SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Grani-Denk 1 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: granisetron
One ml concentrate contains 1 mg of granisetron (equivalent to 1.12 mg granisetron hydrochloride).
Excipient with known effect: sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for injection or infusion.
The solution is a clear, colourless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Grani-Denk 1 mg/ml is indicated in adults for the prevention and treatment of:

- acute nausea and vomiting associated with chemotherapy and radiotherapy.
- post-operative nausea and vomiting.

Grani-Denk 1 mg/ml is indicated for the prevention of delayed nausea and vomiting associated with chemotherapy and radiotherapy.

Grani-Denk 1 mg/ml is indicated in children aged 2 years and above for the prevention and treatment of acute nausea and vomiting associated with chemotherapy.

4.2 Posology and method of administration

Posology

Chemo- and radiotherapy-induced nausea and vomiting (CINV and RINV)

Prevention (acute and delayed nausea)
A dose of 1-3 mg (10-40 µg/kg) of granisetron should be administered either as a slow intravenous injection or as a diluted intravenous infusion 5 minutes prior to the start of chemotherapy. The concentrate for solution should be diluted to 5 ml per mg.

Treatment (acute nausea)
A dose of 1-3 mg (10-40 µg/kg) of granisetron should be administered either as a slow intravenous injection or as a diluted intravenous infusion and administered over 5 minutes. The concentrate for solution should be diluted to 5 ml per mg. Further maintenance doses of granisetron may be administered at least 10 minutes apart. The maximum dose to be administered over 24 hours should not exceed 9 mg.

Combination with adrenocortical steroid
The efficacy of parenteral granisetron may be enhanced by an additional intravenous dose of an adrenocortical steroid e.g. by 8 mg -20 mg dexamethasone administered before the start of the cytostatic therapy or by 250 mg methyl-prednisolone administered prior to the start and shortly after the end of the chemotherapy.

Paediatric population
The safety and efficacy of granisetron in children aged 2 years and above has been well established for the prevention and treatment (control) of acute nausea and vomiting associated with chemotherapy and the prevention of delayed nausea and vomiting associated with chemotherapy. A dose of 10-40 µg/kg body weight (up to 3 mg) should be administered as an i.v. infusion, diluted in 10-30 ml infusion fluid and administered over 5 minutes prior to the start of chemotherapy. One additional dose may be administered within a 24 hour-period if required. This additional dose should not be administered until at least 10 minutes after the initial infusion.

Post-operative nausea and vomiting (PONV)
A dose of 1 mg (10 µg/kg) of granisetron should be administered by slow intravenous injection. The maximum dose of granisetron to be administered over 24 hours should not exceed 3 mg.

For the prevention of PONV, administration should be completed prior to induction of anaesthesia.

Paediatric population
Currently available data are described in section 5.1, but no recommendation on a posology can be made. There is insufficient clinical evidence to recommend administration of the solution for injection to children in prevention and treatment of Post-operative nausea and vomiting (PONV).

Special populations

Elderly and renal impairment
There are no special precautions required for its use in either elderly patients or those patients with renal impairment.

Hepatic impairment
There is no evidence to date for an increased incidence of adverse events in patients with hepatic disorders. On the basis of its kinetics, whilst no dosage adjustment is necessary, granisetron should be used with a certain amount of caution in this patient group (see section 5.2).

Method of administration
Administration may be as either a slow intravenous injection (over 30 seconds) or as an intravenous infusion diluted in 20 to 50 ml infusion fluid and administered over 5 minutes.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

As granisetron may reduce lower bowel motility, patients with signs of sub-acute intestinal obstruction should be monitored following its administration.

As for other 5-HT_3 antagonists, ECG changes including QT interval prolongation have been reported with granisetron. In patients with pre-existing arrhythmias or cardiac conduction disorders this might lead to clinical consequences. Therefore caution should be exercised in patients with cardiac co-morbidities, on cardiotoxic chemotherapy and/or with concomitant electrolyte abnormalities (see section 4.5).

