/2017: Disposizioni integrative e correttive al decreto legislativo 18 Aprile 2016, n. 50;

**PREMESSO**

- che la Regione Lazio, nelle diverse gare centralizzate effettuate per l'approvvigionamento di medicinali, non ha aggiudicato i farmaci acquisibili solo sul mercato estero e che l'Azienda Ospedaliera non può interrompere la somministrazione di tali farmaci ai pazienti in terapia o da trattare in urgenza per non incorrere in interruzione di pubblico servizio;

- che, con note documento n.192986/2021 del 23/09/2021 e n.193315/2021 pari data a integrazione, il Direttore della Farmacia aziendale ha trasmesso la richiesta di acquisto all'estero del principio attivo Lomustina compresse 40 mg., privo di A.I.C., non in commercio in Italia e pertanto acquisibile solo all'estero, indicandone le quantità e le Ditte importatrici Farmaceutica Internazionale Italiana, Profarma Italia, Unipharma, Ottopharma e Interfarmaci, per le necessità di un paziente in cura presso la U.O.C. Oncologia aziendale (all. 1);

- che è stato richiesto l'invio di offerta economica alle Ditte autorizzate citate nella nota di Farmacia, che hanno risposto le Ditte Farmaceutica Internazionale Italiana, Ottopharma, Profarma Italia e Unipharma e che il miglior prezzo per il suddetto principio attivo risulta essere quello proposto dalla Ditta Ottopharma ad € 12,65 a confezione da 10 compresse da 40 mg. +

€ 15,00 per spese di trasporto e con importazione e sdoganamento gratuiti (all. 2);

**RITENUTO** - opportuno, ai sensi dell'art. 36, co. 2, lett. a), del D. Leg.vo n. 50/16 e s.m.i., procedere all'approvvigionamento di detto principio attivo, presso la Ditta autorizzata Ottopharma, nella quantità di n. 500 compresse (CIG Z8633460D);

- necessario nominare Direttore dell'Esecuzione del Contratto il Direttore della U.O.C. Farmacia aziendale, D.ssa Cinzia Monaco;

**RILEVATO** che la spesa complessiva corrispondente ad € 662,50 + Iva 10%, pari ad € 728,75 compresa Iva, è da imputare sui conti economici nn. 501010113000 e 502020107000 del piano dei conti di contabilità economico patrimoniale, anni 2021 e 2022, Centro di Costo SOFA01F04S, nella seguente maniera:
Anno 2021
Conto Economico 501010113000 € 180,89 aut. 1
Conto Economico 502020107000 € 16,50 aut.1
Anno 2022
Conto Economico 501010113000 € 514,86
Conto Economico 502020107000 € 16,50

**TENUTO CONTO** che, ai sensi dell'art. 29 del D.Leg.vo n. 50/2016 e s.m.i., verrà pubblicato sull'apposito sito aziendale l'avviso per la trasparenza;

**ATTESTATO** che il presente provvedimento, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo, ai sensi e per gli effetti di quanto disposto dall'art. 1 della Legge 20/94 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, co. 1, della Legge 241/90, come modificato dalla Legge 15/2005;

**PROPONE**

- di acquistare sul mercato estero, ai sensi dell'art. 36, co. 2, lett. a), del D. Leg.vo n. 50/16 e s.m.i., n. 500 compresse de principio attivo privo di A.I.C. Lomustina compresse 40 mg., presso la Ditta Ottopharma ad € 12,65 a confezione da 10 compresse + € 15,00 per spese di trasporto e con importazione e sdoganamento gratuiti, per le necessità di un paziente in cura presso l'Azienda Ospedaliera San Camillo Forlanini (CIG Z8633460D);

- di contabilizzare la spesa complessiva corrispondente ad € 662,50 + Iva 10%, pari ad € 728,75 compresa Iva, è da imputare sui conti economici nn. 501010113000 e 502020107000 del piano dei conti di contabilità economico patrimoniale, anni 2021 e 2022, Centro di Costo SOFA01F04S, nella seguente maniera:
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Conto Economico 502020107000 € 16,50 aut.1
Anno 2022
Conto Economico 501010113000 € 514,86
Conto Economico 502020107000 € 16,50

- di nominare la D.ssa Cinzia Monaco, Direttore della U.O.C. Farmacia aziendale quale Direttore dell'Esecuzione del Contratto;

- di pubblicare sull'apposito sito aziendale, ai sensi dell'art. 29 del D.Leg.vo n. 50/2016 e s.m.i., l'avviso per la trasparenza;

- di corrispondere il dovuto alla Ditta fornitrice nei limiti del suddetto importo, ad avvenuta esecuzione della fornitura regolarmente effettuata, previa presentazione di appositi documenti contabili conformi alla vigente normativa fiscale.

**IL DIRETTORE U.O.C. ACQUISIZIONE BENI E SERVIZI**
**(DOTT. PAOLO FARFUSOLA)**

## IL DIRETTORE GENERALE f.f.

**VISTE** le deliberazioni della Giunta Regionale Lazio n. 5163 del 30/06/1994 e n. 2041 del 14/03/1996;

**VISTI** l'art. 3 del D.Leg.vo n. 502/92 e successive modificazioni ed integrazioni, nonché l'art. 9 della L.R. n. 18/94;

**VISTA** la nota prot. n. 36573 del 15 gennaio 2021 della Direzione Regionale Salute e Integrazione Sociosanitaria con cui ha espresso parere favorevole all'affidamento dell'incarico di Direttore Generale f.f. dell'Azienda Ospedaliera San Camillo Forlanini al Direttore Amministrativo D.ssa Francesca Milito;

**VISTA** la deliberazione n. 97 del 15 gennaio 2021;

**LETTA** la proposta di deliberazione: "Acquisto all'estero del principio attivo Lomustina compresse 40 mg. privo di A.I.C., non in commercio in Italia, indispensabile alle esigenze di un paziente in cura presso l'Azienda Ospedaliera San Camillo- Forlanini" presentata dal Direttore U.O.C. Acquisizione Beni e Servizi;

**PRESO ATTO** che il Dirigente proponente il presente provvedimento, sottoscrivendolo, attesta che lo stesso, a seguito dell'istruttoria effettuata, nella forma e nella sostanza è totalmente legittimo, ai sensi dell'art. 1 della Legge 20/1994 e successive modifiche, nonché alla stregua dei criteri di economicità e di efficacia di cui all'art. 1, primo comma, della Legge 241/90, come modificato dalla Legge 15/2005;

**VISTI** i pareri favorevoli del Direttore Amministrativo e del Direttore Sanitario;

## DELIBERA

di adottare la proposta di deliberazione di cui sopra e, conseguentemente:

- di acquistare sul mercato estero, ai sensi dell'art. 36, co. 2, lett. a), del D. Leg.vo n. 50/16 e s.m.i., n. 500 compresse de principio attivo privo di A.I.C. Lomustina compresse 40 mg., presso la Ditta Ottopharma ad € 12,65 a confezione da 10 compresse + € 15,00 per spese di trasporto e con importazione e sdoganamento gratuiti, per le necessità di un paziente in cura presso l'Azienda Ospedaliera San Camillo Forlanini (CIG Z8633460D);

- di contabilizzare la spesa complessiva corrispondente ad € 662,50 + Iva 10%, pari ad € 728,75 compresa Iva, è da imputare sui conti economici nn. 501010113000 e 502020107000 del piano dei conti di contabilità economico patrimoniale, anni 2021 e 2022, Centro di Costo SOFA01F04S, nella seguente maniera:

Anno 2021
Conto Economico 501010113000 € 180,89 aut. 1
Conto Economico 502020107000 € 16,50 aut.1

Anno 2022
Conto Economico 501010113000 € 514,86
Conto Economico 502020107000 € 16,50

- di nominare la D.ssa Cinzia Monaco, Direttore della U.O.C. Farmacia aziendale quale Direttore dell'Esecuzione del Contratto;

- di pubblicare sull'apposito sito aziendale, ai sensi dell'art. 29 del D.Leg.vo n. 50/2016 e s.m.i., l'avviso per la trasparenza;

- di corrispondere il dovuto alla Ditta fornitrice nei limiti del suddetto importo, ad avvenuta esecuzione della fornitura regolarmente effettuata, previa presentazione di appositi documenti contabili conformi alla vigente normativa fiscale.

La struttura complessa proponente curerà gli adempimenti consequenziali del presente provvedimento.

La presente deliberazione è composta di n. 69 pagine di cui n. 62 pagine di allegati nei termini indicati.

*Il presente atto è pubblicato nell'Albo dell'Azienda nel sito internet aziendale* www.scamilloforlanini.rm.it *per giorni 15 consecutivi, ai sensi della Legge Regionale 31.10.1996 n. 45.*

**IL DIRETTORE GENERALE f.f.**
**(D.ssa Francesca Milito)**

AZIENDA OSPEDALIERA S. CAMILLO – FORLANINI
Circonvallazione Gianicolense, n.87- 00152 Roma
**Servizio Centrale di Farmacia**
☎ - 06/55556084 ☎ -Fax 06/55552460
**Direttore – dott.ssa Cinzia Monaco**
e-mail – cmonaco@scamilloforlanini.rm.it

All. 1

Prot 56/C

DOTT.SSA TANTURLI

Roma 22/09/2021

UOC Beni e Servizi

Dott. P. Farfusola

*23/09/2021 Documento N. 192986/2021*

**Oggetto: Recepimento Farmaco Procarbazina e richiesta d'offerta farmaco estero Lomustina**

Si inoltra la richiesta di recepimento del lotto 74 presente nella 3° Tranche della gara regionale.

Si richiede inoltre la fornitura del principio attivo Lomustina compresse 40 mg, tale farmaco non è presente in nessuna gara centralizzata ed è un farmaco estero, pertanto si inoltrano i nomi delle società presso cui richiedere l'offerta:

- Interfarmaci
- Intercompany NON ESISTE +
- Unipharma
- Farmacia Internazionale Italiana

Il fabbisogno stimato è di 500 compresse.

Entrambi i farmaci vanno contabilizzati sul C.E. 501010101000 Flusso F

Distinti saluti

Il Direttore

Dott.ssa Cinzia Monaco

Circonvallazione Gianicolense, n.87- 00152 Roma
**Servizio Centrale di Farmacia**
☎ - 06/55556084 ☎ -Fax 06/55552460
**Direttore – dott.ssa Cinzia Monaco**
e-mail – cmonaco@scamilloforlanini.rm.it

58/C

Dott.ssa Tartuni

Roma 23/09/2021

*23/09/2021 Documento N. 193315/2021*

UOC Beni e Servizi

Dott. P. Farfusola

**Oggetto: Recepimento Farmaco Procarbazina e richiesta d'offerta farmaco estero Lomustina**

Ad integrazione della nota 1929/86/2021 relativamente al farmaco Lomustina 40 mg si specifica che il trattamento in associazione al medicinale Procarbazina segue uno schema posologico per sei cicli ogni 8 settimane per un totale di un anno, pertanto ai fini della contabilizzazione per l'anno 2021 sono previste 125 (130) compresse, per l'anno 2022 375 (370) compresse

Il fabbisogno deve essere contabilizzato C.E. 501010113000 Autorizzazione 1.

