Package leaflet: Information for the user

Sodiofolin 50 mg/ml, solution for injection/infusion

Folinic acid (as disodium folinate)

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Sodiofolin is and what it is used for

- Folinic acid, a compound derived from the vitamin B_{12} group, is an antidote to the anticancer medicine methotrexate (rescue therapy).
- Folinic acid increases the action of the anticancer medicine 5-fluorouracil; the two substances are used together for treatment of cancer.

Sodiofolin has been prescribed by your doctor:
- either for the prevention of possible side effects resulting from methotrexate therapy
- or for treatment of cancer in combination therapy with 5-fluorouracil.

2. What you need to know before you use Sodiofolin

Do not use Sodiofolin
- if you are allergic to folinic acid or any of the other ingredients of this medicine (listed in section 6).
- in combination with 5-fluorouracil if you:
  - are breast-feeding,
  - have severe diarrhoea (watery stools or bowel movements),
  - have symptoms of gastrointestinal toxicity such as diarrhoea, feeling or being sick or mouth ulcers. Your doctor will monitor these symptoms until they resolve.
- if you have certain blood disorders (pernicious anaemia or other anaemias due to shortage of vitamin B_{12}).

Your doctor will check these before your treatment.

Warnings and precautions

Sodiofolin injection should only be given to you by an injection into your vein (intravenous injection) or by a drip given into a vein (intravenous infusion) and NOT by any other routes (See section 3. How to use Sodiofolin).

Talk to your doctor, pharmacist or nurse before using Sodiofolin
- if you are elderly or very weak, as you may have a higher risk of side effects.

- if you are suffering from epilepsy, as you have an increased risk of fits (seizures). You will need to have regular blood tests to check the levels of anti-epileptic medicine in your blood.

If you are to receive Sodiofolin and 5-fluorouracil treatment at the same time, take special care,
- if you have had radiotherapy.
- if you have stomach or bowel trouble.
- if you are elderly.

Tell your doctor if the above applies to you before this medicine is used.

Other medicines and Sodiofolin
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

- Sodiofolin is used for the treatment of cancer in combination with 5-fluorouracil. You must be aware that this combination of medicines will increase the effectiveness and side effects of 5-fluorouracil (see section 4 of this leaflet). If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor.
- The effectiveness of folic acid antagonists (e.g. cotrimoxazole, pyrimethamine) will be reduced by Sodiofolin.
- The effectiveness of some medicines (phenytoin, primidone, phenobarbital and succinimides) used to treat convulsion (epilepsy) may be reduced by Sodiofolin which may lead to increased risk of seizures. Your doctor may check blood levels of these medicines and change your dose to prevent increased convulsions (fits).

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
It is unlikely that your doctor will ask you to take/use a folic acid antagonist (e.g. methotrexate, trimethoprim) or 5-fluorouracil whilst you are pregnant or breast-feeding. However, if you have taken/used a folic acid antagonist whilst pregnant or breast-feeding, this medicine (Sodiofolin) may be used to reduce its side effects.

Pregnancy
There are no indications that Sodiofolin induces harmful effects if administered alone during pregnancy.

If you are pregnant, you should only be administered methotrexate if the benefits of your treatment outweigh the possible risks for your child.
If you are given methotrexate although you are pregnant, there are no limitations as to the use of Sodiofolin to diminish or counteract the effects of methotrexate.

Breast-feeding
Sodiofolin alone can be used during breast-feeding when considered necessary.

However, breast-feeding must be discontinued before you take Sodiofolin in combination with methotrexate or 5-fluorouracil.

Driving and using machines
Your ability to drive or use machines is not affected by Sodiofolin, but you should consider your general condition before driving or using machines.

Sodiofolin contains sodium

Vials with 2 ml, 4 ml:
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Vials with 6 ml:
This medicine contains 29.38 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.47% of the recommended maximum daily dietary intake of sodium for an adult.

Vials with 8 ml:
This medicine contains 39.18 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 1.96% of the recommended maximum daily dietary intake of sodium for an adult.

Vials with 10 ml:
This medicine contains 48.97 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 2.45% of the recommended maximum daily dietary intake of sodium for an adult.

Vials with 18 ml:
This medicine contains 88.15 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4.41% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Sodiofolin

Sodiofolin will be given to you
- by an injection into your vein (intravenous injection) or
- by a drip given into a vein (intravenous infusion).

The dose given depends on your size. It varies with your surface area. Technically, this is measured in square metres (m^2), but actually is worked out from your height and weight.

Preventing possible side effects during a therapy with methotrexate (rescue treatment)
Your doctor uses Sodiofolin as a preventive treatment, which follows the administration of methotrexate. Sodiofolin is given intravenously (into your vein). The used amount depends on the measured methotrexate blood levels.

The infusion therapy using Sodiofolin starts not later than 18 to 30 hours after the start of methotrexate infusion.
The infusion therapy using Sodiofolin ends 72 hours after the start of methotrexate infusion at the earliest.

Treatment of cancer using Sodiofolin in combination with 5-fluorouracil
All dose schedules have been determined by clinical studies carried out in large numbers of patients. Your doctor can choose from weekly, monthly or other regimens. All schedules use a combination of the two substances folinic acid (Sodiofolin) and 5-fluorouracil.

