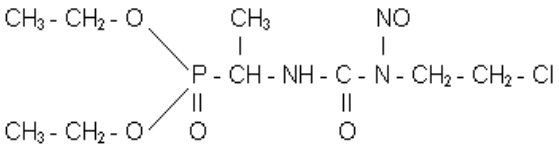
PRODUCT INFORMATION

NAME OF THE MEDICINE

MUPHORAN®
Fotemustine 208 mg

MUPHORAN is fotemustine which has the chemical name: Diethyl 1-[3-(2-chloroethyl)-3-nitrosureido] ethylphosphonate RS

Chemical structure:



Molecular formula: $C_9H_{19}ClN_3O_5P$

Molecular weight (relative): 315.7

DESCRIPTION

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.

Other physicochemical properties:

Partition coefficient:	octanol/water of 15.7-17.9 (pH 2.1- 7.4)
pH:	6.3 (3% aqueous solution)
pKa:	10.4 for the acid group

PHARMACOLOGY

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

Pharmacodynamics

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 G_2M phase.

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

Pharmacokinetics

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.

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.

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.

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.

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 *PRECAUTIONS–Use in Pregnancy* section)
- for lactating women (see *PRECAUTIONS–Use in Lactation* section)
- in combination with the yellow fever vaccine (see *INTERACTIONS WITH OTHER MEDICINES* section)
- in patients with a hypersensitivity to fotemustine, any of the excipients or to nitrosureas.

PRECAUTIONS

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 *DOSAGE AND ADMINISTRATION section*).

Use of MUPHORAN (fotemustine) with live attenuated vaccines or phenytoin is not recommended (see *INTERACTIONS WITH OTHER MEDICINES* section).

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 Hepatic Impairment

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

Use in patients with alcohol-related disorders

A single vial of MUPHORAN (fotemustine) reconstituted contains 3.35 mL of 95% ethanol (equivalent to 2.7g of 100% ethanol) 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.

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 Pregnancy (Category D)

Use of MUPHORAN (fotemustine) is contraindicated in pregnant women and women of childbearing potential who are not using effective contraception. 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.

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.

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.

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).

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.

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.

INTERACTIONS WITH OTHER MEDICINES

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.

Contraindicated combinations

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

Combinations not recommended

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.

Combinations where caution is recommended

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

Interactions 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 *DOSAGE AND ADMINISTRATION* section).

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 O^6 alkyltransferase inhibition provoked by a high dose of dacarbazine, this mode of administration should be avoided.

Interactions 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.

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).

ADVERSE 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 (>1/1000, <1/100); rare (>1/10000, <1/1000); very rare (<1/10000), 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 and reversible neurologic disorders (disorders of consciousness, paresthesia, ageusia)	Uncommon
Gastrointestinal disorders	
Moderate nausea and vomiting within 2 hours following administration	Very common
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 *DOSAGE AND ADMINISTRATION* section)	

Respiratory, thoracic and mediastinal disorders:
Rare cases of lung toxicity (adult acute respiratory distress syndrome) have been observed in combination with dacarbazine) (see *INTERACTIONS WITH OTHER MEDICINES* section). 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 to a potential risk of myelodysplasic syndrome and acute myeloid leukaemia. At high cumulated doses, rare cases were reported with fotemustine, in combination or not with other chemotherapies, with or without radiotherapy.

DOSAGE AND ADMINISTRATION

Prepare the solution immediately prior to administration (see *PRESENTATION AND STORAGE CONDITIONS* section). 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 *PRECAUTIONS section*). 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/m^2.

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 *INTERACTIONS WITH OTHER MEDICINES* section).

OVERDOSAGE

Increased haematological surveillance is recommended in cases of overdose.
There is no known antidote.

PRESENTATION AND STORAGE CONDITIONS

Presentation

Box containing:

- A 10 mg brown vial sealed with a chlorobutyl elastomere seal, containing the active compound: fotemustine (INN) 208 mg
- A 5 mL fine tipped clear glass bottle ampoule containing the solvent (3.35 mL of 95% ethyl alcohol 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 per cent glucose solution for intravenous or intra-arterial administration. The solution must be protected from light.

Shelf Life

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

The reconstituted solution must be used immediately.

Specific Storage Conditions

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

NAME AND ADDRESS OF THE SPONSOR

SERVIER LABORATORIES (AUST.) PTY. LTD.
8 Cato Street,
Hawthorn, Victoria 3122
Australia

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG):

30 April, 1993

DATE OF MOST RECENT AMENDMENT:

28 May, 2015