Si inoltrano in aggiunta due nomi delle società presso cui richiedere l'offerta:

- Profarma Italia
- Ottopharma

Distinti saluti

Il Direttore

Dott.ssa Cinzia Monaco

All. 2

# OFFERTA CEENU E BELUSTINE

Daniela Ferroni <info@finternazionale.it>

mar 28/09/2021 15:05

Posta in arrivo

A:Beni e Servizi <benieservizi@scamilloforlanini.rm.it>;

5 allegati (4 MB)

OFFERTA CEENU E BELUSTINE.pdf; CEENU CPR. 10-40-100 MG. BMS CANADA.pdf; DICHIARAZIONE RESPONSABILITA' CEENU CPR. 40 MG. BMS CANADA.pdf; BELUSTINE BRUCK MEDICLONE INDIA.pdf; DICHIARAZIONE RESPONSABILITA' BELUSTINE CPR. 40 MG. INTERMED-MEDICLONE HEALTH CARE-BRUCK INDIA.pdf;

Gentilissimo Dottor Farfusola,
in allegato quanto in oggetto unitamente a relative schede tecniche e moduli di importazione.

A disposizione per qualsiasi chiarimento
Con i migliori saluti

**FARMACEUTICA INTERNAZIONALE ITALIANA**
**Daniela Ferroni**

**Corso Marconi n° 26**
**28883 – GRAVELLONA TOCE (VB) - ITALIA**
**Tel. 0323/86.55.57**
**Fax: 0323/84.52.67**
**e-mail: ufficio.clienti2@finternazionale.it**
**pec: farminternaz@pec.it**

FARMACEUTICA INTERNAZIONALE ITALIANA S.r.l.
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Corso Marconi, 26 – 28883 GRAVELLONA TOCE
Tel.0323/86.55.57 - 84.08.05 - Fax 0323/84.52.67 cell.339/13.67.875
e-mail: info@finternazionale.it

**Oggetto :** OFFERTA ECONOMICA

Alla c.a. del Dottore Paolo Farfusola

**Gravellona Toce** **28 settembre 2021** Riferimento Cliente Num. 494 OSPEDALE SAN CAMILLO FORLANINI

| Pos. | Nome commerciale | Principio attivo | LOTTO COD C.I.G. | Confezionamento e dosaggio | Ditta produttrice titolare AIC | Paese di origine | Quantità prevista per unità | Prezzo a Voi riservato per cpr. o f.la | Prezzo a Voi riservato per Confezione | Note |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Ceenu | Lomustina | | 20 Cpr. 40 mg. | Bristol Myers Squibb | Canada | | 13,2000 | 264,00 | MINIMO D'ORDINE N. 4 CONFEZIONI - SPESE DI TRASPORTO GRATUITE - TEMPI DI CONSEGNA 10/12 GIORNI LAVORATIVI CIRCA DALLA DATA DI RICEZIONE DELL'ORDINE |
| 2 | Belustine | Lomustina | | 10 Cpr. 40 mg. | Bruck Farma Ltd/mediclone Health Care | India | | 1,5900 | 15,90 | MINIMO D'ORDINE N. 22 CONFEZIONI - SPESE DI TRASPORTO GRATUITE - TEMPI DI CONSEGNA 15 GIORNI LAVORATIVI CIRCA DALLA DATA DI RICEZIONE DELL'ORDINE |
| 3 | Belustine | Lomustina | | 10 Cpr. 40 mg. | Bruck Farma Ltd/mediclone Health Care | India | | 1,4900 | 14,90 | PREZZO RIFERITO A VS. FABBISOGNO DI N. 50 CONFEZIONI - SPESE DI TRASPORTO GRATUITE - TEMPI DI CONSEGNA 15 GIORNI LAVORATIVI CIRCA DALLA DATA DI RICEZIONE DELL'ORDINE |

**Spese di Imballaggio e trasporto: GRATUITE**
**Spese di sdoganamento:** G R A T U I T E
**I.V.A : 10%**

*I prezzi rimarranno invariati salvo aumenti particolarmente significativi disposti dalla casa madre.*

*A disposizione per qualsiasi chiarimento in merito, l'occasione ci è gradita per inviarVi i ns. migliori saluti.*

Pagamento entro 90 gg. Dalla data emissione Fattura

*FARMACEUTICA INTERNAZIONALE ITALIANA S.r.l.*
*UFFICIO OFFERTE*
*Daniela Ferroni*

# *Lomustine Capsules IP 40 mg*
## *BELUSTINE - 40*

R, Only

**COMPOSITION:**

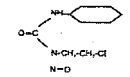
Each hard gelatin capsule contains

| | |
|---|---|
| Lomustine IP | 40 mg |
| Excipients | q.s |

**Colours:** Approved colours used in empty Capsule shell

**DESCRIPTION**

(lomustine [CCNU]) Capsules is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclo-hexyl-1 -nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). is relatively insoluble in water (<0.05 mg per mL). It is relatively unionized at a physiological pH. Inactive ingredients in capsules are: magnesium stearate and mannitol. The structural formula is:



Lomustine is available in 40 mg capsules for oral administration.

**CLINICAL PARMACOLOGY**

Although it is generally agreed that Lomustine alkylates DNA and RNA, it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbarnoylation of amino acids in proteins.

Lomustine may be given orally. Following oral administration of radioactive Lomustine at doses ranging from 30 mg/m² to 100 mg/m² , about half of the radioactivity given was excreted in the form of degradation products within 24 hours.

The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, Lomustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

**INDICATIONS AND USAGE**

Lomustine has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain tumors: both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease: secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

**CONTRAINDICATIONS**

Lomustine should not be given to individuals who have demonstrated a previous hypersensitivity to it.

**WARNINGS**

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Lomustine is cumulative and therefore dosage ad justment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from Lomustine appears to be dose related (see ADVERSE REACTIONS).

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

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Pregnancy: Pregnancy "Category D". Lomustine can cause fetal harm when ad ministered to a pregnant woman. Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**WARNINGS**

(lomustine) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

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 (see **WARNINGS** and **ADVERSE REACTIONS).**

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS).** At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see **Dosage Adjustment Table** under **DOSAGE AND ADMINISTRATION).**

**PRECAUTIONS**

General: In all instances where the use of Lomustine is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Lomustine therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

**Laboratory Tests:** Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

Baseline pulmonary function studies should be conducted along with frequent pulmonary function tests during treatment. Patients with a baseline be-low 70% of the predicted Forced Vital Capacity (FVC) or Carbon Monoxide Diffusing Capacity (DLco) are particularly at risk.

Since Lomustine (lomustine) Capsules may cause liver dysfunction, it is rec ommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lomustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans **(see ADVERSE REACTIONS).** Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

**Pregnancy:** Pregnancy "Category D". **(See WARNINGS.)**

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lomustine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**AND ADMINISTRATION.**

**Information for the Patient:** Patients receiving Lomustine should be given the following information and instructions by the physician:

1. Patients should be told that Lomustine is an anticancer drug and belongs to the group of medicines known as alkylating agents.
2. In order to provide the proper dose of Lomustine, patients should be aware that there may be two or more different types and colors of capsules in the container dispensed by the pharmacist.
3. Patients should be told that Lomustine is given as a single oral dose and will not be repeated for at least 6 weeks.
4. Patients should be told that nausea and vomiting usually last less than 24 hours, although loss of appetite may last for several days.
5. If any of the following reactions occur, notify the physician: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.

**ADVERSE REACTIONS**

**Hematologic Toxicity:** The most frequent and most serious toxicity of Lomustine is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 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 5000 wbc/mm³ . Thirty-six percent developed white blood counts below 3000 wbc/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 leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy.**
**Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.**

**Pulmonary Toxicity:** Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely 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 1100 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 who received related nitrosoureas in childhood and early adolescence (1-16 years) combined with cranial radiotherapy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initially treated at less than five years of age died of delayed pulmonary fibrosis.

**Gastrointestinal Toxicity:** Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if Lomustine is administered to fasting patients.

**Hepatotoxicity:** 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.

**Nephrotoxicity:** Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with Lomustine. Kidney damage has also been reported occasionally in patients receiving lower total doses.

**Other Toxicities:** Stomatitis, alopecia, optic atrophy, and visual disturbances such as blindness have been reported infrequently-Neurological reactions such as disorientation, lethargy, ataxia, and dysarthria have been noted in some patients receiving Lomustine. However, the relationship to medication in these patients is unclear.

**OVERDOSAGE**

No proven antidotes have been established for Lomustine overdosage.

**DOSAGE AND ADMINISTRATION**

The recommended dose of Lomustine in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m² as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks. When Lomustine is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic

| Nadir After Prior Dose | |
|---|---|
| **Leukocytes** | **Platelets** |
| >4000 | > 100,000 |
| 3000-3999 | 75,000-99,999 |
| 2000-2999 | 25,000-74,999 |
| <2000 | < 25,000 |

**A repeat course of Lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/ mm³; leukocytes above 4000/mm³) and this is usually in 6 weeks.**

Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

**STORAGE:**

Store in a well closed container at a temperature not more than 30° C
Store protected from light and humidity.
Keep medicine out of reach of children.

**SHELF LIFE:**

24 Months

**How Supplied**

A HDPE Jar of 10 Capsules

Manufactured by:

Bruck
PHARMA PRIVATE LIMITED

**Marketed by:**
**Mediclone Health Care Pvt Ltd.**
No.10/1 (Old-19/1) Lakshmipuram 2nd Street,
Royapettah, Chennai - 600 014

**MODELLO 10-1**

**Allegato 10**

**AL MINISTERO DELLA SALUTE**
**USMAF-SASN**.....
**UNITA' TERRITORIALE**.....MILANO MALPENSA.....

**Richiesta di importazione di medicinali ai sensi del D.M. 11/02/1997.**

Il sottoscritto Dr. .....

Residente in.....via.....tel.....

Iscritto nell'albo dell'Ordine dei Medici –Chirurghi di .....

Al n°..... cod. regionale.....

chiede di importare il medicinale (contenente il seguente/i principio/i:
LOMUSTINA

nome commerciale: CEENU

forma farmaceutica.....COMPRESSE 40 MG.

nella quantità di numero.....confezioni contenenti.....20 COMPRESSE.....di farmaco cadauna.

Prodotto dalla ditta.....BRISTOL MYERS SQUIBB.....(Specificare il nome dell'Azienda)

Precisa che tale farmaco è regolarmente registrato nel Paese di provenienza: CANADA

Per il trattamento di : .....

Tale farmaco è indispensabile per la cura del Sig. (solo iniziali o codice) .....

Affetto da .....

Dichiaro altresì che il farmaco:

- non ha valida alternativa terapeutica con altri medicinali registrati in Italia
- non contiene sostanze stupefacenti o psicotrope;
- non è un emoderivato;
- verrà impiegato sotto la propria diretta responsabilità, dopo aver ottenuto il consenso informato scritto del paziente;
- che le generalità del paziente ed i documenti relativi al consenso informato sono custoditi presso il medico curante per la durata prevista dalla normativa vigente

Particolari condizioni di conservazione:
Temperatura (es. -20°C, da 2 a 8°C, < 25°, <30°, nessuna indicazione):.....AMBIENTE.....

Altro: .....

Luogo e data _____

_____

*obbligatori

Timbro e firma leggibile del medico *

**Allegato 10**

**MODELLO 10-1**

**AL MINISTERO DELLA SALUTE**
**USMAF-SASN**.....
**UNITA' TERRITORIALE**.....MILANO MALPENSA.....

**Richiesta di importazione di medicinali ai sensi del D.M. 11/02/1997.**

Il sottoscritto Dr. .....

Residente in.....via.....tel.....

Iscritto nell'albo dell'Ordine dei Medici –Chirurghi di .....

Al n°..... cod. regionale.....

chiede di importare il medicinale (contenente il seguente/i principio/i:
LOMUSTINA
.....

nome commerciale: BELUSTINE .....

forma farmaceutica.....COMPRESSE 40 MG.....

nella quantità di numero.....confezioni contenenti.....10 COMPRESSE.....di farmaco cadauna.

