AUSTRALIAN PI:
MUPHORAN® (FOTEMUSTINE) POWDER FOR INJECTION VIAL AND DILUENT AMPOULE

1 NAME OF THE MEDICINE

Fotemustine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 208 mg of fotemustine. The reconstituted solution has a volume of 4.16 mL (i.e. 200 mg of fotemustine in 4 mL of solution).

Diluent with known effects: ethanol, (*see section 6.1 - List of excipients*).

Fotemustine is a pale yellow powder that in accordance with the standards of the European Pharmacopoeia, is slightly soluble in water and soluble in 95% ethanol. An infrared spectrophotometric study carried out on several batches showed no polymorphism.

Fotemustine is a cytostatic anticancer agent of the nitrosourea family with an alkylating and carbamoylating effect with a wide spectrum of experimental antitumoral activity.

3 PHARMACEUTICAL FORM

Sterile powder, and 4 mL diluent for injection.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

The indication "disseminated malignant melanoma", including cerebral metastases, is currently the preferential indication for fotemustine, administered alone or in combination with other anticancer agents.

4.2 DOSE AND METHOD OF ADMINISTRATION

Prepare the solution immediately prior to administration (*see sections 4.4. - Special warnings and precautions for use* and *section 6.4 Special precautions for storage*). Solutions of fotemustine are unstable when exposed to light.

To avoid microbial contamination, the diluted solution must be used as soon as practicable after preparation and any unused solution discarded.

Before starting the fotemustine infusion, verify that the intravenous tube has been placed correctly in the patient in order to avoid extravasation. In case of extravasation, stop the infusion, wash the vein abundantly with 5 % glucose solution (4 mL/min), immobilise the limb and cool with an ice bag to avoid the diffusion of the infusion solution. Aspire the extravasated volume as much as possible and immobilise the limb in an elevated position.

Dissolve the vial of fotemustine with the ampoule of 4 mL of sterile alcohol solution, then, after calculating the dose to be injected, dilute the solution in 5 % isotonic glucose solution for administration by intravenous infusion.

The solution prepared in this way must be administered, protected from light:

- by intravenous infusion over one hour

- by intra-arterial infusion over four hours

In single-agent chemotherapy, treatment consists of:

Induction treatment

Three consecutive administrations at one week intervals, followed by a therapeutic rest period of four to five weeks.

Maintenance treatment

One administration every three weeks.

Blood counts should be performed frequently (see *section 4.4. Special warnings and precautions for use*). It is also recommended to regularly monitor liver function tests during or following induction treatment.

Combination chemotherapy

In combination chemotherapy, the third administration of the induction treatment is omitted. The dose remains 100 mg/m2.

Combination with dacarbazine

Simultaneous administration with dacarbazine should be avoided as rare cases of pulmonary toxicity (adult acute respiratory distress syndrome) have been observed when MUPHORAN (fotemustine) is combined simultaneously, on the same day, with high doses of dacarbazine *(see section 4.5 - Interactions with other medicines and other forms of interactions).*

4.3 CONTRAINDICATIONS

MUPHORAN (fotemustine) is contraindicated:

- in children and adolescents as the benefit/risk ratio has not been established in this population
- in pregnant women due to the known mutagenic and carcinogenic potential of nitrosoureas *(see section 4.6 - Fertility, pregnancy and lactation)*
- for lactating women (*see section 4.6 - Fertility, pregnancy and lactation*)
- in combination with the yellow fever vaccine (*see section 4.5 - Interactions with other medicines and other forms of interactions*)
- in patients with a hypersensitivity to fotemustine, any of the excipients or to nitrosureas.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Avoid any contact with skin, mucosa and any absorption of the reconstituted solution. It is recommended to wear a protective mask and gloves during the preparation of the solution. In event of contact with MUPHORAN (fotemustine), rinse affected area thoroughly with water. Contaminated equipment should be disposed of appropriately (*see section 4.2 - Dose and method of administration).*

Use of MUPHORAN (fotemustine) with live attenuated vaccines or phenytoin is not recommended (*see section 4.5 - Interactions with other medicines and other forms of interactions*).

