SUMMARY OF PRODUCT CHARACTERISTICS

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1. NAME OF THE MEDICINAL PRODUCT

On.setron-Denk 4 mg ODT
On.setron-Denk 8 mg ODT

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: ondansetron

On.setron-Denk 4 mg ODT
Each orodispersible tablet contains 4 mg ondansetron.

Excipients with known effect: Each On.setron-Denk 4 mg orodispersible tablet contains aspartame, sorbitol and less than 1 mmol sodium (23 mg).

On.setron-Denk 8 mg ODT
Each orodispersible tablet contains 8 mg ondansetron.

Excipients with known effect: Each On.setron-Denk 8 mg orodispersible tablet contains aspartame, sorbitol and less than 1 mmol sodium (23 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible tablet

On.setron-Denk 4 mg ODT
White, round, flat orodispersible tablets with bevelled edges and a diameter of 7 mm.

On.setron-Denk 8 mg ODT
White, round, flat orodispersible tablets with bevelled edges and a diameter of 10 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Adults
On.setron-Denk 4 mg ODT
- Treatment of nausea and vomiting in therapy with cytotoxic agents and radiation therapy.

On.setron-Denk 8 mg ODT
- Treatment of nausea and vomiting in therapy with cytotoxic agents and radiation therapy.
- Prevention of nausea and vomiting after surgery.

Children and adolescents
- Ondansetron is indicated in the treatment of nausea and vomiting in therapy with cytotoxic agents
- No studies have been conducted on the use of orally administered ondansetron in the prevention and therapy of nausea and vomiting after surgery. Administration by IV injection is recommended for this purpose.

4.2 Posology and method of administration

Posology

Nausea and vomiting induced by cytotoxic agents and radiation
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Adults
The recommended oral dose is 8 mg taken 1 to 2 hours before chemotherapy or radiation treatment, followed by 8 mg oral every 12 hours for a maximum of 5 days.

For highly emetogenic chemotherapy a single oral dose of up to 24 mg ondansetron taken with 12 mg dexamethasone-21-dihydrogen sodium phosphate, or equivalent oral 1 to 2 hours before chemotherapy, may be used. After the first 24 hours, oral treatment with ondansetron may be continued for up to 5 days after a course of treatment.
The recommended dose for administration is 8 mg to be taken twice daily.

Children and adolescents
The dose for the treatment of nausea and vomiting induced by chemotherapy can be calculated based on body surface area (BSA) or weight. In paediatric clinical studies, ondansetron was given by IV infusion diluted in 25 to 50 mL of saline or other compatible infusion fluid and infused over not less than 15 minutes. Weight-based dosing results in higher total daily doses compared to BSA based dosing (see section 5.2).

There are no data from controlled clinical trials on the use of ondansetron in the prevention of delayed or prolonged nausea and vomiting induced by chemotherapy. There are no data from controlled clinical trials on the use of Ondansetron for radiotherapy-induced nausea and vomiting in children.

Dosing by body surface area (BSA):
Ondansetron should be administered intravenously immediately before chemotherapy at a dose of 5 mg/m^2. The intravenous single dose must not exceed 8 mg.
The administration of oral doses can be administered 12 hours later and may be continued for a period of up to 5 days (see Table 1 below).

The total dose within 24 hours (given as divided doses) must not exceed the adult dose of 32 mg.

Table 1: Dosage based on body surface area in chemotherapy induced nausea and vomiting

Body surface area	**Day 1**	**Days 2-6**
≥ 0.6 m^2 up to ≤ 1.2 m^2	**Initial dose:** 5 mg/m^2 IV **After 12 hours:** 4 mg ondansetron (equivalent to 1 On.setron-Denk 4 mg orodispersible tablet)	**Every 12 hours:** 4 mg ondansetron (equivalent to 1 On.setron-Denk 4 mg orodispersible tablet)
> 1.2 m^2	**Initial dose:** 5 mg/m^2 IV or 8 mg IV **After 12 hours:** 8 mg ondansetron	**Every 12 hours:** 8 mg ondansetron

Dosing by bodyweight (BW):
Weight-based dosing results in higher total daily doses compared to BSA-based dosing (see sections 5.2).
Ondansetron should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The single intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals.

Oral dosing can commence 12 hours later and may be continued for up to 5 days (Table 2).

The total dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg.

Table 2: Dosage based on body weight in chemotherapy induced nausea and vomiting

Body weight	**Day 1**	**Days 2-6**
> 10 kg	Up to 3 doses of 0.15 mg/kg IV every 4 hours	4 mg ondansetron (equivalent to 1 On.setron-Denk 4 mg orodispersible tablet) every 12 hours

For children with a BSA < 0.6 m^2 and a BW up to 10 kg, respectively, adequate dosage forms with a lower strength are available.