Prodotto dalla ditta.....INTERMED/MEDICLONE HEALT CARE/ BRUCK FARMA LTD..... (Specificare il nome dell'Azienda)

Precisa che tale farmaco è regolarmente registrato nel Paese di provenienza: INDIA .....

Per il trattamento di : .....

Tale farmaco è indispensabile per la cura del Sig. (solo iniziali o codice) .....

Affetto da .....

Dichiaro altresì che il farmaco:

- non ha valida alternativa terapeutica con altri medicinali registrati in Italia
- non contiene sostanze stupefacenti o psicotrope;
- non è un emoderivato;
- verrà impiegato sotto la propria diretta responsabilità, dopo aver ottenuto il consenso informato scritto del paziente;
- che le generalità del paziente ed i documenti relativi al consenso informato sono custoditi presso il medico curante per la durata prevista dalla normativa vigente

Particolari condizioni di conservazione:
Temperatura (es. -20°C, da 2 a 8°C, < 25°, <30°, nessuna indicazione):...AMBIENTE.....

Altro: .....

Luogo e data _____

_____

Timbro e firma leggibile del medico *

*obbligatori

# PRODUCT MONOGRAPH

## PrCeeNU*

**(Lomustine-CCNU)**

**Capsules; 10, 40 and 100 mg**

**Antineoplastic Agent**

Bristol-Myers Squibb Canada
Montreal, Canada, H4S 0A4

Date of Preparation:
4 July 1974



Date of Revision:
20 December 2010

Submission control no.: 141760

# PRODUCT MONOGRAPH

## NAME OF DRUG

**CeeNU**

**(Lomustine - CCNU)**

Capsules; 10, 40 and 100 mg

## THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: CeeNU (LOMUSTINE-CCNU) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW IS SEEN.

## ACTION AND CLINICAL PHARMACOLOGY

It is generally agreed that CeeNU (lomustine-CCNU) acts as an alkylating agent but, as with other nitrosoureas, it may also inhibit several key enzymatic processes.

CeeNU may be given orally. Following oral administration of radioactive CeeNU at doses ranging from 30 mg/m² to 100 mg/m², about half of the radioactivity given was excreted within 24 hours. The serum half-life of the drug and/or metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, CeeNU crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50 percent or greater than those measured concurrently in plasma.

## INDICATIONS AND CLINICAL USES

CeeNU (lomustine-CCNU) is indicated as palliative therapy in addition to surgery and radiotherapy or in combination therapy with other chemotherapeutic agents in the following:

1. Brain tumors - both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

2. Hodgkin's Disease – as a secondary therapy, alone or in combination with other active drugs.

**Other Tumors** – CeeNU has been used in combination with other therapeutic agents in lung cancer (squamous cell, anaplastic large cell, and adenocarcinoma), malignant melanoma and breast cancer (advanced disease) only after other conventional methods have failed.

## CONTRAINDICATIONS

CeeNU (lomustine-CCNU) should not be given to individuals who have demonstrated a previous hypersensitivity to it. Also it is contraindicated in patients having severe leukopenia and/or thrombocytopenia.

## WARNINGS

CeeNU (lomustine-CCNU) should be administered by individuals experienced in the use of antineoplastic therapy.

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 CeeNU.

Blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of CeeNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of CeeNU is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND

ADMINISTRATION).

Caution should be used in administering CeeNU to patients with decreased circulating platelets, leukocytes or erythrocytes (see DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from CeeNU appears to be dose related (see ADVERSE REACTIONS).

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

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

**Pregnancy**

Safe use in pregnancy has not been established. CeeNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patients should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

CeeNu is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximating those employed clinically.
Nitrosourea therapy does have carcinogenic potential. The occurrence of acute leukemia and bone marrow dysplasias has been reported in patients following nitrosourea therapy.

CeeNU also affects fertility in male rats at doses somewhat higher than the human dose.

**Nursing Mothers**

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from CeeNU, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

## PRECAUTIONS

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least six weeks after a dose.

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 ($DL_{co}$) are particularly at risk.

Since CeeNU (lomustine-CCNU) may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

**Effects on ability to drive and to use machines**

No studies on the effects on the ability to drive and use machines have been performed.

## ADVERSE REACTIONS

1. Gastrointestinal: Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. The frequency and duration may be reduced by the use of antiemetics prior to dosing and by the administration of CeeNU (lomustine-CCNU) to fasting patients.

2. Hematologic Toxicity: The most frequent and most serious toxicity of CeeNU is delayed myelosuppression. It usually occurs four to six weeks after drug administration and is dose related. Thrombocytopenia occurs at about four weeks post-administration and persists for one to two weeks. Leukopenia occurs at five to six weeks after a dose of CeeNU and persists for one to two weeks.

   Approximately 65% of patients receiving 130 mg/m$^2$ develop white blood counts below 5000 /mm$^3$. Thirty-six percent developed white blood cell counts below 3000 /mm$^3$. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

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

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

3. Pulmonary Toxicity: Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with CeeNU. Onset of toxicity has occurred after an interval of six months or longer from the start of therapy with cumulative doses of CeeNU usually greater than 1100 $mg/m^2$. There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

   Delayed onset pulmonary fibrosis occurring up to 15 years after treatment has been reported in patients with intracranial tumors who received related nitrosoureas during their childhood and early adolescence.

4. Other Toxicities: Stomatitis, alopecia, anemia have been reported infrequently.

   Neurological reactions such as disorientation, lethargy, ataxia and dysarthria have been noted in some patients receiving CeeNU. However, the relationship to medication in these patients is unclear.

5. Nephrotoxicity: Renal abnormalities consisting of decrease in kidney size, progressive azotemia and renal failure have been reported in patients who receive large cumulative doses after prolonged therapy with CeeNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

6. Hepatotoxicity: 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 CeeNU.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

Accidental overdose with CeeNu (lomustine-CCNU) has been reported, including fatal cases. Accidental overdose has been associated with bone marrow suppression, abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

There is no specific antidote for overdose with CeeNU. In the case of overdosage, appropriate supportive measures should be taken

## DOSAGE AND ADMINISTRATION

The recommended dose of CeeNU (lomustine-CCNU) is 130 mg/m² as a single dose by mouth every 6 weeks (see SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL).

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

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/mm$^3$; leukocytes above 4,000/mm$^3$). Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

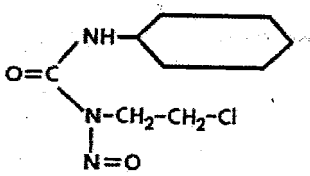
Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

| **Nadir After Prior Dose** | | **Percentage of Prior Dose to be Given** |
|---|---|---|
| **Leukocytes (/mm$^3$)** | **Platelets (/mm$^3$)** | |
| ≥4000 | ≥100,000 | 100% |
| 3000 - 3999 | 75,000 - 99,999 | 100% |
| 2000 - 2999 | 25,000 - 74,999 | 70% |
| < 2000 | < 25,000 | 50% |

When CeeNU is used in combination with myelosuppressive drugs, the doses should be adjusted accordingly.

## PHARMACEUTICAL INFORMATION

**Chemistry:**




**Trade Name:** CeeNU

**Proper Name:** Lomustine

**Chemical Name:** 1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea

**Molecular Formula:** $C_9H_{16}ClN_3O_2$

**Molecular Weight:** 233.71

**Description:** Yellow powder. Soluble in 10% ethanol (0.05 mg/mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg/mL). It is relatively un-ionized at a physiological pH.

## STABILITY

Unopened bottles of CeeNU (lomustine-CCNU) capsules are stable for 36 months at room temperature.

**Storage:** PROTECT FROM LIGHT. Avoid excessive heat (over 40°C).

## AVAILABILITY

The capsules of CeeNU (lomustine-CCNU) are prepared in three dosage strengths: 10 mg, 40 mg, and 100 mg.

All capsules contain mannitol and magnesium stearate as inert ingredients. A desiccant packet is enclosed in each bottle of capsules.

CeeNu capsules are available as follows:

- 10 mg in amber bottles of 20 capsules
- 40 mg in amber bottles of 20 capsules
- 100 mg in amber bottles of 20 capsules

## SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

1. Only the appropriate number of CeeNU (lomustine-CCNU) capsules required for a single administration should be dispensed. Patients should be told that CeeNU is taken as a single oral dose and will not be repeated for at least 6 weeks.

2. Preparation of CeeNU should be done in a vertical laminar flow hood (Biological Safety Cabinet - class II)

3. CeeNU capsules should not be placed in automated counting machines. The counting and pouring of CeeNU should be done carefully and the equipment used should be rinsed with water and then thoroughly cleaned with detergent and water.

4. Personnel handling CeeNU should wear gloves, safety glasses, a mask and disposable protective clothing.

5. Vials and other materials which have come in contact with CeeNU should be segregated and incinerated at 1000°C or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

6. Personnel regularly involved in the preparation and handling of CeeNU should have bi-annual blood examinations.

## PHARMACOLOGY

The following is a summary of the data provided by the studies indicated in the attached list of references.

Kline et al used a biological procedure for the determination of drug levels of CeeNU (lomustine-CCNU). The biological target was L1210 leukemia. A dose response curve was determined for the drug when given simultaneously with the inoculation of a designated number of leukemia cells, using % of cures and median survival time as the parameters of response. The drug was also administered at a series of time intervals prior to the inoculation of leukemia cells and the dose level equivalence at the time of leukemic inoculation was estimated by reference of the observed therapeutic response to that obtained for the standard curve. The curve for percentage retention of administered CeeNU had a shallow slope and the half-life of the drug in the host was estimated to be 94 minutes.

Oliverio et al studied the metabolic fate of CeeNU using the $^{14}C$ label in each of three positions of the molecule; the ethyl, carbonyl, and cyclohexyl moieties. In rodents, 24 hours after intraperitoneal or oral dose of the ethyl or cyclohexyl labelled CeeNU, 75% of the radioactivity appeared in the urine, while about 10-20% of carbonyl or ethyl labelled CeeNU was expired as $^{14}CO_2$. In dogs and monkeys, CeeNU was also rapidly degraded and excretion of $^{14}C$ was primarily in the urine. Plasma levels of $^{14}C$ fell off rapidly in the first hour followed by a slower disappearance. After an intravenous injection, the CSF/plasma ratio of ethyl labelled CeeNU was three, while that for the cyclohexyl-labelled moiety was unity. This agrees with the observation that the cyclohexyl portion of the molecule is 60% plasma protein bound while the ethyl portion is not bound. The results support the suggested intermediate formation of an isocyanate moiety during the degradation of nitrosoureas *in vivo*. The identified metabolites and cyclohexylisocyanate were inactive against L-1210.

Studies conducted to determine the effects of NSC 79037 in polyethoxylated vegetable oil and normal saline (ratio of 1:9) applied topically to the hamster cheek pouch revealed no thromboembolism as concentrations 2.5 mg/ml. The only effect produced with this concentration was a slight decrease in the rate of venule and arteriole blood flow in 1/6 hamsters and a slight to moderate decrease in the venule flow of a second animal. Administration of a concentration at 0.625 mg/ml or the vehicle alone produced no detectable effect.