MUPHORAN (fotemustine) should only be used by experienced cancer physicians in institutions with facilities for the monitoring and management of any post-treatment adverse effects.

Treatment should only be considered when the platelet count and/or granulocyte count is acceptable, with minimum values of 100,000/mm^3 and 2000/mm^3 respectively.

Haematological status

Administration of MUPHORAN (fotemustine) to patients who have already received chemotherapy in the previous four weeks (or six weeks in the case of previous treatment with a nitrosourea) is not recommended.

Blood counts should be performed before each new administration and doses should be adjusted according to the haematological status. The following table may be used as a guide.

Post-dose Haematological status		**Percentage of first dose to be administered for a new course**
Platelets (/mm^3)	**Granulocytes (/mm^3)**	
> 100,000	> 2,000	100 %
100,000 ≥ N > 80,000	2,000 ≥ N > 1,500	75 %
	1,500 ≥ N > 1,000	50 %
N ≤ 80,000	≤ 1,000	N/A - treatment to be postponed

An interval of eight weeks is recommended between the start of induction treatment and the start of maintenance treatment. An interval of three weeks is recommended between two cycles of maintenance treatment.

Maintenance treatment should only be considered when the platelet count and/or granulocyte count is acceptable, with minimum values of 100,000/mm^3 and 2,000/mm^3, respectively.

Liver function tests

Regular monitoring of liver function tests during or following induction treatment is recommended.

Use in patients with alcohol-related disorders

A single vial of MUPHORAN (fotemustine) reconstituted contains 3.35 mL of 96 % ethanol (equivalent to 1.3 g of alcohol per 100mg of fotemustine, equivalent to 32 mL of beer, 13.3 mL of wine) this quantity of alcohol may be harmful to patients suffering from alcoholism and should be taken into consideration in patients with liver disease or epilepsy.

Extravasation

Before commencing the fotemustine infusion, check that the intravenous tube has been placed correctly in the patient in order to avoid extravasation. In case of extravasation, stop the infusion, aspire the extravasated volume as fast as possible and immobilise the limb in an elevated position (*see section 4.2 - Dosage and method of administration*).

Preclinical ophthalmoscopic observations

Fotemustine caused retinal atrophy in rats and retinal detachment in monkeys, at plasma concentrations similar to those observed following IV infusion of the therapeutic dose to patients. The significance of this to humans is unknown. Ophthalmoscopic examinations should be carried out routinely during treatment.

Use in hepatic impairment

There have been no specific studies of MUPHORAN (fotemustine) in this population.

Regular monitoring of liver function tests during or following induction treatment is recommended (*see sections 4.2 - Dosage and method of administration and 4.4 - Special warnings and precautions- Liver function tests*).

Use in renal impairment

Standard doses of MUPHORAN (fotemustine) in a small number of patients presenting with renal impairment did not result in any changes in urea or creatinine. However in the absence of long term experience in a wider patient population it is recommended that patients with impaired renal function be closely monitored.

Use in the elderly

The toxicity of MUPHORAN (fotemustine) has been compared in patients below and above the age of 60 years. Thrombopenia (Grade 3), leukopenia (Grade 3) and gastro-intestinal toxicity (Grade 3) were significantly more frequent in patients over 60 years.

Paediatric use

MUPHORAN is contraindicated in children and adolescents as the benefit/risk ratio has not been established in this population *(see section 4.3 - Contraindications)*.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interaction studies have been performed with MUPHORAN (fotemustine).

No interaction has been observed between MUPHORAN (fotemustine) and medicines acting on the central nervous system such as analgesics, neuroleptics, anxiolytics and those for Parkinson's disease. No interaction with metoclopramide has been reported and there is no data concerning interaction between antiemetic 5HT3 antagonists. The low gastrointestinal toxicity of fotemustine does not usually require such therapy.

