Denk Pharma

Grani-Denk 1 mg/ml

Concentrate for solution for injection or infusion – intravenous use
5-HT_3 receptor antagonist
Active ingredient: Granisetron

Package leaflet:
Information for the user

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.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- 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 Grani-Denk 1 mg/ml is and what it is used for

Grani-Denk 1 mg/ml contains a medicine called granisetron. This belongs to a group of medicines called "5-HT_3 receptor antagonists" or "anti-emetics".

Grani-Denk 1 mg/ml is used to prevent or treat nausea and vomiting (feeling and being sick) caused by other medical treatments, such as chemotherapy or radiotherapy for cancer, and by surgery.

The solution for injection or infusion is for use in adults and children from 2 years of age.

2. What you need to know before you are given Grani-Denk 1 mg/ml

Do not use Grani-Denk 1 mg/ml

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

If you are not sure, talk to your doctor, pharmacist or nurse before having the injection.

Warnings and precautions

Talk to your doctor, pharmacist or nurse before using Grani-Denk 1 mg/ml if you:
- are having problems with your bowel movements because of a blockage of your gut (intestines)
- have heart problems, are being treated for cancer with a medicine that is known to damage your heart or have problems with levels of salts, such as potassium, sodium or calcium, in your body (electrolyte abnormalities)
- are taking other '5-HT_3 receptor antagonist' medicines. These include dolasetron, ondansetron used like Grani-Denk 1 mg/ml in the treatment and prevention of nausea and vomiting.

Serotonin syndrome is an uncommon but potentially life-threatening reaction that can occur with granisetron (see section 4). The reaction can occur if you use granisetron alone but it is more likely to occur if you use granisetron with certain other medicines (in particular fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, venlafaxine, duloxetine).

Other medicines and Grani-Denk 1 mg/ml

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription. This is because Grani-Denk 1 mg/ml can affect the way some medicines work. Also some other medicines can affect the way Grani-Denk 1 mg/ml works.

In particular, tell your doctor, nurse or pharmacist if you are taking the following medicines:
- medicines used to treat an irregular heartbeat
- other '5-HT_3 receptor antagonist' medicines such as dolasetron or ondansetron (see "Warnings and precautions" above)
- phenobarbital, a medicine used to treat epilepsy
- ketoconazole, a medicine used in the treatment of fungal infections
- the antibiotic erythromycin used to treat bacterial infections
- SSRIs (selective serotonin reuptake inhibitors) used to treat depression and/or anxiety. Examples are fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram.
- SNRIs (serotonin noradrenaline reuptake inhibitors) used to treat depression and/or anxiety. Examples are venlafaxine, duloxetine.

Pregnancy and breast-feeding

You should not have this injection if you are pregnant, trying to get pregnant or are breast-feeding, unless your doctor has told you to.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor, pharmacist or nurse for advice before using this medicine.

Driving and using machines

Granisetron is not likely to affect your ability to drive or use any tools or machines.

Grani-Denk 1 mg/ml contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium-free'.

3. How Grani-Denk 1 mg/ml will be given

The injection will be given to you by a doctor or nurse. The dose of Grani-Denk 1 mg/ml varies from one patient to another. It depends on your age, weight, and whether you are being given the medicine to prevent, or treat nausea and vomiting. The doctor will work out how much to give you.

Grani-Denk 1 mg/ml can be given as an injection into the veins (intravenous).

Prevention of feeling or being sick following radio- or chemotherapy

You will be given the injection before your radio- or chemotherapy starts. The injection into your veins will take between 30 seconds and 5 minutes and the dose will usually be between 1 mg and 3 mg. The medicine may be diluted before it is injected.

Treatment of feeling or being sick following radio- or chemotherapy

The injection will take between 30 seconds and 5 minutes and the dose will usually be between 1 mg and 3 mg. The medicine may be diluted before it is injected into your veins. You may be given more injections to stop your sickness after the first dose. There will be at least 10 minutes between each injection. The most granisetron you will be given is 9 mg a day.

Combination with steroids

The effect of the injection may be improved by the use of medicines called adrenocortical steroids. The steroid will be given either as a dose between 8 mg and 20 mg dexamethasone before your radio- or chemotherapy or as 250 mg methyl-prednisolone, which will be given both before and after your radio- or chemotherapy.

Use in children in the prevention or treatment of feeling or being sick following radio- or chemotherapy

Children will be given Grani-Denk 1 mg/ml by injection into the vein as described above with the dose depending on the child's weight. The injections will be diluted and be given before radio- or chemotherapy and will take 5 minutes. Children will be given a maximum of 2 doses a day, at least 10 minutes apart.

Treatment of feeling or being sick following surgery

The injection into your veins will take between 30 seconds and 5 minutes and the dose will usually be 1 mg. The most granisetron you will be given is 3 mg a day.

Use in children in the prevention or treatment of feeling or being sick following surgery

Children should not be given this injection to treat sickness or the feeling of sickness after surgery.

If you are given more Grani-Denk 1 mg/ml than you should

Because the injection or infusion will be given to you by a doctor or nurse, it is unlikely that you will be given too much. However, if you are worried talk to your doctor or nurse. Symptoms of overdose include mild headaches. You will be treated depending on your symptoms.

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.

If you notice the following problem you must see a doctor straight away:

- allergic reactions (anaphylaxis). The signs may include swelling of the throat, face, lips and mouth, difficulty in breathing or swallowing.

Other side effects that may be experienced while using this medicine are:

Very common (affects more than 1 user in 10)
- headache
- constipation. Your doctor will monitor your condition.

Common (affects 1 to 10 users in 100)
- problems sleeping (insomnia)
- changes in how your liver is working shown by blood tests
- diarrhoea

Uncommon (affects 1 to 10 users in 1,000)
- skin rashes or an allergic skin reaction or "nettle-rash" or "hives" (urticaria). The signs may include red, raised itchy bumps.
- changes in the heartbeat (rhythm) and changes seen on ECG readings (electrical recordings of the heart)
- abnormal involuntary movements, such as shaking, muscle rigidity and muscle contractions
- Serotonin Syndrome. The signs may include diarrhoea, nausea, vomiting, high temperature and blood pressure, excessive sweating and rapid heartbeat, agitation, confusion, hallucination, shivering, muscles shakes, jerks or stiffness, loss of coordination and restlessness.

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.

By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Grani-Denk 1 mg/ml

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 ampoule after "Exp". The expiry date refers to the last day of that month.

Shelf-life:
- Unopened ampoule: 3 years.
- After opening: immediate use.
- After dilution: refer to "The following information is intended for healthcare professionals only".

Store below 25 °C. Do not freeze.

Keep the ampoules in the outer packaging to protect contents from light.

For single use only. Discard remaining contents after use.

Do not use Grani-Denk 1 mg/ml if you notice that the solution is not clear and free from particles.

Do not throw away any medicines via wastewater. 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

Pharmacological properties

Pharmacotherapeutic group: Antiemetics and antinauseants, serotonin (5-HT_3) antagonists

ATC code: A04AA02

Granisetron is a potent anti-emetic and highly selective antagonist of 5-hydroxytryptamine (5-HT_3) receptors. Radioligand binding studies have demonstrated that granisetron has negligible affinity for other receptor types including 5-HT and dopamine D2 binding sites.

Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported.

In vitro studies have shown that the cytochrome P450 sub-family 3A4 (involved in the metabolism of some of the main narcotic agents) is not modified by granisetron. Although ketoconazole was shown to inhibit the ring oxidation of granisetron *in vitro,* this action is not considered clinically relevant.

Although QT-prolongation has been observed with 5-HT_3 receptors antagonists, this effect is of such occurrence and magnitude that it does not bear clinical significance in normal subjects. Nonetheless it is advisable to monitor both ECG and clinical abnormalities when treating patients concurrently with drugs known to prolong the QT.

Pharmacokinetic properties

Pharmacokinetics of the oral administration is linear up to 2.5-fold of the recommended dose in adults. It is clear from the extensive dose-finding programme that the antiemetic efficacy is not unequivocally correlated with either administered doses or plasma concentrations of granisetron.

A fourfold increase in the initial prophylactic dose of granisetron made no difference in terms of either the proportion of patient responding to treatment or in the duration of symptoms control.

Distribution: Granisetron is extensively distributed, with a mean volume of distribution of approximately 3 l/kg. Plasma protein binding is approximately 65%.

Biotransformation: Granisetron is metabolized primarily in the liver by oxidation followed by conjugation. The major compounds are 7-OH-granisetron and its sulphate and glycuronide conjugates. Although antiemetic properties have been observed for 7-OH-granisetron and indazoline N-desmethyl granisetron, it is unlikely that these contribute significantly to the pharmacological activity of granisetron in man.

In vitro liver microsomal studies show that granisetron's major route of metabolism is inhibited by ketoconazole, suggestive of metabolism mediated by the cytochrome P-450 3A subfamily.

Elimination: Clearance is predominantly by hepatic metabolism. Urinary excretion of unchanged granisetron averages 12% of dose while that of metabolites amounts to about 47% of dose. The remainder is excreted in faeces as metabolites. Mean plasma half-life in patients by the oral and intravenous route is approximately 9 hours, with a wide inter-subject variability.

What Grani-Denk 1 mg/ml contains

The active substance is granisetron (as hydrochloride).

Each 1 ml ampoule contains 1 mg granisetron as granisetron hydrochloride in a 1 ml sterile concentrate for solution.

Each 3 ml ampoule contains 3 mg granisetron as granisetron hydrochloride in a 3 ml sterile concentrate for solution.

The other ingredients are sodium chloride, citric acid monohydrate, sodium hydroxide and water for injections.

General classification for supply

Medicinal product subject to medical prescription.

What Grani-Denk 1 mg/ml looks like and contents of the pack

Grani-Denk 1 mg/ml is a clear, colourless concentrate for solution for injection or infusion.

Pack size: Grani-Denk 1 mg/ml is available in packs of 5 ampoules containing 1 ml or 3 ml of concentrate for solution each.

Marketing Authorisation Holder

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Manufacturer

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This leaflet was last revised in 09/2018.

Information for Botswana
Scheduling status: S2
Registration number:
BOT1703146 (5 x 1 ml)
BOT1703147 (5 x 3 ml)
Date of publication: 08/2017

The following information is intended for healthcare professionals only.

INSTRUCTIONS FOR THE PREPARATION OF: Grani-Denk 1 mg/ml

Concentrate for solution for injection or infusion

Please read the entire contents of this instruction prior to the preparation of this medicinal product.

A. PHARMACEUTICAL FORM

Grani-Denk 1 mg/ml is supplied as a concentrate for solution for intravenous injection or intravenous infusion in colourless glass ampoules with a capacity of 1 ml or 3 ml containing a sterile and clear solution.

B. PREPARATION FOR INTRAVENOUS ADMINISTRATION

In adults, Grani-Denk 1 mg/ml can be administered as an intravenous bolus injection over at least 30 seconds diluted with an infusion solution. The contents of a 1 ml ampoule can be diluted to a volume of 5 ml, and the contents of a 3 ml ampoule can be diluted to a volume of 15 ml.

Grani-Denk 1 mg/ml can also be diluted in 20–50 ml infusion solution and then given over 5 minutes as an intravenous infusion.

In children, Grani-Denk 1 mg/ml should be diluted to a total volume of 10–30 ml and administered by intravenous infusion over 5 minutes.

Grani-Denk 1 mg/ml is compatible with the following solutions:

- Sodium chloride for injection 0.9% (w/v)
- Sodium chloride 0.18% (w/v) and glucose 4% for injection
- Glucose for injection 5% (w/v)
- Hartmann's solution
- Sodium lactate for injection 1.87% (w/v)
- Mannitol injection solution 10%
- Sodium hydrogen carbonate for injection 1.4% (w/v)
- Sodium hydrogen carbonate for injection 2.74% (w/v)
- Sodium hydrogen carbonate for injection 4.2% (w/v)

Grani-Denk 1 mg/ml should only be diluted with one of these infusion solutions.
Grani-Denk 1 mg/ml must not be mixed with any other medicinal products.

For single use only. The product should be used immediately after opening the ampoule. Chemical and physical stability has been demonstrated for 24 hours at max. 25 °C in normal room lighting, protected from direct sunlight. From a microbiological point of view, the medicinal 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– 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Store below 25 °C.
Do not freeze.
Keep ampoules in outer packaging to protect contents from light.

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