No thromboembolism was observed in the hamster cheek pouch microcirculation after single intrajugular injections of CeeNU in polyethoxylated vegetable oil and normal saline at doses ranging from 0.3125 to 20.0 mg/kg. However, a dosage of 0.625, 1.25, 2.5, 5.0, 10.0 or 20.0 mg/kg produced a decrease in

cheek pouch venule blood flow varying from slight to moderate-severe. A slight to moderate-severe decrease in blood flow was also noted in the arterioles at drug levels ranging from 1.25 to 20 mg/kg with some vasoconstriction recorded at the 3 highest levels. At 20.0 mg/kg WBC stickiness was reported only once. The "no effect" level appeared to be 0.3125 mg/kg. Injection of the vehicle alone at volumes equivalent to those employed with 2.5, 5.0, 10.0, and 20.0 mg/kg drug dosages produced some vasoconstriction and a decrease in the rate of arteriole and venule blood flow. Microcirculation appeared normal when the vehicle alone was injected at a volume equivalent to that of a 1.25 mg/kg drug dosage. A mean recovery time of 17 minutes (5-35) was required for normal flow after intravenous injection in hamsters treated with the drug, compared to a mean recovery period of 6 minutes (2-10) in those receiving only the polyethoxylated vegetable oil and saline vehicle. It was concluded that cardiovascular effects observed were, in part, due to the vehicle employed.

Comparison of mortality levels in mice and rats for single oral doses of BiCNU and CeeNU on a mg/kg, $mg/m^2$, or mmole/kg basis revealed that BiCNU was twice as toxic as CeeNU.

## TOXICOLOGY

The toxicity of CeeNU (lomustine-CCNU) was investigated primarily by the Mason Research Institute under contract with the National Cancer Institute. The parenteral toxicity of CeeNU may be summarized as follows:

a) Single Dose (IV infusion):

Dog: Maximum tolerated dose (MTD) - 0.625 mg/kg
Primary toxicity = Depressed hematopoiesis, lymphoid tissue.
Secondary toxicity - Delayed hepatotoxicity

Rhesus Monkey: MTD = 1.25 mg/kg
Primary toxicity = nephrotoxicity
Secondary toxicity - Depressed hematopoiesis, hepatotoxicity.

b) Multiple Dose (IV infusion):

Dog: 2 or 3 doses of 1.25 mg/kg given at weekly intervals = cumulative hepatotoxicity.

The toxicity of CeeNU given orally may be summarized as follows:

a) Single Dose (capsules)

Dog: MTD = 2.0 mg/kg

b) Multiple Dose (capsules - dog, gavage - monkey)

Dog: MTD - 0.65 mg/kg/day x 14
Rhesus Monkey: MTD = 0.15 mg/kg/day x 14

c) Delayed Hepatotoxicity (capsules)

Dog: A single oral dose of 4 mg/kg produced hepatotoxicity that persisted for 2-3 months after drug treatment.

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**Area Governo delle Risorse Strumentali- U.O.C. Acquisizione Beni e Servizi**
**Ufficio Acquisizione Farmaci e Diagnostici**

*San Camillo Forlanini*
*Prot. Uscita N. 0034284/2021*
*Del 28/09/2021*

0034284/2021

Ditta Farmaceutica Internazionale Italiana
info@finternazionale.it

**OGGETTO:** Richiesta offerta farmaco.

Codesta Ditta, qualora lo ritenga di propria convenienza e senza alcun impegno da parte di questa Azienda, è invitata a far pervenire una offerta per il seguente principio attivo necessario alle **esigenze dell'anno 2021**:

- N. 500 compresse LOMUSTINA 40 MG

Unitamente all'offerta economica, che rimarrà fissa e valida per tutto il periodo di fornitura, si chiede di **indicare obbligatoriamente l'eventuale costo per le spese di sdoganamento e trasporto.**

Considerato il carattere di estrema urgenza della richiesta, la risposta dovrà pervenire via mail all'indirizzo benieservizi@scamilloforlanini.rm.it entro il 30/9/2021.

Distinti saluti

Il Direttore
(Dott. Paolo Farfusola)

PF/mf

# R: RICHIESTA OFFERTA LOMUSTINA

## Info Ottopharma <info@OTTOPHARMA.COM>

mar 28/09/2021 12:55

A:Beni e Servizi <benieservizi@scamilloforlanini.rm.it>;

3 allegati (4 MB)

MODULO IMPORTAZIONE D.M. 11.02.1997.pdf; 12844.pdf; Belustine 40 mg CPS Mediclone India.pdf;

Buongiorno,
in allegato nostra migliore offerta e scheda tecnica.

Si allega modulo di importazione necessario da allegare all'ordine.

N.B.: In fase di compilazione modulo, nome medico, timbro e firma dovranno combaciare ed essere leggibili (NON SONO AMMESSI TIMBRI SCRITTI A MANO).
Si prega di utilizzare unicamente il modulo da noi inoltratovi e di compilare correttamente tutti i campi per evitare il blocco della merce in dogana.

Cordiali Saluti / Best regards

Marco.

OTTOPHARMA S.r.l.
Via Novara, 38 - 28021 Borgomanero (NO) | P.IVA - C.F. 02457060032
Tel.+39 0322 255639 | Tel. +39 393 8030590 | Fax 0322- 060732 | Mail info@ottopharma.com | Web www.ottopharma.com



-----Messaggio originale-----
Da: benieservizi@scamilloforlanini.rm.it <benieservizi@scamilloforlanini.rm.it>
Inviato: martedì 28 settembre 2021 11:29
A: Info Ottopharma <info@OTTOPHARMA.COM>; benieservizi@scamilloforlanini.rm.it
Oggetto: RICHIESTA OFFERTA LOMUSTINA

OttoPharma

## *PROPOSTA DI FORNITURA*

Spett.le

**AZIENDA OSPEDALIERA SAN CAMILLO FORLANINI**
CIRC. GIANICOLENSE, 87

152 ROMA RM

| N° | Data | Pagina | Cliente |
|---|---|---|---|
| **12844** | **28/09/21** | **1** | **81** |

| Spedizione | Porto |
|---|---|
| **A MEZZO CORRIERE** | **FRANCO** |

| Cod. Pag. | Modalità Pagamento |
|---|---|
| **1** | **60 GG BONIFICO D.F.** |

| Codice Articolo | Descrizione Articolo | UM | Quantità | Prezzo Unitario | Prezzo Confezione |
|---|---|---|---|---|---|
| FAR0100 | BELUSTINE 40MG 10CPRS | CF | 1 | 1,265 | **12,65** |
| | (LOMUSTINE) | | | | |
| | SPESE TRASPORTO | | | | **15,00** |
| | PRODUTTORE:MEDICLONE | | | | |
| | PROVENIENZA:INDIA | | | | |
| | CONSEGNA:10-12 GG LAVORATIVI | | | | |
| | Tutti i prezzi sono da | | | | |
| | intendersi I.V.A. 10% esclusa | | | | |
| | Spese di importazione: | | | | |
| | GRATUITE | | | | |
| | >>Valida fino al 31/12/2021<< | | | | |
| | **Salvo aumenti disposti dalla | | | | |
| | ditta produttrice. | | | | |

GLI ORDINI ANDRANNO INOLTRATI A: E-MAIL: ordini@ottopharma.com – CODICE NSO: XPT58Z4N



**OTTOPHARMA S.r.l.**
Sede Operativa: Via Italia, 14 – 28045 Invorio (NO) Tel: 0322/255639 Fax: 0322/060732 - P.IVA - C.F. 02457060032
| www.ottopharma.com | info@ottopharma.com

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

# *Lomustine Capsules IP 40 mg*

## *BELUSTINE - 40*

R. Only

**COMPOSITION:**

Each capsule contains

| | |
|---|---|
| Lomustine IP | 40 mg |
| Excipients | q.s |

**Colours:** Approved colours used in empty Capsule shell

**DESCRIPTION**

(lomustine [CCNU]) Capsules is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclo-hexyl-1 -nitrosoures. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). is relatively insoluble in water (<0.05 mg per mL). It is relatively unionized at a physiological pH. Inactive ingredients in capsules are: magnesium stearate and mannitol. The structural formula is:

Lomustine is available in 40 mg capsules for oral administration.

**CLINICAL PARMACOLOGY**

Although it is generally agreed that Lomustine alkylates DNA and RNA; it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins.

Lomustine may be given orally. Following oral administration of radioactive Lomustine at doses ranging from 30 mg/m2 to 100 mg/m2, about half of the radioactivity given was excreted in the form of degradation products within 24 hours.

The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, Lomustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

**INDICATIONS AND USAGE**

Lomustine has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain tumors: both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease: secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

**CONTRAINDICATIONS**

Lomustine should not be given to individuals who have demonstrated a previous hypersensitivity to it.

**WARNINGS**

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from Lomustine appears to be dose related (see ADVERSE REACTIONS).

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

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Pregnancy: Pregnancy "Category D". Lomustine can cause fetal harm when administered to a pregnant woman. Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**WARNINGS**

(lomustine) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

Bone marrow suppression, notably thrombocytopenia and leukope nia, 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 (see **WARNINGS** and **ADVERSE REACTIONS**).

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS**). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see **Dosage Adjustment Table** under **DOSAGE AND ADMINISTRATION**).

**PRECAUTIONS**

General: In all instances where the use of Lomustine is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Lomustine therapy should be carried out with caution and with adequate consideration of the further

need for the drug and alertness as to possible recurrence of toxicity.

**Laboratory Tests:** Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

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 (lomustine) Capsules may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lomustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans **(see ADVERSE REACTIONS).** Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

**Pregnancy:** Pregnancy "Category D". **(See WARNINGS.)**

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lomustine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric Use:** See ADVERSE REACTIONS, Pulmonary Toxicity, and DOSAGE AND ADMINISTRATION.

**Information for the Patient:** Patients receiving Lomustine should be given the following information and instructions by the physician.

1. Patients should be told that Lomustine is an anticancer drug and belongs to the group of medicines known as alkylating agents.
2. In order to provide the proper dose of Lomustine, patients should be aware that there may be two or more different types and colors of capsules in the container dispensed by the pharmacist.
3. Patients should be told that Lomustine is given as a single oral dose and will not be repeated for at least 6 weeks.
4. Patients should be told that nausea and vomiting usually last less than 24 hours, although loss of appetite may last for several days.
5. If any of the following reactions occur, notify the physician: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.

**ADVERSE REACTIONS**

**Hematologic Toxicity:** The most frequent and most serious toxicity of Lomustine is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadmin-istration and persists for 1 to 2 weeks. Leukopenia occurs at 5 to 8 weeks af¬ter a dose of Lomustine and persists for 1 to 2 weeks. Approximately 85% of pa¬tients receiving 130 mg/m2 develop white blood counts below 5000 wbc/mm3. Thirty-six percent developed white blood counts below 3000 wbc/mm. Throm-bocytopenia 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 leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy.**

**Anemia also occurs, but is less frequent and less severe than throm-bocytopenia or leukopenia.**

**Pulmonary Toxicity:** Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with Lomustine. Onset of tox¬icity has occurred after an interval of 6 months or longer from the start of therapy with cumulative doses of Lomustine usually greater than 1100 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 treat¬ment has been reported in patients who received related nitrosoureas in child¬hood and early adolescence (1-18 years) combined with cranial radiothar¬apy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initially treated at less than five years of age died of delayed pulmonary fibrosis.

**Gastrointestinal Toxicity:** Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if Lomustine is adminis¬tered to fasting patients.

**Hepatotoxicity:** 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.

**Nephrotoxicity:** Renal abnormalities consisting of progressive azotemia, de¬crease in kidney size and renal failure have been reported in patients who re-ceived large cumulative doses after prolonged therapy with Lomustine. Kidney dam-age has also been reported occasionally in patients receiving lower total doses.

**Other Toxicities:** Stomatitis, alopecia, optic atrophy, and visual distur¬bances such as blindness have been reported infrequently. Neurological reactions such as disorientation, lethargy, ataxia, and dysarthria have been noted in some patients receiving Lomustine. However, the relation¬ship to medication in these patients is unclear.