Combined use which is contraindicated (see *section 4.3 – Contraindications* and *section 4.4 - Special warnings and precautions for use*)

Combination of MUPHORAN (fotemustine) and yellow fever vaccine is contraindicated due to the risk of fatal systemic vaccine-induced disease (*see section 4.3 - Contraindications*).

Combined use not recommended (see *section 4.4 - Special warnings and precautions for use*):

Phenytoin

Combination of MUPHORAN (fotemustine) and phenytoin is not recommended due to the risk of seizures through decreased gastrointestinal absorption of phenytoin by MUPHORAN (fotemustine),

or risk of enhanced toxicity or loss of efficacy of MUPHORAN (fotemustine) through an increase in its hepatic metabolism by phenytoin.

Live attenuated vaccines (except yellow fever)

Combination of MUPHORAN (fotemustine) and live attenuated vaccines is not recommended due to the risk of systemic vaccine-induced disease, which can be fatal. This risk is increased in subjects who are already immunosuppressed due to the underlying disease. Use an inactivated vaccine when such a vaccine exists.

Combined use which requires caution:

Immunosuppressants

Caution is recommended with the combination of MUPHORAN (fotemustine) and immunosuppressants due to the possibility of excessive immunosuppression with risk of lymphoproliferation.

Combined use specific to MUPHORAN (fotemustine):

Dacarbazine

Do not administer MUPHORAN (fotemustine) and dacarbazine simultaneously. An interval of one week should be left between the last administration of MUPHORAN (fotemustine) and the first day of a course of dacarbazine (*see section 4.2 - Dose and method of administration*).

With high doses of dacarbazine:

As pulmonary toxicity (acute respiratory distress syndrome) has been observed following the sequential administration of dacarbazine-fotemustine, likely due to O6 alkyltransferase inhibition provoked by a high dose of dacarbazine, this mode of administration should be avoided.

Combined use common to cytotoxics

Anticoagulants

Anticoagulant treatments are commonly used in neoplastic disease due to the increased risk of thrombosis. If patients are treated with oral anticoagulants, the INR should be checked more frequently because of the considerable variation in blood clotting during the course of these diseases, which is complicated by the risk of interaction that exists between oral anticoagulants and antineoplastic chemotherapy.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Fotemustine affected fertility in male dogs. Complete azospermia was observed at doses of ≥ 3.5 mg/kg (about 70 mg/m^2) IV in a one year study, using the clinical therapeutic protocol. Testicular atrophy was seen in rats given ≥ 22.5 mg/kg/week for four weeks.

Use in pregnancy

Use of MUPHORAN (fotemustine) is contraindicated in pregnant women and women of childbearing potential who are not using effective contraception *(see section 4.3 - Contraindications)*. MUPHORAN (fotemustine) should be used in conjunction with effective contraception in women of childbearing potential.

No reproductive studies have been carried out with fotemustine because of its reactivity. However, related nitrosoureas have been shown to be teratogenic and embryotoxic in animal studies.

Information for male patients.

Male patients should be advised to use effective contraception while taking MUPHORAN (fotemustine).

Use in lactation

Use of MUPHORAN (fotemustine) in lactating women is contraindicated *(see section 4.3 - Contraindications).*

There is no data on the effects of MUPHORAN (fotemustine) in lactating women. As it is unknown whether fotemustine or its metabolites are excreted in human milk, the risk to newborns/infants cannot be excluded.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

While no studies on the effects on the ability to drive vehicles and use machines have been performed, driving is not advisable immediately following the administration of MUPHORAN (fotemustine).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of safety profile

The main adverse effects observed during clinical trials were haematological, and could affect the three blood lines. This toxicity is delayed and characterised by anaemia, thrombocytopenia and leukopenia (all commonly observed) with nadirs occurring respectively four to five weeks and five to six weeks after the first dose of the induction treatment. Pancytopenia may also occur.

The haematological toxicity may be accentuated in patients who have previously received chemotherapy and/or in combination with other drugs likely to induce haematopoietic toxicity.

