Package leaflet: Information for the user

Gemcitabine 100 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, 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 Gemcitabine 100 mg/ml Concentrate for Solution for Infusion is and what it is used for
2. What you need to know before you take Gemcitabine 100 mg/ml Concentrate for Solution for Infusion
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1. What Gemcitabine 100 mg/ml Concentrate for Solution for Infusion is and what it is used for

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion belongs to a group of medicines called "cytotoxics". These medicines kill dividing cells, including cancer cells.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion may be given alone or in combination with other anti-cancer medicines, depending on the type of cancer.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion 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 take Gemcitabine 100 mg/ml Concentrate for Solution for Infusion

Do not take Gemcitabine 100 mg/ml Concentrate for Solution for Infusion
- 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
Talk to your doctor, pharmacist or nurse before taking Gemcitabine 100 mg/ml Concentrate for Solution for Infusion.

Before the first infusion you will have samples of your blood taken to evaluate if you have sufficient kidney and liver function. Before each infusion you will have samples of your blood taken to evaluate if you have enough blood cells to receive Gemcitabine 100 mg/ml Concentrate for Solution for Infusion. Your doctor may decide to change the dose or delay treating you depending on your general condition and if your blood cell counts are too low. Periodically you will have samples of your blood taken to evaluate your kidney and liver function.

Please tell your doctor if:
- you have, or have previously had liver disease, heart disease ,vascular disease or problems with your kidneys..
- you have recently had, or are going to have radiotherapy as there may be an early or late radiation reaction with gemcitabine.
- you have been vaccinated recently 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.
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- you develop breathing difficulties or feel very weak and are very pale (may be a sign of problems with your lungs or kidney failure).
- you are suffering from alcoholism, as this medicinal product contains ethanol (alcohol)
- you are suffering from epilepsy, as this medicinal product contains ethanol (alcohol).
- you experience capillary leak syndrome (CLS) when fluids from your small blood vessels leak out into the tissue. Symptoms can include swelling of the legs, face and arms, weight gain, hypoalbuminaemia (too little of the matter called protein in the blood), severe hypotension (low blood pressure), acute renal impairment and pulmonary oedema (lungs fill with fluid).
- you expereince posterior reversible encephalopathy syndrome (PRES). Symptoms include consciousness impairment, seizure activity, headache, visual abnormalities, focal neurological signs and acute high blood pressure.

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 100 mg/ml Concentrate for Solution for Infusion
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines including vaccinations.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding or think you may be pregnant or are planning to have a baby, tell your doctor. The use of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion should be avoided during pregnancy. Your doctor will discuss with you the potential risk of taking Gemcitabine 100 mg/ml Concentrate for Solution for Infusion during pregnancy. You must discontinue breast-feeding during Gemcitabine 100 mg/ml Concentrate for Solution for Infusion treatment.

Fertility
Men are advised not to father a child during and up to 6 months following treatment with Gemcitabine 100 mg/ml Concentrate for Solution for Infusion. 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 100 mg/ml Concentrate for Solution for Infusion may make you feel sleepy, particularly if you have consumed any alcohol. The amount of alcohol in this medicinal product may impair your ability to drive or use machines. Do not drive a car or use machinery until you are sure that treatment with Gemcitabine has not made you feel sleepy.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion contains ethanol anhydrous 44 % w/v, i.e. up to 9.9 g per maximum daily dose (2250 mg), equivalent to 250 ml beer or 100 ml wine per dose.
- Harmful for those suffering from alcoholism.
- To be taken into account in pregnant or breast-feeding 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.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion contains 206 mg (9.0 mmol) of sodium per maximum daily dose (2250 mg).
- To be taken into consideration by patients on a controlled sodium diet.

3. How to take Gemcitabine 100 mg/ml Concentrate for Solution for Infusion

The recommended dose of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion 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 100 mg/ml Concentrate for Solution for 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 Gemcitabine by infusion into one of your veins. The infusion will last approximately 30 minutes.

This medicinal product is not recommended for use in children under 18 years of age.

If you have further questions on the use of this product 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); (allergic 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 (common).
- Irregular heart rate (arrhythmia) (frequency not known).
- 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 (haemolytic uraemic syndrome). It may be fatal (uncommon).
- 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 encephalopathy syndrome) (very rare)

- Severe rash with itching, blistering or peeling of the skin (Stevens-Johnson syndrome, toxic epidermal necrolysis) (very rare).
- 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.