**OVERDOSAGE**

No proven antidotes have been established for Lomustine overdosage.

**DOSAGE AND ADMINISTRATION**

The recommended dose of Lomustine in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m2 as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m2 every 6 weeks. When Lomustine is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic

| Nadir After Prior Dose | |
|---|---|
| Leukocytes | Platelets |
| >4000 | > 100,000 |
| 3000-3999 | 75,000-99,999 |
| 2000-2999 | 25,000-74,999 |
| <2000 | < 25,000 |

**A repeat course of Lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/ mm³; leukocytes above 4000/mm³) and this is usually in 6 weeks.**

Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

**STORAGE:**

Store protected from light and moisture.

**SHELF LIFE:**

24 Months

**How Supplied**

A HDPE Jar of 10 Capsules

Manufactured by:
INTERMED
No. 4, G.K.Industrial Estate,Arcot Road,
Porur, Chennai - 600 116

Marketed by:
Medicione Health Care Pvt. Ltd.,
29, Bio-Pavillion, Velichai,
Kolathur P.O., Chennai - 600 048. INDIA

**Allegato**
**AL MINISTERO DELLA SALUTE**
**USMAF-SASN LOMBARDIA, PIEMONTE E VALLE D'AOSTA**
**UNITA' TERRITORIALE TORINO CASELLE**

**Richiesta di importazione di medicinali ai sensi del D.M. 11/02/1997.**

Il sottoscritto Dr. .....
Residente in..... via .....
tel.....iscritto nell'Albo dell'Ordine dei Medici-
Chirurghi di ..... al n..... cod. regionale.....
..... chiede di importare il medicinale (contenente il seguente/i
principio/i attivo/i):.....
nome commerciale: .....
forma farmaceutica .....
nella quantità di numero ..... confezioni contenenti .....
di farmaco cadauna. prodotto dalla ditta: ..... (specificare il nome dell'azienda )
Precisa che tale medicinale è regolarmente registrato nel Paese di provenienza: .....
per il trattamento di .....
Tale medicinale è indispensabile per la cura del Sig. (iniziali o codice) .....
affetto da: .....
Motivo per cui viene richiesta la scorta di reparto****.....

Dichiara altresì che il farmaco:

- non ha valida alternativa terapeutica con altri medicinali registrati in Italia;
- non contiene sostanze stupefacenti o psicotrope;
- non è un emoderivato;
- verrà impiegato sotto la propria diretta responsabilità, dopo aver ottenuto il consenso informato scritto del paziente;
- che le generalità del paziente ed i documenti relativi al consenso informato sono custoditi presso il medico curante per la durata prevista dalla normativa vigente.

Particolari condizioni di conservazione del medicinale:
Temperatura (es. -20°C, da 2 a 8°C, < 25°, <30°, nessuna indicazione): .....
Altro: .....

Luogo e data _____

_____
Timbro e firma leggibile del medico

_____
Timbro e firma leggibile del Servizio Farmaceutico

****Da compilare solo in caso di scorta reparto

**Area Governo delle Risorse Strumentali- U.O.C. Acquisizione Beni e Servizi**
**Ufficio Acquisizione Farmaci e Diagnostici**

*San Camillo Forlanini*
*Prot. Uscita N. 0034276/2021*
*Del 28/09/2021*

0034276/2021

Ditta Ottopharma
info@ottopharma.com

**OGGETTO:** Richiesta offerta farmaco.

Codesta Ditta, qualora lo ritenga di propria convenienza e senza alcun impegno da parte di questa Azienda, è invitata a far pervenire una offerta per il seguente principio attivo necessario alle **esigenze dell'anno 2021:**

- N. 500 compresse LOMUSTINA 40 MG

Unitamente all'offerta economica, che rimarrà fissa e valida per tutto il periodo di fornitura, si chiede di **indicare obbligatoriamente l'eventuale costo per le spese di sdoganamento e trasporto.**

Considerato il carattere di estrema urgenza della richiesta, la risposta dovrà pervenire via mail all'indirizzo benieservizi@scamilloforlanini.rm.it entro il 30/9/2021.

Distinti saluti

Il Direttore
(Dott. Paolo Farfusola)

PF/mt

PROFARMA S.r.l.s.
Sede legale e operativa: Via Galileo Galilei 17 63100 Ascoli Piceno (AP) – Italy
Tel +39 0736 261002 Fax +39 0736 395803 Mob. +39 366 4049597
e-mail: info@profarmaitalia.com
www.profarmaitalia.com

**01/10/2021**
**Spett.le Farmacia**

Oggetto: **Proposta commerciale Belustine cps 40 mg**

Gentile dottoressa/dottore,
Sottoponiamo alla Vostra attenzione, nostra migliore offerta, relativa al farmaco **Belustine cps 40 mg**.
Specifiche offerta:

| | |
|---|---|
| Nome Prodotto: | **Belustina - 40** |
| Produttore: | Mediclone Healthcare (India) |
| Principio Attivo: | Lomustina |
| Dosaggio e formulazione: | cps da 40mg |
| Confezione: | 10 cps |
| Prezzo confezione: | € 18,21 |
| Spese di Trasporto: | 100€ per ordini inferiori a 50 conf.<br>Incluse per ordini superiori a 50 conf. |
| Tempi di Consegna: | 10-15 giorni |
| IVA: | 10% |
| Pagamento: | 60 gg. DF FM |

Qualora siate interessati non esitiate a contattarci. Restiamo a disposizione per qualsiasi informazione.

Cordialmente

Manuel Monopoli
profarma ITALIA
Divisione Vendite
manuel.monopoli@profarmaitalia.com
mob. +39 366 4049597

# *Lomustine Capsules IP 40 mg*
## BELUSTINE - 40

R, Only

**COMPOSITION:**

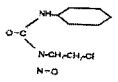
Each hard gelatin capsule contains

| | |
|---|---|
| Lomustine IP | 40 mg |
| Excipients | q.s |

**Colours:** Approved colours used in empty Capsule shell

**DESCRIPTION**

(lomustine [CCNU]) Capsules is one of the nitrosoureas used in the treatment of certain neoplastic diseases. It is 1-(2-chloro-ethyl)-3-cyclo-hexyl-1 -nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. is soluble in 10% ethanol (0.05 mg per mL) and in absolute alcohol (70 mg per mL). is relatively insoluble in water (<0.05 mg per mL). It is relatively unionized at a physiological pH. Inactive ingredients in capsules are: magnesium stearate and mannitol. The structural formula is:




Lomustine is available in 40 mg capsules for oral administration.

**CLINICAL PARMACOLOGY**

Although it is generally agreed that Lomustine alkylates DNA and RNA, it is not cross resistant with other alkylators. As with other nitrosoureas, it may also inhibit several key enzymatic processes by carbarnoylation of amino acids in proteins.

Lomustine may be given orally. Following oral administration of radioactive Lomustine at doses ranging from 30 mg/m² to 100 mg/m² , about half of the radioactivity given was excreted in the form of degradation products within 24 hours.

The serum half-life of the metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at physiological pH, Lomustine crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50% or greater than those measured concurrently in plasma.

**INDICATIONS AND USAGE**

Lomustine has been shown to be useful as a single agent in addition to other treatment modalities, or in established combination therapy with other approved chemotherapeutic agents in the following:

Brain tumors: both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

Hodgkin's Disease: secondary therapy in combination with other approved drugs in patients who relapse while being treated with primary therapy, or who fail to respond to primary therapy.

**CONTRAINDICATIONS**

Lomustine should not be given to individuals who have demonstrated a previous hypersensitivity to it.

**WARNINGS**

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.

The bone marrow toxicity of Lomustine is cumulative and therefore dosage ad justment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Pulmonary toxicity from Lomustine appears to be dose related (see ADVERSE REACTIONS).

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

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Pregnancy: Pregnancy "Category D". Lomustine can cause fetal harm when ad ministered to a pregnant woman. Lomustine is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. There are no adequate and well controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**WARNINGS**

(lomustine) should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

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 (see **WARNINGS** and **ADVERSE REACTIONS).**

Since the major toxicity is delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose (see **ADVERSE REACTIONS).** At the recommended dosage, courses of Lomustine should not be given more frequently than every 6 weeks.The bone marrow toxicity of Lomustine is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see **Dosage Adjustment Table** under **DOSAGE AND ADMINISTRATION).**

**PRECAUTIONS**

**General:** In all instances where the use of Lomustine is considered for chemotherapy, the physician must evaluate the need and usefulness of the drug against the risks of toxic effects or adverse reactions. Most such adverse reactions are reversible if detected early. When such effects or reactions do occur, the drug should be reduced in dosage or discontinued and appropriate corrective measures should be taken according to the clinical judgment of the physician. Reinstitution of Lomustine therapy should be carried out with caution and with adequate consideration of the further need for the drug and alertness as to possible recurrence of toxicity.

**Laboratory Tests:** Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least 6 weeks after a dose.

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 (lomustine) Capsules may cause liver dysfunction, it is rec ommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** Lomustine is carcinogenic in rats and mice, producing a marked increase in tumor incidence in doses approximating those employed clinically. Nitrosourea therapy does have carcinogenic potential in humans **(see ADVERSE REACTIONS).** Lomustine also affects fertility in male rats at doses somewhat higher than the human dose.

**Pregnancy:** Pregnancy "Category D". **(See WARNINGS.)**

**Nursing Mothers:** It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Lomustine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**AND ADMINISTRATION.**

**Information for the Patient:** Patients receiving Lomustine should be given the following information and instructions by the physician:

1. Patients should be told that Lomustine is an anticancer drug and belongs to the group of medicines known as alkylating agents.
2. In order to provide the proper dose of Lomustine, patients should be aware that there may be two or more different types and colors of capsules in the container dispensed by the pharmacist.
3. Patients should be told that Lomustine is given as a single oral dose and will not be repeated for at least 6 weeks.
4. Patients should be told that nausea and vomiting usually last less than 24 hours, although loss of appetite may last for several days.
5. If any of the following reactions occur, notify the physician: fever, chills, sore throat, unusual bleeding or bruising, shortness of breath, dry cough, swelling of feet or lower legs, mental confusion, or yellowing of eyes and skin.

**ADVERSE REACTIONS**

**Hematologic Toxicity:** The most frequent and most serious toxicity of Lomustine is delayed myelosuppression. It usually occurs 4 to 6 weeks after drug administration and is dose related. Thrombocytopenia occurs at about 4 weeks postadministration and persists for 1 to 2 weeks. Leukopenia occurs at 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 5000 wbc/mm³ . Thirty-six percent developed white blood counts below 3000 wbc/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 leukemia and bone marrow dysplasias have been reported in patients following long-term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.**

**Pulmonary Toxicity:** Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely 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 1100 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 who received related nitrosoureas in childhood and early adolescence (1-16 years) combined with cranial radiotherapy for intracranial tumors. There appeared to be some late reduction of pulmonary function of all long-term survivors. This form of lung fibrosis may be slowly progressive and has resulted in death in some cases. In this long-term study of carmustine, all those initially treated at less than five years of age died of delayed pulmonary fibrosis.

**Gastrointestinal Toxicity:** Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. Prior administration of antiemetics is effective in diminishing and sometimes preventing this side effect. Nausea and vomiting can also be reduced if Lomustine is administered to fasting patients.

**Hepatotoxicity:** 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.

**Nephrotoxicity:** Renal abnormalities consisting of progressive azotemia, decrease in kidney size and renal failure have been reported in patients who received large cumulative doses after prolonged therapy with Lomustine. Kidney damage has also been reported occasionally in patients receiving lower total doses.