Increased haematological and gastrointestinal toxicity may be observed in the elderly.

Tabulated list of adverse effects

The following undesirable effects have been observed during treatment with MUPHORAN (fotemustine) and ranked under the following frequency:

Very common (> 1/10); common (> 1/100, < 1/10); uncommon (> 1/1,000, < 1/100); rare (> 1/10,000, < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from the available data).

MedDRA System organ class **Undesirable Effects**	**Frequency**
Blood and lymphatic system disorders	
Thrombocytopaenia	Very common
Leucopaenia (grade 3-4)	

Anaemia (grade 3-4)	
Nervous system disorders	
Transient neurologic disorders without sequela (disorders of consciousness, paresthesia, ageusia)	Uncommon
Gastrointestinal disorders	
Nausea	Very common
Vomiting within 2 hours following administration	
Diarrhoea	Common
Abdominal pain	
Hepato-biliary disorders	
Moderate transient and reversible increases in transaminases	Very common
Moderate transient and reversible increases in alkaline phosphatases	
Moderate transient and reversible increases in bilirubin	
Hepatitis	Not known
Skin and subcutaneous tissue disorders	
Pruritus	Uncommon
Renal and urinary disorders	
Transient increase in blood urea	Uncommon
General disorders and administration site conditions	
Febrile episode	Common
Phlebitis (swelling, pain, redness of the vein) at the injection site in case of extravasations (*see sections 4.2 Dosage and method of administration and 4.4 Special warnings and precautions for use*)	

Respiratory, thoracic and mediastinal disorders:

Rare cases of lung toxicity (adult acute respiratory distress syndrome) have been observed in combination with dacarbazine) (*see section 4.5 - Interactions with other medicines and other forms of interactions*). Pulmonary toxicity (interstitial pneumopathy) has also been reported with fotemustine.

Neoplasms benign, malignant and unspecified (including cysts and polyps):

Antineoplastic agents and in particular alkylating agents were associated with a potential risk of myelodysplasic syndrome and acute myeloid leukaemia. At high cumulated doses, rare cases were reported with fotemustine either alone or in combination with other chemotherapies, and with or without radiotherapy.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

Increased haematological surveillance is recommended in cases of overdose.

There is no known antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Fotemustine is a cytostatic antineoplastic agent whose chemical formula includes a bioiostere of alanine (1-amino ethylphosphonic acid) in order to facilitate cellular penetration and passage across the blood-brain barrier.

In animal pharmacology, its spectrum of anticancer activity is very wide and is exerted on tumours of various histological types and in various anatomical sites, particularly cerebral and visceral.

As a result of its alkylating and carbamoylating effect, it exerts a potent cytostatic activity on cells in cycle, inducing accumulation of cells in G2M phase.

It does not have any hepatic, pulmonary or renal glutathione reductase inhibitory activity. Immunotoxicity studies demonstrate sparing of NK cellular activity.

Clinical trials

In man, clinical studies in the indication of "disseminated malignant melanoma" have demonstrated the efficiency of MUPHORAN (fotemustine) both in terms of the response rate and the duration of responses, and by the responses obtained on cerebral metastatic sites.

5.2 PHARMACOKINETIC PROPERTIES

Distribution and metabolism

In animals, the tissue distribution is rapid and very extensive. Fotemustine crosses the blood-brain barrier (two to five minutes after bolus administration in the rat, it is detected in the brain at sufficiently high levels to be active).

In man, during administration by intravenous infusion, the plasma levels of fotemustine are close to the steady-state value after 45 minutes. After the end of the infusion, plasma levels go down rapidly and three hours later the molecule can no longer be detected in the blood.

The binding to plasma proteins is quantitatively low (25 to 30 %) and essentially concerns acid alpha-1-glycoprotein and albumin.