Other side effects with Gemcitabine 100 mg/ml Concentrate for Solution for Infusion may include:

Very common (may affects more than 1 in 10 people)
- Low white blood cells
- Low platelet count
- 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
- Oedema (swelling of ankles, fingers, feet, face)

Common (may affect up to 1 in 10 people)
- Anorexia (poor appetite)
- 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)
- Interstitial pneumonitis (scarring of the air sacs of the lung)
- Spasm of the airways (wheeze)
- Abnormal chest X ray/scan (scarring of the lungs)
- Heart failure
- Stroke
- Serious liver damage, including liver failure
- Kidney failure

Rare (may affect up to 1 in 1000 people)
- Low blood pressure
- Skin scaling, ulceration or blister formation
- Injection site reactions
- Gangrene of fingers or toes
- Fluid in the lungs
- Adult Respiratory Distress Syndrome (severe lung inflammation causing respiratory failure)

- Radiation recall (a skin rash like severe sunburn) which can occur on skin that has previously been exposed to radiotherapy.
- Radiation toxicity: scarring of the air sacs of the lung associated with radiation therapy
- Inflammation of the blood vessels (peripheral vasculitis)
- Sloughing of skin and severe skin blistering

Very rare (may affect up to 1 in 10,000 people)
- Increased platelet count
- Ischaemic colitis (inflammation of the lining of the large bowel, caused by reduced blood supply)

- 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
- 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.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse This includes any side effects not listed in this leaflet.You can also report side effects directly via the national reporting system(see contact details below). By reporting side effects you can help provide more information on the safety of this medicine.

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

5. How to store Gemcitabine 100 mg/ml Concentrate for Solution for Infusion

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

This medicinal product does not require any special storage conditions.

After opening before dilution:
Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

After dilution:
Chemical and physical in-use stability after dilution in 0.9 % sodium chloride solution has been demonstrated for 60 days at 25°C and 2 °C to 8 °C.
From a microbiological point of view, the solution for infusion 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 condition.

Do not use this medicine after the expiry date (EXP) which is stated on the carton and vial. The expiry date refers to the last day of that month.

This medicine will be prepared and administered to you by healthcare staff. Any unused medicine must be disposed of by the healthcare staff.

6. Contents of the pack and other information

What Gemcitabine 100 mg/ml Concentrate for Solution for Infusion contains:

- The active substance is gemcitabine. Each ml of the concentrate for solution for infusion contains 100 mg gemcitabine (as gemcitabine hydrochloride). Each vial contains either 200 mg, 1000 mg, 1500 mg or 2000 mg gemcitabine (as gemcitabine hydrochloride).
- The other ingredients are macrogol 300, propylene glycol, ethanol anhydrous, sodium hydroxide (for pH adjustment), hydrochloric acid, concentrated (for pH adjustment).

What Gemcitabine 100 mg/ml Concentrate for Solution for Infusion looks like and contents of the pack

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion concentrate for solution for infusion is a clear, colourless to slightly yellow solution.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion is in clear glass vials sealed with rubber stoppers and aluminium flip-off seals.

Pack sizes
1 x 2 ml vial
1 x 10 ml vial
1 x 15 ml vial
1 x 20 ml vial

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Accord Healthcare Limited
Sage House
319, Pinner Road
North Harrow,
Middlesex, HA1 4HF
United Kingdom

This medicinal product is authorised in the Member States of the EEA under the following names:

Name of the Member State	Name of the medicinal product
The Netherlands	Gemcitabine Accord 100 mg/ml Concentraat voor Oplossing voor Infusie
Austria	Gemcitabin Accord 100 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Belgium	Gemcitabine Accord Healthcare 100 mg/ml Solution à Diluer pour Perfusion / concentraat voor oplossing voor infusie / Konzentrat zur Herstellung einer Infusionslösung
Bulgaria	Gemcitabine Accord 100 mg/ml Concentrate for Solution for Infusion
Cyprus	Gemcitabine Accord 100 mg Concentrate for Solution for Infusion
Czech Republic	Gemcitabine Accord 100 mg/ml Koncentrát pro Přípravu Infuzního Roztoku
Germany	Gemcitabine Accord 100 mg/ml Konzentrat zur Herstellung einer Infusionslösung
Denmark	Gemcitabin Accord
Estonia	Gemcitabine Accord 100 mg/ml
Greece	GEMCITABINE / ACCORD

