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Physician Package Insert

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MUPHORAN®

POWDER AND SOLVENT FOR INFUSION

1. NAME OF THE MEDICINAL PRODUCT

MUPHORAN

Powder and solution to be diluted for parenteral use (infusion).

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder:
Fotemustine ..... 208.00 mg
for one vial
Solvent:
96 percent (v/v) ethyl alcohol ..... 3,35 ml
Water for injections ..... q.s.f. 4,00 ml
for an ampoule

The reconstituted solution represents a volume of 4.16 ml, i.e. 200 mg of fotemustine in 4 ml of solution.
For the excipients, refer to 6.1.

3. PHARMACEUTICAL FORM

Powder and solution to be diluted for parenteral use (infusion).

4. CLINICAL DATA

4.1 THERAPEUTIC INDICATIONS

Disseminated malignant melanoma.

4.2 DOSAGE AND ADMINISTRATION

Prepare the solution immediately prior to administration.
Dissolve the contents of the fotemustine vial with the 4 ml ampoule of sterile alcoholic solution, then after having calculated the dose to be injected, dilute the solution in 5 % isotonic glucose solution for administration as an intravenous infusion.

The solution once prepared must be protected from light:
Administer by intravenous infusion over a period of one hour.

- **In single agent chemotherapy**, the treatment consists of:
  - ➢ Induction treatment: 3 consecutive administrations at weekly intervals followed by a 4 to 5 week therapeutic rest period.
  - ➢ Maintenance treatment: one administration every 3 weeks. The usual dose is 100 mg/m^2.

- **In combination chemotherapy**, the 3rd administration of the induction treatment is cancelled. The dose remains 100 mg/m^2.

Association with dacarbazine
Rare cases of pulmonary toxicity (acute adult respiratory distress syndrome) have been observed when fotemustine is combined simultaneously, on the same day, with high doses of dacarbazine.
Simultaneous administration should be avoided (See 4.5 Interactions with other medicinal products and other forms of interaction).
The combination should be administered in accordance with the following recommended schedule:

Induction treatment:
- ➢ fotemustine 100 mg/m^2/day on days 1 and 8,
- ➢ dacarbazine 250 mg/m^2/day on days 15, 16, 17 and 18.
  - a 5 week therapeutic rest period, then:

Maintenance treatment: every 3 weeks.
- ➢ fotemustine 100 mg/m^2/day on day 1,
- ➢ dacarbazine 250 mg/m^2/day on days 2, 3, 4 and 5.

4.3 CONTRA-INDICATIONS

- ➢ Pregnancy, breast-feeding.
- ➢ In combination with:
  - yellow fever vaccine (See 4.5 Interactions with other drugs and other forms of interaction).

4.4 Special warnings and precautions for use

SPECIAL WARNINGS
Avoid all contact with the skin and mucous membranes and any absorption of the reconstituted solution. It is recommended that a mask and protective gloves be worn during preparation of the solution. Wash any splashes abundantly with water.
Contaminated materials must be disposed of safely.
Children: no studies have been carried out in children.
This drug is not recommended with live attenuated vaccines, phenytoin and fosphenytoin (See 4.5. Interactions with other drugs and other forms of interaction).

PRECAUTIONS FOR USE
- ➢ It is recommended not to administer this drug to patients who have received chemotherapy within the previous 4 weeks (or 6 weeks in the case of previous treatment with a nitrosourea).
- ➢ The administration of MUPHORAN can only be considered when the platelet count and/or granulocyte count is acceptable 100000/mm^3 and 2000/mm^3, respectively.

  Blood counts must be performed before each new administration and the doses should be adjusted in relation to the hematological status.
  The following table can be used as a guide.

Platelets (/mm3)	Granulocytes (/mm3)	Percentage of the administered dose
> 100 000	> 2000	100 %
100 000 ≥ N > 80 000	2 000 ≥ N > 1 500	75 %
	1 500 ≥ N > 1 000	50 %
N ≤80 000	≤1000	postpone the treatment

- ➢ An interval of 8 weeks between the start of induction treatment and the start of maintenance treatment is recommended. An interval of 3 weeks is recommended between two cycles of maintenance treatment.
- ➢ Maintenance treatment can only be envisaged when the platelet count and/or granulocyte count is acceptable 100000/mm^3 and 2000/mm^3, respectively.
- ➢ It is recommended to perform liver function tests during and following induction treatment.

This drug contains 80 % ethanol volume (alcohol), which equals 1.3g of alcohol for 100 mg of fotemustine, the equivalent of 32 ml of beer or 13.3 ml of wine. This quantity may be dangerous for alcoholic patients. This should also be taken into consideration in high-risk patients such as those with hepatic disorders or epilepsy.

4.5 INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION

***Interactions common to all cytotoxics**
Due to an increased thrombotic risk during tumoral affections, an anticoagulant treatment is often used.
The large intra-individual variability of coagulability during these affections, added to the eventuality of an interaction between the oral anti-coagulants and the anti-cancer chemotherapy, requires, if it is decided to administer the patient with oral anti-coagulants, an increase in the frequency of INR tests.