Excretion

After administration in man of the drug labelled with ^{14}C on the chloroethyl group, the radioactivity is slowly eliminated with a terminal half-life of 83 hours. About 50 to 60 % of the radioactivity administered is detected in the urine, 30 to 40 % of which is detected during the first 24 hours, but the unchanged molecule is not detected in the urine. 5 % of the radioactivity is eliminated in the faeces and less than 0.2 % in the form of expired CO_2.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Fotemustine is both mutagenic (Salmonella typhimurium, E. coli reverse mutation tests) and clastogenic (mouse micronucleus test, in vitro human lymphocyte assay). Fotemustine had significant transforming effects in cell transformation studies (Syrian hamster embryo cells, BALB/3T3 cells).

Carcinogenicity

Antineoplastic agents and in particular alkylating agents were associated with a potential risk of myelodysplasic syndrome and acute myeloid leukaemia. At high cumulated doses, rare cases were reported with fotemustine, either alone or in combination with other chemotherapies, and with or without radiotherapy (*see section 4.3 - Contraindications and section 4.8 - Adverse effects (Undesirable Effects*)).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

There are no excipients.

Diluent with known effects; solvent: ethanol 80 %V/V (i.e. ethanol 96 % V/V with water for injections).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Shelf life of the powder in the sterile vial: 2 years.

The diluted solution for intravenous administration must be used immediately.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Storage

Keep in the refrigerator at a temperature of between +2 °C and +8 °C.

After reconstitution, the diluted solution for intravenous administration must be protected from light.

Handling and Spill Procedures

Items used to prepare MUPHORAN (fotemustine), or articles associated with body waste should be placed in a closed system and disposed of in a manner such that personnel and the environment are not contaminated. Relevant regulations and practice standards concerning the disposal of cytotoxic waste should be followed.

If a spill occurs, restrict access to the affected area. Wear protective clothing and footwear, suitable gloves, a mask and eye protection and follow relevant spill cleaning procedures. Relevant regulations and practice standards concerning the disposal of cytotoxic waste should be followed.

6.5 NATURE AND CONTENTS OF CONTAINER

A cardboard box containing:

- A 10 mg brown vial sealed with a chlorobutyl elastomere seal, containing 208 mg of the active compound fotemustine

- A 5 mL fine tipped clear glass bottle ampoule containing the solvent (3.35 mL of 96% ethanol and water for injections q.s. to 4 mL).

The reconstituted solution has a volume of 4.16 mL (i.e. 200 mg of fotemustine in 4 mL of solution).

All or part of this volume (depending on the dose administered) is diluted in 250 to 400 mL of 5 % glucose solution for intravenous or intra-arterial administration.

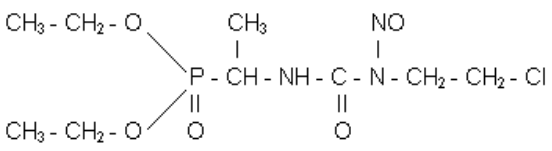
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

The active component of MUPHORAN is fotemustine which has the chemical name, *(RS)*-diethyl {1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl} phosphonate. Fotemustine is a nitrosurea derivative. It is a pale yellow powder slightly soluble in water and soluble in 95 % ethanol. It has a pH of 6.3 (0.3 % aqueous solution), a pKa of 10.4 for the acid group and a partition coefficient octanol/water of 15.7-17.9 (pH 2.1- 7.4).

Chemical structure:



Molecular formula: $C_9H_{19}ClN_3O_5P$

Molecular weight (relative): 315.7

CAS number: 92118-27-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription only medicine

8 SPONSOR

Servier Laboratories (Aust.) Pty Ltd
www.servier.com.au
8 Cato Street
Hawthorn 3122, Victoria, Australia

9 DATE OF FIRST APPROVAL

30 April 1993

10 DATE OF REVISION

08 November 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.4	Updated 'use in patients with alcohol related disorders' and added 'Extravasation' to align with the Reference Safety Information
6.4	Added Handling and Spill Procedures to align with Reference Safety Information
6.5	Change in the specification of ethanol to comply with the European Pharmacopoeia
6.7	Added the CAS number