Name of the Member State	Name of the medicinal product
Spain	Gemcitabina Accord 100 mg/ml concentrado para solución para perfusión
Finland	Gemcitabine Accord 100 mg/ml Infuusiokonsentraatti, Liuosta Varten
Hungary	Gemcitabine Accord 100 mg/ml Concentrate for Solution for Infusion
Ireland	Gemcitabine 100 mg/ml Concentrate for Solution for Infusion
Italy	GEMCITABINA ACCORD
Latvia	Gemcitabine Accord 100 mg/ml koncentrāts infūziju šķīduma pagatavošanai
Lithuania	Gemcitabine Accord 100mg/ml koncentratas infuziniam tirpalui
Malta	Gemcitabine 100 mg/ml Concentrate for Solution for Infusion
Norway	Gemcitabine Accord
Poland	Gemcitabinum Accord
Portugal	Gemcitabine Accord
Slovak Republic	Gemcitabine 100 mg/ml concentrate for solution for infusion
Romania	Gemcitabina 100 mg / ml concentrat pentru soluţie perfuzabilă.
Sweden	Gemcitabine Accord

This leaflet was last revised in 12/2018 .

The following information is intended for healthcare professionals only:

Instructions for use, handling and disposal.

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion requires appropriate dilution before use. The concentration of gemcitabine in Gemcitabine 100 mg/ml Concentrate for Solution for Infusion differs from other gemcitabine products.

Concentration must be noticed (100 mg/ml) or life-threatening overdose may occur.
Gemcitabine 100 mg/ml Concentrate for Solution for Infusion must be diluted before use.

- Use aseptic techniques during preparation of gemcitabine for intravenous infusion administration.

- Gemcitabine concentrate for solution for infusion is a clear, colourless to slightly yellow solution with a concentration of 100 mg/ml gemcitabine. The total quantity of the Gemcitabine 100 mg/ml Concentrate for Solution for Infusion required for an individual patient should be diluted with sterile sodium chloride 9 mg/ml (0.9%) solution. Further dilution with the same diluent can be done to a final concentration of 0.1 to 9mg/ml. Diluted solution is a clear colourless to slightly yellow solution.

- DEHP (di-(2-ethylhexyl) phthalate) content may leach from PVC containers upon storage of diluted solution of gemcitabine concentrate for solution for infusion in the plasticised polyvinyl chloride (PVC) containers. Consequently, the preparation, storage and administration of diluted solution should be carried out using non-PVC-containing equipment.

- Special precautions for storage

  After opening before dilution:
  Each vial is for single use and should be used immediately after opening. If not used immediately, in-use storage times and conditions are the responsibility of the user.

  After dilution:
  Chemical and physical in-use stability after dilution in 0.9 % sodium chloride solution has been demonstrated for 60 days at 25°C and 2 °C to 8 °C.
  From a microbiological point of view, the solution for infusion 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 condition.

Preparation of the infusion solution

Gemcitabine 100 mg/ml Concentrate for Solution for Infusion contains 100 mg gemcitabine per ml concentrate solution. The concentrate solution should be diluted prior to administration.

- If the vials are stored under refrigeration, allow the required number of boxes of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion to stand below 25°C for 5 minutes before use. More than one vial of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion may be necessary to obtain the required dose for the patient.

- Aseptically withdraw the required amount of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion using a calibrated syringe.

- The required volume of Gemcitabine 100 mg/ml Concentrate for Solution for Infusion must be injected into infusion bag containing sodium chloride 9 mg/ml (0.9%) solution for infusion.

Mix the infusion bag manually using a rocking motion. Further dilution with the same diluent can be done to a final concentration of approximately 0.1 to 9 mg/ml Considering the maximum dose of ~ 2.25 g Gemcitabine ,the concentration of 4.5mg/ml (achieved with 500 ml of diluent) to 9mg/ml (achieved with 250 ml of diluent) corresponds to the osmolarity of approximately 1000 mOsmol/Kg to 1700 mOsmol/Kg.

- As with all parenteral medicinal products, Gemcitabine infusion solution should be inspected visually for particulate matter and discolouration prior to administration. If particulate matter is observed, do not administer.

Preparation and administration precautions

The normal safety precautions for cytostatic agents must be observed when preparing and disposing of the infusion solution. 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.

Disposal

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