Cross-sensitivity between 5-HT_3 antagonists (e.g. dolasetron, ondansetron) has been reported.

Serotonin syndrome
There have been reports of serotonin syndrome with the use of 5-HT_3 antagonists either alone, but mostly in combination with other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRIs), and serotonin noradrenaline reuptake inhibitors (SNRIs). Appropriate observation of patients for serotonin syndrome-like symptoms is advised.

Grani-Denk 1 mg/ml contains sodium, but less than 1 mmol (23 mg) sodium per ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

As for other 5-HT_3 antagonists, cases of ECG modifications including QT prolongation have been reported with granisetron. In patients concurrently treated with medicinal products known to prolong QT interval and/or which are arrhythmogenic, this may lead to clinical consequences (see section 4.4).

In studies in healthy subjects, no evidence of any interaction has been indicated between granisetron and benzodiazepines (lorazepam), neuroleptics (haloperidol) or anti-ulcer medicinal products (cimetidine). Additionally, granisetron has not shown any apparent medicinal product interaction with emetogenic cancer chemotherapies.

No specific interaction studies have been conducted in anaesthetised patients.

Serotonergic medicinal products (e.g. SSRIs and SNRIs)
There have been reports of serotonin syndrome following concomitant use of 5-HT_3 antagonists and other serotonergic medicinal products (including SSRIs and SNRIs) (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited amount of data from the use of granisetron in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure**,** it is preferable to avoid the use of granisetron during pregnancy.

Breast-feeding
It is unknown whether granisetron or its metabolites are excreted in human milk. As a precautionary measure, breast-feeding should not be advised during treatment with Grani-Denk 1 mg/ml.

Fertility
In rats, granisetron had no harmful effects on reproductive performance or fertility.

4.7 Effects on ability to drive and use machines

Grani-Denk 1 mg/ml is not expected to impair the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
The most frequently reported adverse reactions for granisetron are headache and constipation which may be transient. ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

Summary of adverse reactions
The following list of adverse reactions is derived from clinical trials and post-marketing data associated with granisetron and other 5-HT_3 antagonists.

Frequency categories are as follows:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1,000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1,000
Very rare: < 1/10,000

Immune system disorders
Uncommon: hypersensitivity reactions e.g. anaphylaxis, urticaria

Psychiatric disorders
Common: insomnia

Nervous system disorders
Very common: headache
Uncommon: extrapyramidal reactions, Serotonin syndrome

Cardiac disorders
Uncommon: QT prolongation

Gastrointestinal disorders
Very common: constipation
Common: diarrhoea

Hepatobiliary disorders
Common: elevated hepatic transaminases (occurred at a similar frequency in patients receiving comparator therapy)

Skin and subcutaneous tissue disorders
Uncommon: rash

Description of selected adverse reactions
As for other 5-HT_3 antagonists, ECG changes including QT prolongation have been reported with granisetron (see sections 4.4 and 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

There is no specific antidote for granisetron. In the case of overdose with the injection, symptomatic treatment should be given. Doses of up to 38.5 mg of granisetron as a single injection have been reported, with symptoms of mild headache but no other reported sequelae.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiemetics and antinauseants, Serotonin (5-HT_3) antagonists
ATC code: A04AA02

Neurological mechanisms, serotonin-mediated nausea and vomiting
Serotonin is the main neurotransmitter responsible for emesis after chemo- or radio-therapy. The 5-HT_3 receptors are located in three sites: vagal nerve terminals in the gastrointestinal tract and chemoreceptor trigger zones located in the *area postrema* and the *nucleus tractus solidarius* of the vomiting center in the brainstem. The chemoreceptor trigger zones are located at the caudal end of the fourth ventricle (*area postrema*). This structure lacks an effective blood-brain barrier, and will detect emetic agents in both the systemic circulation and the cerebrospinal fluid. The vomiting centre is located in the brainstem medullary structures. It receives major inputs from the chemoreceptor trigger zones, and a vagal and sympathetic input from the gut.

