Gemcitabine 40 mg/ml
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Package leaflet: Information for the user

Gemcitabine 40 mg/ml concentrate for solution for infusion

gemcitabine

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, nurse or pharmacist.
- 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 Gemcitabine is and what it is used for

Gemcitabine belongs to a group of medicines called "cytotoxics". These medicines kill dividing cells, including cancer cells.

This medicine may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer.

This medicine is used in the treatment of the following types of cancer:

- non-small cell lung cancer (NSCLC), alone or together with cisplatin
- pancreatic cancer
- breast cancer, together with paclitaxel
- ovarian cancer, together with carboplatin
- bladder cancer, together with cisplatin.

2. What you need to know before you use Gemcitabine

Do not use Gemcitabine:

- if you are allergic to gemcitabine or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and Precautions:

Before the first infusion you will have samples of your blood taken to check if your liver and kidneys are working well enough for you to receive this medicine. Before each infusion you will have samples of your blood taken to check if you have enough blood cells to receive Gemcitabine. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood call counts are too low. Periodically you will have samples of your blood taken to check how well your kidney and liver are working.

Talk to your doctor, nurse or hospital pharmacist before using Gemcitabine.

If you have, or have previously had liver disease, heart disease, vascular disease or problems with your kidneys talk to your doctor or hospital pharmacist as you may not be able to receive Gemcitabine.

If you have recently had, or are going to have radiotherapy, please tell your doctor as there may be an early or late radiation raction with Gemcitabine.

If you have been vaccinated recently, please tell your doctor as this can possibly cause bad effects with Gemcitabine.

If during treatment with this medicine, you get symptoms such as headache with confusion, seizures (fits) or changes in vision, call your doctor right away. This could be a very rare nervous system side effect named posterior reversible encephalopathy syndrome.

If you develop breathing difficulties or feel very weak and are very pale, please tell your doctor as this may be a sign of kidney failure or problems with your lungs.

If you develop generalised swelling, shortness of breath or weight gain, please tell your doctor as this may be a sign og fluid leaking from your small blood vessels into the tissue.

If you are suffering from alcoholism, as this medicinal product contains ethanol (alcohol)

If you are suffering from epilepsy, as this medicinal product contains ethanol (alcohol)

Children and adolescents

This medicine is not recommended for use in children under 18 years of age due to insufficient data on safety and efficacy.

Other medicines and Gemcitabine:

Please tell your doctor or hospital pharmacist if you are taking or have recently taken any other medicines, including vaccinations and medicines obtained without a prescription.

The amount of alcohol in this medicinal product may alter the effects of other medicines.

Pregnancy, breast-feeding and fertility

Pregnancy

If you are pregnant, or thinking about becoming pregnant, tell your doctor. The use of gemcitabine should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking gemcitabine during pregnancy.

Breast-feeding

If you are breast-feeding, tell your doctor. You must discontinue breast-feeding during gemcitabine treatment.

Fertility

Men are advised not to father a child during and up to 6 months following treatment with Gemcitabine. If you would like to father a child during the treatment or in the 6 months following treatment, seek advice from your doctor or pharmacist. You may want to seek counselling on sperm storage before starting your therapy.

Driving and using machines

Gemcitabine may make you feel sleepy, particularly if you have consumed any alcohol. Do not drive a car or use machinery until you are sure that gemcitabine treatment has not made you feel sleepy.

The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Gemcitabine contains ethanol and sodium:

Ethanol

This medicinal product contains 42.1% ethanol (alcohol) which corresponds to 421 mg ethanol per ml of concentrate, i.e.:

- up to 2.1 g of ethanol per 5 ml vial, equivalent to 42 ml of beer, 18 ml of wine.
- up to 10.5 g of ethanol per 25 ml vial, equivalent to 210 ml of beer, 88 ml of wine.
- up to 21.1 g of ethanol per 50 ml vial, equivalent to 421 ml of beer, 175 ml of wine.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breastfeeding women, children and high-risk groups such as patients with liver disease or epilepsy.

The amount of alcohol in this medicinal product may alter the effects of other medicines.

The amount of alcohol in this medicinal product may impair your ability to drive or use machines.

Sodium

The 200 mg vial contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

The 1000 mg vial contains 92.5 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 4.63% of the recommended maximum daily dietary intake of sodium for an adult.