The following schedules have been used in adults and elderly in the treatment of advanced cancer of the colon and rectum and are given as examples. There are no data on the use of these combinations in children. Your doctor will explain to you how this works and how often you will receive your medicine:

1. Weekly schedule of 5-fluorouracil and Sodiofolin. This involves either:

   - a 2 hour intravenous infusion (‘drip’) of Sodiofolin, followed by a single intravenous injection of 5-fluorouracil (‘Moderately high dose 5-fluorouracil treatment’).

   or

   - a 1 – 2 hour intravenous infusion of Sodiofolin, followed by a 24 hour infusion of 5-fluorouracil (‘High dose 5-fluorouracil treatment’)

   given weekly in cycles of 6 weeks according to your response. The 6 week cycle may be repeated after an interval of 2 weeks, if necessary, and the number of cycles will depend on the response of the tumour.

2. Monthly schedule of 5-fluorouracil and Sodiofolin.

This involves single intravenous injections of Sodiofolin, followed by a single intravenous injection of 5-fluorouracil, given once a day together for 5 successive days (= 1 cycle). The cycle is repeated after 4 weeks, and then according to the response of the tumour.

This schedule may be followed at a higher dose ('Moderately high dose Sodiofolin') or alternatively, at a lower dose ('Low dose Sodiofolin').

If you are given more Sodiofolin than you should
It is very unlikely that you will receive more Sodiofolin than you should. You will be monitored by a doctor or a nurse during the treatment with this medicine to ensure safe and proper administration of the solution.
Excessive amounts of Sodiofolin may abolish the therapeutic effect of folic acid antagonists.
Should overdose of the combination of 5-fluorouracil and Sodiofolin occur, the overdose instructions for 5-fluorouracil should be followed.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been observed when Sodiofolin was administered:

If you experience any of the following **side effects,** please **consult your doctor or hospital immediately**:

Rare: may affect up to 1 in 1 000 people
- increase in the frequency of **convulsions (fits)** if you are epileptic

Very rare: may affect up to 1 in 10 000 people
- sudden itchy rash, including mild or severe allergic reactions (e.g. swelling of the hands, feet, ankles, face, lips, tongue, mouth or throat [which may cause difficulty in swallowing or breathing], chest pain and you may feel you are going to faint) as these are signs of **allergic reactions** such as sensitisation (state of being sensitive) and urticaria (hives)

The following other side effects have been observed:

Uncommon: may affect up to 1 in 100 people
- fever

Rare: may affect up to 1 in 1 000 people
- difficulty sleeping (insomnia), agitation and depression after high doses
- problems with the digestive system (after high doses)

Sodiofolin can enhance the action and the side effects of the anticancer medicine 5-fluorouracil.
If you receive Sodiofolin in combination with an anticancer medicine containing fluoropyrimidines, it is more likely that you experience the following side effects of this other medicine.

If you experience any of the following **side effects** please **consult your doctor or hospital immediately**:

Very common: may affect more than 1 in 10 people
- *weekly <u>and</u> monthly regime:*
  sudden sore throat, fever, tiredness, mouth ulcers or unexplained bleeding and bruising as this may be signs of a **reduction in the number of blood cells** and may become life-threatening
- *weekly regime:*
  stomatitis (mild to moderate ulceration of the mouth) or severe **diarrhoea** (watery stools or bowel movements) and drying out as these conditions may become life-threatening as well

The following other side effects have been observed:

Very common: may affect more than 1 in 10 people
- inflammation of the lining of the intestine (gut) and mouth (life-threatening conditions have occurred)

Common: may affect up to 1 in 10 people
- redness and swelling of the palms of the hands or the soles of the feet which may cause the skin to peel (hand-foot-syndrome)

Not known: frequency cannot be estimated from the available data
- elevated ammonia level in the blood

Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities.

<u>Monthly regime</u>

Very common: may affect more than 1 in 10 people
- vomiting (being sick), nausea (feeling sick)

No enhancement of other 5-fluorouracil induced toxicities (e.g. neurotoxicity) was observed.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Sodiofolin

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C).

Keep the vial in the outer carton in order to protect from light.

6. Contents of the pack and other information

What Sodiofolin contains
- The active substance is folinic acid (as disodium folinate).
- The other ingredients are sodium hydroxide, hydrochloric acid and water for injection.

What Sodiofolin looks like and contents of the pack
Sodiofolin is a slightly yellow, clear solution for injection/infusion.

One 2 ml / 4 ml / 6 ml / 8 ml / 10 ml / 18 ml vial contains 109.3 mg / 218.6 mg / 327.9 mg / 437.2 mg / 546.5 mg / 983.7 mg disodium folinate equivalent to 100 mg / 200 mg / 300 mg / 400 mg / 500 mg / 900 mg folinic acid.

Sodiofolin is supplied in sealed glass vials in packs of 1 or 5. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer
medac
Gesellschaft für klinische Spezialpräparate mbH
Theaterstr. 6
22880 Wedel
Germany

This medicine is authorised in the Member States of the European Economic Area and in the United Kingdom (Northern Ireland) under the following names:

Germany	Oncofolic 50 mg/ml, Injektions-/Infusionslösung
United Kingdom (Northern Ireland)	Sodiofolin 50 mg/ml, solution for injection/infusion

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