**Other Toxicities:** Stomatitis, alopecia, optic atrophy, and visual disturbances such as blindness have been reported infrequently-Neurological reactions such as disorientation, lethargy, ataxia, and dysarthria have been noted in some patients receiving Lomustine. However, the relationship to medication in these patients is unclear.

**OVERDOSAGE**

No proven antidotes have been established for Lomustine overdosage.

**DOSAGE AND ADMINISTRATION**

The recommended dose of Lomustine in adult and pediatric patients as a single agent in previously untreated patients is 130 mg/m² as a single oral dose every 6 weeks. In individuals with compromised bone marrow function, the dose should be reduced to 100 mg/m² every 6 weeks. When Lomustine is used in combination with other myelosuppressive drugs, the doses should be adjusted accordingly.

Doses subsequent to the initial dose should be adjusted according to the hematologic

| Nadir After Prior Dose | |
|---|---|
| **Leukocytes** | **Platelets** |
| >4000 | > 100,000 |
| 3000-3999 | 75,000-99,999 |
| 2000-2999 | 25,000-74,999 |
| <2000 | < 25,000 |

**A repeat course of Lomustine should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/ mm³; leukocytes above 4000/mm³) and this is usually in 6 weeks.**

Adequate number of neutrophils should be present on a peripheral blood smear. Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.

**STORAGE:**

Store in a well closed container at a temperature not more than 30° C
Store protected from light and humidity.
Keep medicine out of reach of children.

**SHELF LIFE:**
24 Months

**How Supplied**
A HDPE Jar of 10 Capsules

Manufactured by:

Bruck Pharma Private Limited

**Marketed by:**
**Mediclone Health Care Pvt Ltd.**
No.10/1 (Old-19/1) Lakshmipuram 2nd Street,
Royapettah, Chennai - 600 014

**Area Governo delle Risorse Strumentali- U.O.C. Acquisizione Beni e Servizi**
**Ufficio Acquisizione Farmaci e Diagnostici**

*San Camillo Forlanini*
*Prot. Uscita N. 0034272/2021*
*Del 28/09/2021*

0034272/2021

Ditta Profarma Italia
manuel.monopoli@profarmaitalia.com

**OGGETTO:** Richiesta offerta farmaco.

Codesta Ditta, qualora lo ritenga di propria convenienza e senza alcun impegno da parte di questa Azienda, è invitata a far pervenire una offerta per il seguente principio attivo necessario alle **esigenze dell'anno 2021**:

- N. 500 compresse LOMUSTINA 40 MG

Unitamente all'offerta economica, che rimarrà fissa e valida per tutto il periodo di fornitura, si chiede di **indicare obbligatoriamente l'eventuale costo per le spese di sdoganamento e trasporto.**

Considerato il carattere di estrema urgenza della richiesta, la risposta dovrà pervenire via mail all'indirizzo benieservizi@scamilloforlanini.rm.it entro il 30/9/2021.

Distinti saluti

Il Direttore
(Dott. Paolo Tarfusola)

PF/mt

**Unipharma SA**
Via Figino, 6
6917 – Barbengo Lugano – Switzerland
Tel. +41 91 985 62 11
Fax. +41 91 985 62 22
E-mail: sales@unipharma.ch

Cert. N°23997

# Offerta cliente

M-COM 05

| | | | |
|---|---|---|---|
| **DESTINATARIO** | 4688 | **OFFERTA N°** | 2021-21004215 |
| **Azienda:** | Ospedale C. Forlanini | **Città:** | Roma |
| **Persona di riferimento:** | Crocifissa GAGLIANO | **Reparto:** | Farmacia interna |
| **Fax:** | benieservizi@scamilloforlanini.rm.it | **Telefono:** | |
| **MITTENTE** | | | |
| **Autore messaggio:** | SAPORITO Ilenia | **Telefono:** | 0041 91 985 62 11 |
| **Cambio mese corrente** | EUR 0.94 (pari a CHF 1.00) | **Lugano,** | 29.09.2021 |

**Oggetto: Prot. N. 0034282/2021 - Lomustina**

Egregi signori,
con riferimento alla vostra richiesta in oggetto abbiamo il piacere di allegare: listino prezzi, costi di spedizione e condizioni di vendita.

Per ulteriori informazioni potete contattare i numeri seguenti:

**Ufficio vendite e pronta disponibilità**
Direttore: Maurizio Nanni
Collaboratori: Monica Colombo, Federico Wessel, Ilenia Saporito, Mariangela Li Greci

Orari d'ufficio da lunedì a venerdì $08^{00}$–$12^{00}$/$13^{00}$–$17^{30}$
E-mail: sales@unipharma.ch
Reperibilità nelle 24 ore al di fuori dell'orario d'ufficio telefonando semplicemente al numero abituale: 0041 91 985 62 11
Disponiamo del sito www.unipharma.ch al quale potete accedere per cercare i prodotti di cui necessitate.

**Centro di documentazione scientifica e servizio informazione sui farmaci svizzeri ed esteri**
Direttore tecnico: Antonella Calvelli, *farmacista*

*Banche dati*: Compendium, Rote Liste, Vidal, Pharmavista, Tropimed, Phyto, Martindale, Medical letter, Internet e vasta documentazione tratta da riviste, pubblicazioni, biblioteche, ecc.

| | | |
|---|---|---|
| **Ufficio di Sanità Aeroportuale** | Ciampino | Tel/Fax 06 7949 4220 |
| **Corriere TNT** | | Numero verde 199 803 868 |

Ci auguriamo che la nostra offerta sia di vostro interesse e, assicurandovi fin da ora un servizio rapido ed accurato, distintamente vi salutiamo.

UNIPHARMA SA

SAPORITO Ilenia

**Unipharma SA**
Via Figino, 6
6917 – Barbengo Lugano – Switzerland
Tel. +41 91 985 62 11
Fax. +41 91 985 62 22
E-mail: sales@unipharma.ch

Cert. N°23997

**Offerta cliente**

M-COM 05

# OFFERTA N°2021-21004215
# VALIDA DAL 29.09.2021 AL 29.10.2021

| Nr Art | Descrizione | Produttore | Titolare AIC | Origine | Conservazione | gg consegna | Prezzo EUR | Prezzo unitario EUR | Quantità | Totale |
|---|---|---|---|---|---|---|---|---|---|---|
| 59053 | Ceenu 40 mg 20 caps | Bristol Myers Squibb | Bristol Myers Squibb | Canada | temperatura ambiente | 3 | 264.17 | 13.20850 | 500 | 6'604.25 |

Composizione:

| Nr Art | Prodotto | DenominazionePrincipale | Dose |
|---|---|---|---|
| 59053 | Ceenu 40 mg 20 caps | Lomustinum (INN.L12.L) | 40 mg |

Costi di spedizione, imballo e sdoganamento:
Per spedizione in unica soluzione del materiale offerto, spedizione gratuita

**Totale offerta (IVA esclusa): EUR 6'604.25**

Note

CEENU 40 MG 20 CAPS: Attenzione: 5 confezioni disponibili immediatamente.

**Unipharma SA**
Via Figino, 6
6917 – Barbengo Lugano – Switzerland
Tel. +41 91 985 62 11
Fax. +41 91 985 62 22
E-mail: sales@unipharma.ch

Cert. N°23997

**Offerta cliente**

M-COM 05

# CONDIZIONI DI VENDITA UNIPHARMA SA

**Prezzi**

Tutti i prezzi comunicati per scritto si intendono in franchi svizzeri (CHF) o EURO, IVA esclusa e non includono il costo dell'imballaggio, del trasporto e dello sdoganamento.
In linea di massima vengono applicati i prezzi riportati nei listini in vigore e nelle offerte salvo variazioni di listino da parte del fornitore principale.

**Accettazione degli ordini**

Nessun valore minimo economico è richiesto.
Gli ordini vengono accettati con l'indicazione del prezzo in CHF o EURO al cambio concordato.

**Fatturazione**

Le fatture vengono emesse in CHF/EURO al cambio sopra menzionato.

**Termine di consegna**

Se un ordine al momento del suo arrivo si riferisce del tutto o in parte a merce non disponibile sarà nostra cura informare di ciò il cliente, avvisandolo dell'avvenuta ordinazione vincolante da parte nostra della merce che verrà riservata a suo nome.
Le spedizioni avvengono

- in giornata per le specialità registrate in Svizzera presso Swissmedic
- entro 20 giorni per le specialità da ordinare all'estero, conformemente alla disponibilità del fornitore principale.

La consegna al vostro domicilio è garantita entro e non oltre 48 ore dalla spedizione.

**Trasporto**

Le spese di trasporto, se non concordato diversamente, sono a carico del cliente.
I trasporti vengono effettuati secondo le indicazioni delle Aziende produttrici rispettando la catena del freddo, se necessario.

**Formalità doganali**

Ufficio di entrata della merce: Ciampino o Ponte Chiasso (CO)
La dichiarazione di Nulla osta è da intestare all'Ufficio doganale di sanità aerea di Ciampino.

**Consegna della merce**

La merce viene consegnata all'indirizzo indicato dal cliente con gli obblighi di dogana ed anticipo IVA e spese di trasporto già assolti.
Per l'IVA a carico del cliente, da noi anticipata e fatturata, sarà rimessa in originale la bolla doganale da allegare ai documenti contabili.

**Pagamento**

Le fatture devono essere saldate entro 90 giorni dalla data della fattura, versando l'importo sul nostro conto 247-959.570.62J – IBAN CH88 0024 7247 9595 7062J – Swift UBSWCHZH80A presso UBS SA – 6900 Lugano

**Garanzia**

Per i danni riscontrati all'arrivo dev'essere fatta riserva al vettore. Altri danni (difetti del materiale, consegna errata o quantità mancanti) devono esserci comunicati entro 8 giorni dal ricevimento della merce. I reclami avanzati oltre tale termine non potranno più essere presi in considerazione. La nostra responsabilità cessa alla consegna del prodotto.
Escludiamo ogni responsabilità per danni causati alle persone, alle cose o ai beni dall'utilizzo della merce oggetto della fornitura. Sono escluse le richieste di risarcimento di clienti o terzi destinate a riparare eventuali danni causati dall'utilizzo della merce oggetto dei fornitura, quindi di null'altro – in particolare secondo i principi di responsabilità del prodotto – salvo diversamente prescritto per legge.

**Ritorni**

Ritorni di merce sono accettati solo se preventivamente concordati.

**Richiamo del prodotto**

In caso di ritiro di specialità o di un lotto per ragioni di sicurezza da parte del fabbricante, il cliente viene immediatamente informato. Il cliente dovrà comunicare ad Unipharma il numero di pezzi giacenti presso i propri magazzini e procedere al reso entro 7 giorni dal ricevimento dell'avviso di richiamo. A ricevimento della merce verrà emessa nota di credito.

**Foro competente**

Per qualsiasi controversia, se non diversamente concordato, viene applicato il Diritto Svizzero: il foro competente è quello di Lugano.

# PRODUCT MONOGRAPH

## PrCeeNU*

**(Lomustine-CCNU)**

**Capsules; 10, 40 and 100 mg**

**Antineoplastic Agent**

Bristol-Myers Squibb Canada
Montreal, Canada, H4S 0A4

Date of Preparation:

4 July 1974

* TM of Bristol-Myers Squibb Company
used under license by Bristol-Myers Squibb Canada

Date of Revision:
February 17, 2016

Submission control no.: 188932

# PRODUCT MONOGRAPH

## NAME OF DRUG

**CeeNU**

**(Lomustine - CCNU)**

Capsules; 10, 40 and 100 mg

## THERAPEUTIC CLASSIFICATION

Antineoplastic Agent

CAUTION: CeeNU (LOMUSTINE-CCNU) IS A POTENT DRUG AND SHOULD BE USED ONLY BY PHYSICIANS EXPERIENCED WITH CANCER CHEMOTHERAPEUTIC DRUGS (SEE WARNINGS AND PRECAUTIONS). BLOOD COUNTS AS WELL AS RENAL AND HEPATIC FUNCTION TESTS SHOULD BE TAKEN REGULARLY. DISCONTINUE THE DRUG IF ABNORMAL DEPRESSION OF BONE MARROW IS SEEN.