The 2000 mg vial contains 185 mg sodium (main component of cooking/table salt) in each vial. This is equivalent to 9.25% of the recommended maximum daily dietary intake of sodium for an adult.

3. How to use Gemcitabine

The usual dose of Gemcitabine is 1000-1250 mg for every square metre of your body's surface area. Your height and weight are measured to work out the surface area of your body. Your doctor will use this body surface area to work out the right dose for you. This dosage may be adjusted, or treatment may be delayed depending on your blood cell counts and on your general condition.

How frequently you receive your Gemcitabine infusion depends on the type of cancer that you are being treated for.

A hospital pharmacist or doctor will have diluted the Gemcitabine concentrate before it is given to you.

You will always receive this medicine only after dilution by infusion into one of your veins. The infusion will last approximately 30 minutes.

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

4. Possible side effects

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

You must contact your doctor immediately if you notice any of the following:

- Bleeding from the gums, nose or mouth or any bleeding that would not stop, reddish or pinkish urine, unexpected bruising (since you might have less platelets than normal which is very common).
- Tiredness, feeling faint, becoming easily breathless or if you look pale (since you might have less haemoglobin than normal which is very common)
- Mild to moderate skin rash (very common)/ itching (common), or fever (very common); (allergeic reactions)
- Temperature of 38°C or greater, sweating or other signs of infection (since you might have less white blood cells than normal accompanied by fever also known as febrile neutropenia) (common)
- Pain, redness, swelling or sores in your mouth (stomatitis) (common)
- Irregular heart rate (arrhythmia) (uncommon)
- Extreme tiredness and weakness, purpura or small areas of bleeding in the skin (bruises), acute renal failure (low urine output or no urine output), and signs of infection. These may be features of thrombotic microangiopathy (clots forming in small blood vessels) and haemolytic uraemic syndrome, which may be fatal.
- Difficulty breathing (it is very common to have mild breathing difficulty soon after the Gemcitabine infusion which soon passes, however uncommonly or rarely there can be more severe lung problems).
- Severe chest pain (myocardial infarction) (rare)
- Severe hypersensitivity/allergic reaction with severe skin rash including red itchy skin, swelling of the hands, feet, ankles, face, lips, mouth or throat (which may cause difficulty in swallowing or breathing), wheezing, fast beating heart and you may feel you are going to faint (anaphylactic reaction)(very rare)
- Generalised swelling, shortness of breath or weight gain, as you might have fluid leakage from small blood vessels into the tissues (capillary leak syndrome) (very rare)
- Headache with changes in vision, confusion, seizures or fits (posterior reversible encephlaopathy syndrome) (very rare)
- Severe rash with itching, blistering or peeling of the skin (Stevens-Johnson syndrome, toxic epidermal necrolysis) (very rare)

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The following information is intended for healthcare professionals only:
Instruction for use
Cytotoxic

Handling

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. Pregnant personnel should not handle the product. Handling of the solution for infusion should be done in a safety box and protective coats and gloves should be used.
If no safety box is available, the equipment should be supplemented with a mask and protective glasses.
If the preparation comes into contact with the eyes, this may cause serious irritation. The eyes should be rinsed immediately and thoroughly with water. If there is lasting irritation, a doctor should be consulted. If the solution is spilled on the skin, rinse thoroughly with water.

Instructions for dilution

Instructions for dilution should be strictly followed in order to avoid adverse events.
The only approved diluent for dilution of Gemcitabine 40 mg/ml concentrate for solution for infusion is sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative).

1. Use aseptic technique during dilution of gemcitabine for intravenous infusion administration.
2. **<u>The total quantity</u>** of the gemcitabine 40 mg/ml concentrate for solution for infusion required for an individual patient **<u>should be diluted into at least 500 ml of sterile sodium chloride 9 mg/ml (0.9%) solution for injection (without preservative) and infused over 30 min.</u>** Further dilution with the same diluent can be done. Diluted solution is a clear colourless or light straw-coloured solution.
3. Parenteral medicinal products should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

Any unused product or waste material should be disposed of in accordance with local requirements.

