

MUPHORAN

NAME OF DRUG

Registered trade name : MUPHORAN

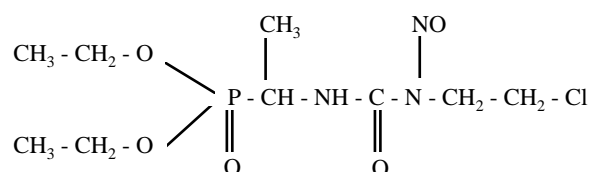
INN (recommended) : fotemustine

Chemical name : diethyl 1-[3-(2-chloroethyl)-3-nitrosoureido] ethylphosphonate RS

DESCRIPTION

Formulae

Structural Formula:



Molecular Formula: C₉H₁₉ClN₃O₅P

Molecular Weight (relative): 315.7

Physicochemical Properties

- Physical form: pale yellow powder
- Solubility: results obtained show that fotemustine, in accordance with the standards of the European pharmacopoeia is slightly soluble in water and soluble in 95% v/v ethanol.
- pH: 6.3 (0.3% aqueous solution)
- pKa: 10.4 for the acid group
- Polymorphism: an infrared spectrophotometric study carried out on several batches shows no polymorphism
- Partition coefficient: octanol/water: 15.7 - 17.9 (pH 2.1 - 7.4)

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 bioisostere 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.

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

Pharmacokinetics

In animals, the tissue distribution is rapid and very extensive. Fotemustine crosses the blood-brain barrier (2 to 5 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 ¹⁴C 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 CO₂.

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

Children

As no studies have been conducted, it is not recommended to use fotemustine in children in the present state of knowledge.

Pregnancy

Because of the known mutagenic and carcinogenic potential of nitrosoureas, administration to pregnant women is contraindicated.

Contraindicated in lactation.

WARNING

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 case of splashing profusely rinse with water.

Contaminated equipment should be disposed of safely.

PRECAUTIONS

Fotemustine should only be used by experienced cancer physicians in institutions with facilities for the monitoring and management of any likely consequence of treatment.

Treatment can only be considered when the platelet count and/or granulocyte count is acceptable, with minimum values of $100,000/\text{mm}^3$ and $2000/\text{mm}^3$ respectively.

It is recommended not to administer the product to patients who have already received chemotherapy in the previous 4 weeks (or 6 weeks in the case of previous treatment with a nitrosourea).

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

AFTER THE DOSE		PERCENTAGE OF FIRST DOSE TO BE ADMINISTERED FOR A NEW COURSE
Platelets ($/\text{mm}^3$)	Granulocytes ($/\text{mm}^3$)	
$> 100\ 000$	> 2000	100 %
$100\ 000 > N > 80\ 000$	$2000 > N > 1\ 500$	75 %
	$1\ 500 > N > 1000$	50 %
$N < 80\ 000$	$< 1\ 000$	Postponement of Treatment

An interval of 8 weeks after the start of induction treatment and 3 weeks after each cycle of maintenance treatment is recommended.

It is recommended to regularly monitor liver function tests during or following induction treatment.

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.

Carcinogenicity/Mutogenicity

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 Renal Impairment

Standard doses of 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 Hepatic Impairment

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

USE IN PREGNANCY/FERTILITY

Category D- 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. The use of fotemustine in pregnant women and women of child-bearing age should be avoided where possible, particularly during the first trimester. In any individual case the potential hazard to the foetus must be balanced against the expected benefit to the mother. 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 4 weeks.

USE IN LACTATION

There is no data on the effects of fotemustine in lactation.

USE IN THE ELDERLY

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

INTERACTIONS WITH OTHER DRUGS

No interaction has been observed between fotemustine and compounds acting on the CNS such as antiepileptics, analgesics, neuroleptics, anxiolytics and antiparkinson. 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.

Pulmonary toxicity (acute respiratory distress syndrome) has been observed after the sequential combination dacarbazine - fotemustine, likely due to O⁶ alkyltransferase inhibition provoked by a high dose of dacarbazine.

This mode of combination should be avoided.

ADVERSE REACTIONS

Principally: delayed haematological toxicity characterised by thrombocytopenia and leukopenia with a nadir occurring 4 to 5 weeks and 5 to 6 weeks respectively after the first administration.

- Moderate nausea and vomiting may be observed during the 2 hours following the injection.
- Moderate, transient and reversible rises in transaminases, alkaline phosphatase and bilirubin may also be observed.
- Phlebitis at the injection site, febrile episode, pruritus, abdominal pain, diarrhoea, transient rise in blood urea, transient and reversible neurological disorders (disturbance of consciousness, paraesthesiae, agueusia) have been rarely reported (between 0.5 and 4% of cases).

An increased haematological and gastro-intestinal toxicity may be observed in the elderly.

DOSAGE AND ADMINISTRATION

Prepare the solution immediately prior to administration (see "PRESENTATION"). Solutions of fotemustine are unstable when exposed to light.

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

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

In a single-agent chemotherapy, treatment consists of:

- induction treatment: three consecutive administrations at one week intervals, followed by a therapeutic rest period of 4 to 5 weeks.

- maintenance treatment: one administration every 3 weeks

The usual dosage is 100 mg/sqm.

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

Blood counts should be performed frequently (see "PRECAUTIONS"). It is also recommended to regularly monitor liver function tests during or following induction treatment.

OVERDOSAGE

Increased haematological surveillance.

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:
 - 95% ethyl alcohol 3.35 ml
 - water for injections q.s. 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.

POISONS SCHEDULE AND STORAGE

S4 – Prescription-only Medicine

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

AUSTRALIAN SPONSOR

Servier Laboratories (Aust) Pty Ltd
8 Cato Street, Hawthorn, Victoria 3122, Australia

ABN 54 004 838 500

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NEW ZEALAND SPONSOR

Servier Laboratories (NZ) Ltd

2nd Floor, 29 Union Street, Auckland, New Zealand