*Combinations contra-indicated (see **4.3 CONTRA-INDICATIONS**)*

+ Yellow fever vaccine: risk of widespread fatal vaccinal disease.

*Combinations not recommended (See **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**):*

+ Phenytoin (and by extrapolation, fosphenytoin)
Risk of onset of convulsions from a decrease in the digestive absorption by the cytostatic of phenytoin alone, otherwise risk of an increase in toxicity and a loss of efficacy of the cytotoxic by an increase in the hepatic metabolism by phenytoin or by fosphenytoin.

+ Live attenuated vaccines (except yellow fever vaccine)
Risk of widespread vaccinal disease, possibly fatal.
The risk is increased in subjects already immunodepressed by subjacent disease.
Use an inactive vaccine if one exists (poliomyelitis).

Combinations to be taken into account:
+ Immunodepressors
Excessive immunodepression with a risk of lymphoproliferation.

*** Interactions specific to MUPHORAN (Fotemustine)**
Combinations requiring precautions for use

+ Dacarbazine.
With high doses of dacarbazine: risk of pulmonary toxicity (acute adult respiratory distress syndrome).
Do not use simultaneously, rather respect a delay of one week between the last administration of fotemustine and the first day of treatment with dacarbazine (See 4.2 Dosage and administration).

4.6 PREGNANCY AND LACTATION
MUPHORAN is contra-indicated during pregnancy and breast-feeding.

4.7 Effects on ability to drive and use machines
Not applicable.

4.8 UNDESIRABLE EFFECTS
During clinical trials, the principal undesirable effects are of a hematological, and could affect all three lines. This toxicity is delayed and characterised by anaemia (14%), as well as by thrombopenia (40.3 %) and by leukopenia (46.3 %) with nadirs occurring respectively 4 to 5 weeks and 5 to 6 weeks after the first dose of the induction treatment. Pancytopenia can also occur.

The reported undesirable effects are listed below by system-organ class and frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <1/1000), very rare (<1/10,000) and not known (cannot be estimated from the available data).

Blood and lymphatic system disorders

Very common:
- Thrombocytopenia, leukopenia (grade 3-4),
- Anaemia (grade 3-4).

Nervous system disorders

Uncommon:
- Transient and reversible neurological disturbances (consciousness disorders, paraesthesia, ageusia).

Gastrointestinal disorders

Very common:

- Moderate nausea and vomiting within the 2 hours following the injection.

Common:
- Diarrhoea, abdominal pain.

Renal and urinary disorders

Uncommon:
- Transient increase in urea.

Skin and sub-cutaneous tissue disorders

Uncommon:
- Pruritus.

General disorders and administration site conditions

Common:
- Febrile episode,
- Irritation of the vein at the site of injection.

Hepatobiliary disorders

Very common:
- Moderate, transient and reversible increases in transaminases, alkaline phosphatase and bilirubin.

- Rare cases of pulmonary toxicity (adult acute respiratory distress syndrome) have been observed in association with dacarbazine (See section 4.5 Interaction with other medicinal products).

- Antineoplastic agents – in particular alkylating agents – have been connected with a potential risk of myelodysplastic syndrome and acute myeloid leukaemia. With high cumulative doses, rare cases were reported with MUPHORAN, either in combination with other chemotherapies or on its own, and either with or without radiotherapy.

4.9 OVERDOSAGE
Increased hematological monitoring.
There is no known antidote.

5. PHARMACODYNAMIC PROPERTIES
Fotemustine is a cytostatic anticancer agent of the nitrosourea group, with an alkylating and carbamylating action, and a large experimental anti-tumor activity.
Its chemical formula contains a bioisoster of alanine (amino-1-ethylphosphonic acid) which facilitates cellular penetration and passage across the blood-brain barrier.

5.2 PHARMACOKINETIC PROPERTIES
In man, after intravenous infusion, the plasmatic elimination kinetics are mono- or bi- exponential with a short terminal half-life.
The molecule is almost totally metabolised.
Binding to plasma proteins is low (25 to 30 %).
Fotemustine crosses the blood-brain barrier.

5.3 Preclinical safety data
Not applicable

6. PHARMACEUTICAL DATA

6.1. List of excipients
Solvent: 80% v/v ethanol (or 96% v/v ethanol and water for injectable preparations).

6.2. Incompatibilities
Not applicable

6.3. Shelf-life
2 years protected from light.

6.4. Special storage precautions
To be stored in the refrigerator between +2°C and +8°C and protect from light.

The reconstituted solution must be used immediately.

6.5. Nature and contents of container
Muphoran Vial: Brown glass vial containing sterile powder.
Solvent for Muphoran: Glass Ampoules containing 4 ml solvent.

7. MARKETING AUTHORISATION HOLDER

LES LABORATOIRES SERVIER
22 RUE GARNIER
92200 NEUILLY SUR SEINE CEDEX
FRANCE

8. DRUG REGISTRATION NO: 067142825100.

9. MANUFACTURED BY
Laboratoires Thissen S.A., Braine L'Alleud, Belgium

10. LICENSE HOLDER:
Mediline Ltd., 22 Ben Gurion St., Herzlia 46785

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