Following exposure to radiation or cytotoxic substances, serotonin (5-HT) is released from enterochromaffine cells in the small intestinal mucosa, which are adjacent to the vagal afferent neurons on which 5-HT_3 receptors are located. The released serotonin activates vagal neurons via the 5-HT_3 receptors which lead ultimately to a severe emetic response mediated via the chemoreceptor trigger zone within the *area postrema*.

Mechanism of action
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 D_2 binding sites.

Chemotherapy- and radiotherapy-induced nausea and vomiting
Granisetron administered intravenously has been shown to prevent nausea and vomiting associated with cancer chemotherapy in adults and children 2 to 16 years of age.

Post-operative nausea and vomiting
Granisetron administered intravenously has been shown to be effective for prevention and treatment of post-operative nausea and vomiting in adults.

Pharmacological properties of granisetron
Interaction with neurotropic and other active substances through its activity on P 450-cytochrome has been reported (see section 4.5).

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 (see section 4.4), 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 (see section 4.5).

Paediatric population
Clinical application of granisetron was reported by Candiotti et al. A prospective, multicentre, randomized, double-blind, parallel-group study evaluated 157 children 2 to 16 years of age undergoing elective surgery. Total control of postoperative nausea and vomiting during the first 2 hours after surgery was observed in most patients.

5.2 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 (see section 4.5).

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.

Pharmacokinetics in special populations
Renal failure
In patients with severe renal failure, data indicate that pharmacokinetic parameters after a single intravenous dose are generally similar to those in normal subjects.

Hepatic impairment
In patients with hepatic impairment due to neoplastic liver involvement, total plasma clearance of an intravenous dose was approximately halved compared to patients without hepatic involvement. Despite these changes, no dosage adjustment is necessary (see section 4.2).

Elderly patients
In elderly subjects after single intravenous doses, pharmacokinetic parameters were within the range found for non-elderly subjects.

Paediatrics
In children, after single intravenous doses, pharmacokinetics are similar to those in adults when appropriate parameters (volume of distribution, total plasma clearance) are normalized for body weight.

5.3 Preclinical safety data

Preclinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, reproductive toxicity and genotoxicity. Carcinogenicity studies revealed no special hazard for humans when used in the recommended human dose. However, when administered in higher doses and over a prolonged period of time the risk of carcinogenicity cannot be ruled out.

A study in cloned human cardiac ion channels has shown that granisetron has the potential to affect cardiac repolarisation via blockade of HERG potassium channels. Granisetron has been shown to

block both sodium and potassium channels, which potentially affects both depolarization and repolarization through prolongation of PR, QRS, and QT intervals. This data helps to clarify the molecular mechanisms by which some of the ECG changes (particularly QT and QRS prolongation) associated with this class of agents occur. However, there is no modification of the cardiac frequency, blood pressure or the ECG trace. If changes do occur, they are generally without clinical significance.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Citric acid monohydrate
Sodium hydroxide
Water for injections

6.2 Incompatibilities

Grani-Denk 1 mg/ml must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened ampoule: 36 months

After opening: The product should be used immediately after opening the ampoule. For single use only. Discard remaining contents after use.

After dilution: 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.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

Colourless glass ampoules with 1 ml or 3 ml nominal volume.
Pack sizes: 5 x 1 ml or 5 x 3 ml

6.6 Special precautions for disposal and other handling

Preparation for the intravenous administration

For single use only. Dilute before use.

Adults
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.

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.

Children from 2 years of age
To prepare a dose of 10-40 µg/kg body weight, the appropriate volume is withdrawn and diluted with infusion solution (as for adults) to a total volume of 10-30 ml.

As a general precaution, Grani-Denk 1 mg/ml must not be mixed with other medicinal products.

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

7. MARKETING AUTHORISATION HOLDER

Denk Pharma GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

88766.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

13.03.2013

10. DATE OF REVISION OF THE TEXT

11/2017

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription