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Physician Package Insert

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# MUPHORAN®

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POWDER AND SOLVENT FOR INFUSION

**MUPHORAN**

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

I.N.N. : Fotemustine

## QUALITATIVE AND QUANTITATIVE COMPOSITION

Powder:

Fotemustine ..... 208.00 mg

for one vial

Solvent:

95 percent (v/v) ethyl alcohol ..... 3,35 ml

Water for injections ..... q.s.f. 4,00 ml

for an ampoule

The reconstituted solution represent a volume of 4.16 m l, i.e. 200 mg of fotemustine in 4 ml of solution.

## THERAPEUTIC INDICATIONS

As monochemotherapy or in combination with other chemotherapeutic agents, e.g., dacarbazine, in disseminated malignant melanoma.

## DOSAGE AND ADMINISTRATION

Prepare the solution immediately prior to administration.
Dissolve the contents of the fotem ustine 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**: administered by intravenous infusion over a period of one hour.

- **In single agent chemotherapy**, the treatment consists of:
  - ➢ induction treatm ent: 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 chemotherap**y, the 3$^{rd}$ administration of the induction treatment is cancelled. The dose remains 100 mg/m$^2$.

## CONTRA-INDICATIONS

➢ Pregnancy, breast-feeding.
➢ In association with:
- yellow fever vaccine,
- phenytoin as a prophy lactic treatment (see Interactions with other drugs and other forms of interaction).

This drug is generally not recommended in combination with live attenuated vaccines.

## SPECIAL WARNINGS

Avoid all contact with the skin and m ucous m embranes 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.

## PRECAUTIONS FOR USE

➢ It is recommended not to adm inister this drug to patients who have received chem otherapy 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 100 000/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 (/mm$^3$) | Granulocytes (/mm$^3$) | 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 grany ulocyte count is acceptable 100000/mm$^3$ and 2000/mm$^3$, respectively.

➢ It is recommended to perform liver function tests during and following induction treatment.

## INTERACTIONS WITH OTHER DRUGS AND OTHER FORMS OF INTERACTION

***Interactions common to all cytotoxics**

Due to an increased thrombotic risk during tumoral affections, a anti-coagulant 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 :*

+ **Phenytoin** (introduced in prophylaxis due to the convulsive effect of certain anti-cancerous drugs).
  *Applies to doxorubicin, daunorubicin, carboplatine, cisplatine, carmustine, vincristine, vinblastine, bleomycin, methotrexate.*
  Risk of onset of convulsions from a decrease in the digestive absorption of phenytoin by the cytostatic.
+ **Yellow fever vaccine**: risk of widespread fatal vaccinal disease.

*Combinations not recommended :*

+ **Live attenuated vaccines** (except yellow fever)
  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 requiring precautions for use :*

+ **Phenytoin** (in cases of previous chemotherapy treatment).
  *Applies to doxorubicin, daunorubicin, carboplatine, cisplatine, carmustine, vincristine, vinblastine, bleomycin, methotrexate.*
  Risk of onset of convulsions from a decrease in the digestive absorption of phenytoin by the cytostatic.
  For a short time associate with an anticonvulsive benzodiazepin.

*Combinations to be taken into account :*

+ **Ciclosporine (by Tacrolimus extrapolation),**
  Applies to doxorubicin, etoposide.
  Excessive immunodepression with a risk of lymphoproliferation.

*** Interactions specific to MUPHORAN**

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. This type of administration should be avoided.
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.

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

**UNDESIRABLE EFFECTS**

The principal undesirable effects are of a hematological order. This toxicity is delayed and characterised 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.
The hematoxicity may be accentuated by previous chemotherapy and/or in combination with other drugs likely to induce hematopoietic toxicity.

Have also been observed :
- ➢ moderate nausea and vomiting during the 2 hours following the injection (46.7 %).
- ➢ a m oderate, transient and reversible increase in transaminases, alcaline phosphatases and in bilirubin (29.5 %).

More rarely observed :
- ➢ febrile episodes (3.3 %),
- ➢ irritation of the vein at the site of injection (2.9 %),
- ➢ diarrhea (2.6 %),
- ➢ abdominal pain (1.3 %),
- ➢ transient increase in urea (0.8 %),
- ➢ pruritus (0.7 %),
- ➢ transient and reversible neurological disturbances (consciousness disorders, paresthesia, ageusia) (0.7 %),
- ➢ rare cases of pulmonary toxicity (acute adult respiratory distress syndrome) have been observed in association with dacarbazine (see Interactions with other drugs).

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

**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.

**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.

**STORAGE**
Store in a refrigerator and protect from light.

**PRESENTATION**
Muphoran Vial: Vials containing sterile powder.
Solvent for Muphoran: Ampoules of 4 ml.

**DRUG REGISTRATION NO:**
067142825100.

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