## ACTION AND CLINICAL PHARMACOLOGY

It is generally agreed that CeeNU (lomustine-CCNU) acts as an alkylating agent but, as with other nitrosoureas, it may also inhibit several key enzymatic processes.

CeeNU may be given orally. Following oral administration of radioactive CeeNU at doses ranging from 30 mg/m$^2$ to 100 mg/m$^2$about half of the radioactivity given was excreted within 24 hours. The serum half-life of the drug and/or metabolites ranges from 16 hours to 2 days. Tissue levels are comparable to plasma levels at 15 minutes after intravenous administration.

Because of the high lipid solubility and the relative lack of ionization at a physiological pH, CeeNU crosses the blood-brain barrier quite effectively. Levels of radioactivity in the CSF are 50 percent or greater than those measured concurrently in plasma.

## INDICATIONS AND CLINICAL USES

CeeNU (lomustine-CCNU) is indicated as palliative therapy in addition to surgery and radiotherapy or in combination therapy with other chemotherapeutic agents in the following:

1. Brain tumors - both primary and metastatic, in patients who have already received appropriate surgical and/or radiotherapeutic procedures.

2. Hodgkin's Disease – as a secondary therapy, alone or in combination with other active drugs.

**Other Tumors** – CeeNU has been used in combination with other therapeutic agents in lung cancer (squamous cell, anaplastic large cell, and adenocarcinoma), malignant melanoma and breast cancer (advanced disease) only after other conventional methods have failed.

## CONTRAINDICATIONS

CeeNU (lomustine-CCNU) should not be given to individuals who have demonstrated a previous hypersensitivity to it. Also it is contraindicated in patients having severe leukopenia and/or thrombocytopenia.

## WARNINGS

CeeNU (lomustine-CCNU) should be administered by individuals experienced in the use of antineoplastic therapy.

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 CeeNU.

Blood counts should be monitored weekly for at least 6 weeks after a dose (see ADVERSE REACTIONS). At the recommended dosage, courses of CeeNU should not be given more frequently than every 6 weeks.

The bone marrow toxicity of CeeNU is cumulative and therefore dosage adjustment must be considered on the basis of nadir blood counts from prior dose (see Dosage Adjustment Table under DOSAGE AND ADMINISTRATION).

Caution should be used in administering CeeNU to patients with decreased circulating platelets, leukocytes or erythrocytes (see DOSAGE AND ADMINISTRATION).

Pulmonary toxicity including pulmonary infiltration and fibrosis (often fatal) from CeeNU appears to be dose related (see ADVERSE REACTIONS).

Liver and renal function tests should be monitored periodically (see ADVERSE REACTIONS).

Concomitant use of CeeNU with a live virus vaccine may potentiate the replication of the vaccine virus and/or may increase the adverse reaction of the vaccine virus because normal defense mechanisms may be suppressed by CeeNU. Vaccination with a live vaccine in a patient taking CeeNU may result in severe infection. Patient's antibody response to vaccines may be decreased. The use of live vaccines should be avoided and individual specialist advice sought (see PRECAUTIONS, Drug Interactions).

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

CeeNU is carcinogenic in rats and mice, producing a marked increase in tumour incidence in doses approximating those employed clinically.

Nitrosourea therapy does have carcinogenic potential. Long-term use of nitrosoureas has been reported to be possibly associated with the development of secondary malignancies. The occurrence of acute leukemia and bone marrow dysplasias has been reported in patients following nitrosourea therapy.

CeeNU can have a mutagenic effect. Men treated with CeeNU 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 CeeNU therapy. CeeNU also affects fertility in male rats at doses somewhat higher than the human dose.

**Pregnancy**

Safe use in pregnancy has not been established. CeeNU is embryotoxic and teratogenic in rats and embryotoxic in rabbits at dose levels equivalent to the human dose. If this drug is used during pregnancy, or if the patient becomes pregnant while taking (receiving) this drug, the patients should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

**Nursing Mothers**

Due to the lipophilic nature of CeeNU, it is likely to be excreted in breast milk. As a risk to the nursing child exists, a decision should be made whether to discontinue breastfeeding or to discontinue CeeNU therapy.

## PRECAUTIONS

Due to delayed bone marrow suppression, blood counts should be monitored weekly for at least six weeks after a dose.

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 ($DL_{co}$) are particularly at risk.

Since CeeNU (lomustine-CCNU) may cause liver dysfunction, it is recommended that liver function tests be monitored periodically.

Renal function tests should also be monitored periodically.

**Effects on ability to drive and to use machines**

No studies on the effects on the ability to drive and use machines have been performed.

**Drug Interactions**

No drug interaction studies have been performed. It is unknown which hepatic enzymes are involved in lomustine-CCNU metabolism in humans. Animal studies suggest that CYP2C19, CYP2D6 and CYP3A4 are involved.

Drug-drug interactions of CeeNU with anti-epileptic drugs

Co-administration of some antiepileptic drugs and CeeNU can lead to complications secondary to pharmacokinetic interactions between the drugs.

Co-administration of enzyme-inducing antiepileptic drugs (e.g., carbamazepine, and phenytoin) may result in decreased blood concentration and reduced efficacy of CeeNU. Concurrent use of CeeNU with enzyme-inducing antiepileptic drugs should be avoided.

Co-administration of valproic acid or other enzyme-inhibiting drugs may impair the metabolism and increase the toxicity of CeeNU. Caution should be exercised when valproic acid and CeeNU are co-administered.

The toxic effects of valproic acid may be increased when combined with CeeNU.

Co-administration of CeeNU with phenytoin may lead to a decrease of phenytoin levels and a decrease in seizure control.

Other Interactions

There is increased risk of fatal systemic vaccine disease with the concomitant use of live vaccines. Live vaccines are not recommended in immunosuppressed patients including patients treated with CeeNU (see WARNINGS).

## ADVERSE REACTIONS

1. Gastrointestinal: Nausea and vomiting may occur 3 to 6 hours after an oral dose and usually lasts less than 24 hours. The frequency and duration may be reduced by the use of antiemetics prior to dosing and by the administration of CeeNU (lomustine-CCNU) to fasting patients.

2. Hematologic Toxicity: The most frequent and most serious toxicity of CeeNU is delayed myelosuppression. It usually occurs four to six weeks after drug administration and is dose related. Thrombocytopenia occurs at about four weeks post-administration and persists for one to two weeks. Leukopenia occurs at five to six weeks after a dose of CeeNU and persists for one to two weeks.

   Approximately 65% of patients receiving 130 mg/m$^2$ develop white blood counts below 5000 /mm$^3$. Thirty-six percent developed white blood cell counts below 3000 /mm$^3$. Thrombocytopenia is generally more severe than leukopenia. However, both may be dose-limiting toxicities.

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

The occurrence of acute leukemia and bone marrow dysplasias have been reported in patients following long term nitrosourea therapy. Anemia also occurs, but is less frequent and less severe than thrombocytopenia or leukopenia.

3. Pulmonary Toxicity: Pulmonary toxicity characterized by pulmonary infiltrates and/or fibrosis has been reported rarely with CeeNU. Onset of toxicity has occurred after an interval of six months or longer from the start of therapy with cumulative doses of CeeNU usually greater than 1100 mg/m$^2$. There is one report of pulmonary toxicity at a cumulative dose of only 600 mg.

   Over a 25 years follow-up time of 17 childhood / adolescent cancer survivors of intracranial tumors treated with a related nitrosourea, 2 (12%) died of early onset pulmonary fibrosis (between 0-3 years post treatment) and 7 (41%) died of late onset pulmonary fibrosis (between 6 and 25 years post treatment). Of the remaining eight patients, seven had radiologic and physiologic (*i.e.*, lung function) evidence of upper zone pulmonary fibrosis. Patients treated at younger age seemed to be at greater risk of developing pulmonary fibrosis.

4. Other Toxicities: Stomatitis, alopecia, anemia have been reported infrequently.

   Neurological reactions such as disorientation, lethargy, ataxia and dysarthria have been noted in some patients receiving CeeNU. However, the relationship to medication in these patients is unclear.

5. Nephrotoxicity: Renal abnormalities consisting of decrease in kidney size, progressive azotemia and renal failure have been reported in patients who receive large cumulative doses after prolonged therapy with CeeNU and related nitrosoureas. Kidney damage has also been reported occasionally in patients receiving lower total doses.

6. Hepatotoxicity: 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 CeeNU.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

For management of a suspected drug overdose, please contact your regional Poison Control Centre.

Accidental overdose with CeeNu (lomustine-CCNU) has been reported, including fatal cases. Accidental overdose has been associated with bone marrow suppression, abdominal pain, diarrhea, vomiting, anorexia, lethargy, dizziness, abnormal hepatic function, cough, and shortness of breath.

There is no specific antidote for overdose with CeeNU. In the case of overdosage, appropriate supportive measures should be taken.

Because of the lipophilic nature of the drug, the product is not dialyzable.

## DOSAGE AND ADMINISTRATION

The recommended dose of CeeNU (lomustine-CCNU) is 130 $mg/m^2$ as a single dose by mouth every 6 weeks (see SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL).

In individuals with compromised bone marrow function, the dose should be reduced to 100 $mg/m^2$ every 6 weeks.

A repeat course of CeeNU should not be given until circulating blood elements have returned to acceptable levels (platelets above 100,000/$mm^3$; leukocytes above 4,000/$mm^3$). Blood counts should be monitored weekly and repeat courses should not be given before 6 weeks because the hematologic toxicity is delayed and cumulative.



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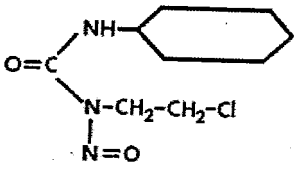
Doses subsequent to the initial dose should be adjusted according to the hematologic response of the patient to the preceding dose. The following schedule is suggested as a guide to dosage adjustment:

| Nadir After Prior Dose | | Percentage of Prior Dose to be Given |
|---|---|---|
| **Leukocytes (/mm$^3$)** | **Platelets (/mm$^3$)** | |
| ≥4000 | ≥100,000 | 100% |
| 3000 - 3999 | 75,000 - 99,999 | 100% |
| 2000 - 2999 | 25,000 - 74,999 | 70% |
| < 2000 | < 25,000 | 50% |

When CeeNU is used in combination with myelosuppressive drugs, the doses should be adjusted accordingly.

## PHARMACEUTICAL INFORMATION

**Chemistry:**




**Trade Name:** CeeNU

**Proper Name:** Lomustine

**Chemical Name:** 1-(2-chloroethyl)-3 cyclohexyl-1-nitrosourea

**Molecular Formula:** $C_9H_{16}ClN_3O_2$

**Molecular Weight:** 233.71

**Description:** Yellow powder. Soluble in 10% ethanol (0.05 mg/mL) and in absolute alcohol (70 mg per mL). It is relatively insoluble in water (<0.05 mg/mL). It is relatively un-ionized at a physiological pH.

## STABILITY

Unopened bottles of CeeNU (lomustine-CCNU) capsules are stable for 36 months at room temperature.