Storage conditions

<u>After first opening:</u>

Chemical and physical in-use stability after first opening has been demonstrated for 3 days at 25°C.
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

<u>Shelf life after dilution:</u>

Chemical and physical in-use stability after dilution in 0.9 % sodium chloride solution has been demonstrated for 3 days at 2°C to 8°C or at 30°C.
From a microbiological point of view, the product should be used immediately. If not used

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Other side effects with Gemcitabine may include:

Very common (may affect more than 1 in 10 people)
- Low white blood cells
- Difficulty breathing
- Vomiting
- Nausea
- Hair loss
- Liver problems: found through abnormal blood test results
- Blood in urine
- Abnormal urine tests: protein in urine
- Flu like symptoms including fever,
- Swelling of ankles, fingers, feet, face (oedema)

Common (may affect up to 1 in 10 people)
- Poor appetite (anorexia)
- Headache
- Insomnia
- Sleepiness
- Cough
- Runny nose
- Constipation
- Diarrhoea
- Itching
- Sweating
- Muscle pain
- Back pain
- Fever
- Weakness
- Chills
- Infections

Uncommon (may affect up to 1 in 100 people)
- Scarring of the air sacs of the lung (interstitial pneumonitis)
- Wheeze
- Scarring of the lungs (abnormal chest X ray/scan)
- Heart failure
- Kidney failure
- Serious liver damage, including liver failure
- Stroke

Rare (may affect up to 1 in 1,000 people)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Sloughing of the skin and severe skin blistering
- Injection site reactions
- Severe lung inflammation causing respiratory failure (adult respiratory distress syndrome)
- A skin rash like severe sunburn which can occur on skin that has previously been exposed to radiotherapy (radiation recall).
- Fluid in the lungs
- Scarring of the air sacs of the lung associated with radiation therapy (radiation toxicity)
- Gangrene of fingers or toes
- Inflammation of blood vessels (peripheral vasculitis)

Very rare (may affect up to 1 in 10,000 people)
- Inflammation of the lining of the large bowel, caused by reduced blood supply (ischaemic colitis)
- Increased platelet count
- Low haemoglobin level (anaemia), low white blood cells and low platelet count will be detected by a blood test.
- Thrombotic microangiopathy: clots forming in small blood vessels

Not known: frequency cannot be estimated from the available data
- Sepsis: when bacteria and their toxins circulate in the blood and starts to damage the organs
- Pseudocellulitis: Skin redness with swelling

You might have any of these symptoms and/or conditions. You must tell your doctor as soon as possible when you start experiencing any of these side effects.

If you are concerned about any side effects, talk to your doctor.

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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

Malta
ADR Reporting
The Medicines Authority
Post-Licensing Directorate
203 Level 3, Rue D'Argens
GŻR-1368 Gżira
Website: www.medicinesauthority.gov.mt
e-mail: postlicensing.medicinesauthority@gov.mt

5. How to store Gemcitabine

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 carton and label after EXP. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage condition.

After first opening:

Chemical and physical in-use stability after first opening has been demonstrated for 3 days at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless opening has taken place in controlled and validated aseptic conditions.

Shelf life after dilution(Solution for Infusion):

Chemical and physical in-use stability after dilution in 0.9 % w/v sodium chloride solution has been demonstrated for 3 days at 2°C to 8°C or at 30°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

This medicine is for single use only. Discard any unused contents.

If the solution appears discoloured or contains visible particles, it should be discarded.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Gemcitabine contains

The active substance is gemcitabine (as hydrochloride). Each ml of concentrate for solution for infusion contains 40 mg gemcitabine as gemcitabine hydrochloride.

Each 5 ml vial contains 200 mg gemcitabine (as hydrochloride)

Each 25 ml vial contains 1000 mg gemcitabine (as hydrochloride)

Each 50 ml vial contains 2000 mg gemcitabine (as hydrochloride).

The other ingredients are: Ethanol (96%), sodium hydroxide (E524) (for pH adjustment), hydrochloric acid (E507) (for pH adjustment) and water for injections

What Gemcitabine looks like and contents of the pack

This medicinal product is a concentrate for solution for infusion.

Gemcitabine is a concentrate for solution for infusion and a clear, colourless to slightly yellow solution, free from visible particles.

Each pack contains 1 vial of 5 ml, 25 ml or 50 ml of solution.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Fresenius Kabi Oncology Plc.
Lion Court, Farnham Road, Bordon
Hampshire, GU350NF
United Kingdom

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