**Storage:** PROTECT FROM LIGHT. Avoid excessive heat (over 40EC).

## AVAILABILITY

The capsules of CeeNU (lomustine-CCNU) are prepared in three dosage strengths: 10 mg, 40 mg, and 100 mg.

All capsules contain mannitol and magnesium stearate as inert ingredients.

CeeNu capsules are available as follows:

- 10 mg in bottles of 20 capsules
- 40 mg in bottles of 20 capsules
- 100 mg in bottles of 20 capsules

## SPECIAL INSTRUCTIONS FOR USE, HANDLING AND DISPOSAL

1. Only the appropriate number of CeeNU (lomustine-CCNU) capsules required for a single administration should be dispensed. Patients should be told that CeeNU is taken as a single oral dose and will not be repeated for at least 6 weeks.

2. Preparation of CeeNU should be done in a vertical laminar flow hood (Biological Safety Cabinet - class II)

3. CeeNU capsules should not be placed in automated counting machines. The counting and pouring of CeeNU should be done carefully and the equipment used should be rinsed with water and then thoroughly cleaned with detergent and water.

4. Personnel handling CeeNU should wear gloves, safety glasses, a mask and disposable protective clothing.

5. Vials and other materials which have come in contact with CeeNU should be segregated and incinerated at 1000EC or more. Sealed containers may explode. Intact vials should be returned to the manufacturer for destruction. Proper precautions should be taken in packaging these materials for transport.

6. Personnel regularly involved in the preparation and handling of CeeNU should have bi-annual blood examinations.

## PHARMACOLOGY

The following is a summary of the data provided by the studies indicated in the attached list of references.

Kline et al used a biological procedure for the determination of drug levels of CeeNU (lomustine-CCNU). The biological target was L1210 leukemia. A dose response curve was determined for the drug when given simultaneously with the inoculation of a designated number of leukemia cells, using % of cures and median survival time as the parameters of response. The drug was also administered at a series of time intervals prior to the inoculation of leukemia cells and the dose level equivalence at the time of leukemic inoculation was estimated by reference of the observed therapeutic response to that obtained for the standard curve. The curve for percentage retention of administered CeeNU had a shallow slope and the half-life of the drug in the host was estimated to be 94 minutes.

Oliverio et al studied the metabolic fate of CeeNU using the $^{14}C$ label in each of three positions of the molecule; the ethyl, carbonyl, and cyclohexyl moieties. In rodents, 24 hours after intraperitoneal or oral dose of the ethyl or cyclohexyl labelled CeeNU, 75% of the radioactivity appeared in the urine, while about 10-20% of carbonyl or ethyl labelled CeeNU was expired as $^{14}CO_2$. In dogs and monkeys, CeeNU was also rapidly degraded and excretion of $^{14}C$ was primarily in the urine. Plasma levels of $^{14}C$ fell off rapidly in the first hour followed by a slower disappearance. After an intravenous injection, the CSF/plasma ratio of ethyl labelled CeeNU was three, while that for the cyclohexyl-labelled moiety was unity. This agrees with the observation that the cyclohexyl portion of the molecule is 60% plasma protein bound while the ethyl portion is not bound. The results support the suggested intermediate formation of an isocyanate moiety during the degradation of nitrosoureas *in vivo*. The identified metabolites and cyclohexylisocyanate were inactive against L-1210.

Studies conducted to determine the effects of NSC 79037 in polyethoxylated vegetable oil and normal saline (ratio of 1:9) applied topically to the hamster cheek pouch revealed no thromboembolism as concentrations 2.5 mg/ml. The only effect produced with this concentration was a slight decrease in the rate of venule and arteriole blood flow in 1/6 hamsters and a slight to moderate decrease in the venule flow of a second animal. Administration of a concentration at 0.625 mg/ml or the vehicle alone produced no detectable effect.

No thromboembolism was observed in the hamster cheek pouch microcirculation after single intrajugular injections of CeeNU in polyethoxylated vegetable oil and normal saline at doses ranging from 0.3125 to

20.0 mg/kg. However, a dosage of 0.625, 1.25, 2.5, 5.0, 10.0 or 20.0 mg/kg produced a decrease in cheek pouch venule blood flow varying from slight to moderate-severe. A slight to moderate-severe decrease in blood flow was also noted in the arterioles at drug levels ranging from 1.25 to 20 mg/kg with some vasoconstriction recorded at the 3 highest levels. At 20.0 mg/kg WBC stickiness was reported only once. The "no effect" level appeared to be 0.3125 mg/kg. Injection of the vehicle alone at volumes equivalent to those employed with 2.5, 5.0, 10.0, and 20.0 mg/kg drug dosages produced some vasoconstriction and a decrease in the rate of arteriole and venule blood flow. Microcirculation appeared normal when the vehicle alone was injected at a volume equivalent to that of a 1.25 mg/kg drug dosage. A mean recovery time of 17 minutes (5-35) was required for normal flow after intravenous injection in hamsters treated with the drug, compared to a mean recovery period of 6 minutes (2-10) in those receiving only the polyethoxylated vegetable oil and saline vehicle. It was concluded that cardiovascular effects observed were, in part, due to the vehicle employed.

Comparison of mortality levels in mice and rats for single oral doses of BiCNU and CeeNU on a mg/kg, $mg/m^2$, or mmole/kg basis revealed that BiCNU was twice as toxic as CeeNU.

## TOXICOLOGY

The toxicity of CeeNU (lomustine-CCNU) was investigated primarily by the Mason Research Institute under contract with the National Cancer Institute. The parenteral toxicity of CeeNU may be summarized as follows:

a) Single Dose (IV infusion):

Dog: Maximum tolerated dose (MTD) - 0.625 mg/kg
Primary toxicity = Depressed hematopoiesis, lymphoid tissue.
Secondary toxicity - Delayed hepatotoxicity

Rhesus Monkey: MTD = 1.25 mg/kg
Primary toxicity = nephrotoxicity
Secondary toxicity - Depressed hematopoiesis, hepatotoxicity.

b) Multiple Dose (IV infusion):

Dog: 2 or 3 doses of 1.25 mg/kg given at weekly intervals = cumulative hepatotoxicity.

The toxicity of CeeNU given orally may be summarized as follows:

a) Single Dose (capsules)

Dog: MTD = 2.0 mg/kg

b) Multiple Dose (capsules - dog, gavage - monkey)

Dog: MTD - 0.65 mg/kg/day x 14
Rhesus Monkey: MTD = 0.15 mg/kg/day x 14

c) Delayed Hepatotoxicity (capsules)

Dog: A single oral dose of 4 mg/kg produced hepatotoxicity that persisted for 2-3 months after drug treatment.

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**MODELLO 10-1**

**Allegato 10**

**AL MINISTERO DELLA SALUTE**
**USMAF-SASN**
**UFFICIO DOGANALE DI** _____

**Richiesta di importazione di medicinali ai sensi del D.M. 11/02/1997.**

Il sottoscritto Medico curante Dr. _____

residente in _____ prov. _____ via _____

tel. _____ iscritto nell'Albo dell'Ordine dei Medici-Chirurghi di _____

al n. _____ codice regionale _____

operante presso il Reparto / Divisione di _____

dell'Ospedale/ASL _____

chiede di importare dall'estero il seguente medicinale:

Principio/i attivo/i: Lomustinum (INN.L12.L)
Nome commerciale: ceenu
Forma farmaceutica: capsule
Dosaggio specialità: 40 mg
Nella quantità di nr.: _____ confezioni contenenti nr. 20 unità di farmaco cadauna
Prodotto dalla ditta: Bristol Myers Squibb
Titolare estero AIC: Bristol Myers Squibb
Precisa che tale medicinale è regolarmente registrato nel Paese di provenienza: Canada
Per il trattamento di: _____
Tale medicinale è indispensabile per la cura del Sig. (solo iniziali o codice): _____
Affetto da: _____
Motivo per cui viene richiesta la scorta di reparto*: _____

Dichiara altresì che il farmaco:

- non ha valida alternativa terapeutica con altri medicinali registrati in Italia;
- non contiene sostanze stupefacenti o psicotrope;
- non è un emoderivato;
- verrà impiegato sotto la propria diretta responsabilità, dopo aver ottenuto il consenso informato scritto del paziente o, in caso di minori o incapaci, di chi esercita la patria potestà;
- che le generalità del paziente ed i documenti relativi al consenso informato sono custoditi presso il medico curante per la durata prevista dalla normativa vigente;
- in caso di richiesta per scorta, che il quantitativo richiesto non supera i 90 giorni di terapia per paziente.

Particolari condizioni di conservazione del medicinale:
Temperatura (es. -20°C, da 2 a 8°C, <25°C, <30°C, nessuna indicazione): temperatura ambiente

Altro: _____

Luogo e data: _____

**Il Dirigente del Servizio Farmaceutico**
***Timbro e firma leggibile per esteso***

**Il Medico Curante**
***Timbro e firma leggibile per esteso***

**Da compilare solo in caso di richiesta di importazione per costituire una scorta di reparto*

**Area Governo delle Risorse Strumentali- U.O.C. Acquisizione Beni e Servizi**
**Ufficio Acquisizione Farmaci e Diagnostici**

*San Camillo Forlanini*
*Prot. Uscita N. 0034282/2021*
*Del 28/09/2021*

0034282/2021

Ditta Unipharma
wessel@unipharma.ch

**OGGETTO:** Richiesta offerta farmaco.

Codesta Ditta, qualora lo ritenga di propria convenienza e senza alcun impegno da parte di questa Azienda, è invitata a far pervenire una offerta per il seguente principio attivo necessario alle **esigenze dell'anno 2021**:

- N. 500 compresse LOMUSTINA 40 MG

Unitamente all'offerta economica, che rimarrà fissa e valida per tutto il periodo di fornitura, si chiede di **indicare obbligatoriamente l'eventuale costo per le spese di sdoganamento e trasporto.**

Considerato il carattere di estrema urgenza della richiesta, la risposta dovrà pervenire via mail all'indirizzo benieservizi@scamilloforlanini.rm.it entro il 30/9/2021.

Distinti saluti

Il Direttore
(Dott. Paolo Farinsola)

PF/mt

# U.O.C. Programmazione Strategica e Controllo di Gestione

## ALLEGATO " ASSUNZIONE AUTORIZZAZIONI "

*Il presente Allegato costituisce parte integrante della proposta*

*di deliberazione :* BSDG 366 / 2021

*Il Dirigente addetto al controllo del budget, con la sottoscrizione del presente atto, attesta che lo stesso non comporta scostamenti sfavorevoli rispetto al budget economico/investimenti generale aziendale.*

*Voce del Conto Economico / Patrimoniale su cui si imputa la spesa:*

| Scheda Budget N° | SUB N° | Mod N° | Conto | Budget 2021 | Utilizzato | Presente prenotazione | Residuo disponibile |
|---|---|---|---|---|---|---|---|
| 1 | 34 | | 501010113000 | 192.485,00 | 191.205,00 | 180,89 | 1099,11 |
| 1 | 35 | | 502020107000 | 135.000,00 | 102.452,74 | 16,5 | 32.530,76 |
| | | | | | | | |
| | | | | | | | |
| | | | | | | | |
| TOTALE PRESENTE AUTORIZZAZIONE € : | | | | | | | |

| Conto Economico/Patrimoniale | DESCRIZIONE |
|---|---|
| 501010113000 | MEDICINALI ESTERI |
| 502020107000 | SERV. TRASP (NON SANITARI) |
| | |
| | |

Data 05/10/2021

*Il Direttore:* Dr.ssa Miriam Piccinini ..... (Firma)