Elderly
No alteration of oral dose or frequency of administration is required.

Patients with renal impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg ondansetron should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels

no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

Prevention of nausea and vomiting after surgery
Adults
For the prevention of postoperative nausea and vomiting ondansetron may be administered either orally or by a slow intravenous injection.

For the prevention of postoperative nausea and vomiting the recommended oral dose is 16 mg taken one hour prior to anaesthesia.

For treatment of established post-operative nausea and vomiting, ondansetron administration by slow IV injection is recommended.

Children and adolescents (aged 1 month to 17 years)
No studies have been conducted on the use of orally administered ondansetron in the prevention or treatment of postoperative nausea and vomiting; slow IV injection (not less than 30 seconds) is recommended for this purpose.

There are limited data on the use of ondansetron in the treatment of postoperative nausea and vomiting in children below 2 years of age.

Elderly
There is limited experience in the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly. However ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

Patients with renal impairment
No alteration of daily dosage or frequency of dosing, or route of administration are required.

Patients with hepatic impairment
Clearance of ondansetron is significantly reduced and serum half-life significantly prolonged in subjects with moderate or severe impairment of hepatic function. In such patients a total daily dose of 8 mg ondansetron should not be exceeded.

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine. Consequently in such patients repeat dosing will give drug exposure levels no different from those of the general population. No alteration of daily dosage or frequency of dosing is required.

Mode of administration
Oral use (allow to disintegrate on the tongue and swallow).

Before taking each individual On.setron-Denk orodispersible tablet, please detach it at the designated perforation, carefully remove the cover foil by gently pulling it off, beginning at the corner marked with a black edge and remove the orodispersible tablet carefully. Do not push the orodispersible tablet through the foil.

4.3 Contraindications

Concomitant use with apomorphine (see section 4.5)

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

Additionally for On.setron-Denk 4 mg ODT

Must not be used in children with a body surface area of less than 0.6 m^2 or with a body weight up to 10 kg.
For correct oral dosage in this patient group, more appropriate dosage forms of ondansetron are available.

Additionally for On.setron-Denk 8 mg ODT
Must not be used in children.
For correct oral dosage in this patient group, more appropriate dosage forms of ondansetron (e.g. On.setron-Denk 4 mg ODT) are available.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. Respiratory events should be treated symptomatically and clinicians should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of Torsade de Pointes have been reported in patients using ondansetron. Avoid ondansetron in patients with congenital long QT syndrome. Ondansetron should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities.

Hypokalaemia and hypomagnesaemia should be corrected prior to ondansetron administration.

As ondansetron is known to increase large bowel transit time, patients with signs of subacute intestinal obstruction should be monitored following administration.

In patients with adenotonsillar surgery prevention of nausea and vomiting with ondansetron may mask occult bleeding. Therefore, such patients should be followed carefully after ondansetron.

Serotonin syndrome
Concomitant administration of ondansetron and buprenorphine or serotonergic agents, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants may result in serotonin syndrome, a potentially life-threatening condition (see section 4.5).

If concomitant treatment with buprenorphine or serotonergic agents is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.

If serotonin syndrome is suspected, a dose reduction or discontinuation of therapy should be considered depending on the severity of the symptoms.

Children and adolescents
Paediatric population receiving ondansetron with hepatotoxic chemotherapeutic agents should be monitored closely for impaired hepatic function.

This medicine contains aspartame and sorbitol
Contains aspartame as a source of phenylalanine and may be harmful for people with phenylketonuria.
Neither non-clinical nor clinical data are available to assess aspartame use in infants below 12 weeks of age.

Patients with hereditary fructose intolerance (HFI) should not take/be given this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

There is no evidence that ondansetron either induces or inhibits the metabolism of other drugs commonly coadministered with it. Specific studies have shown that there are no interactions when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolised by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other enzymes and should result in little or no significant change in overall ondansetron clearance or dose requirement.

Use of ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias. Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Apomorphine
Based on reports of profound hypotension and loss of consciousness when ondansetron was administered with apomorphine hydrochloride, concomitant use with apomorphine is contraindicated.

Phenytoin, Carbamazepine and Rifampicin
In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine, and rifampicin), the oral clearance of ondansetron was increased and ondansetron blood concentrations were decreased.

Serotonergic Drugs (e.g. SSRIs and SNRIs) and buprenorphine
Ondansetron should be used cautiously when co-administered with buprenorphine or serotonergic medicinal products, such as MAO inhibitors, selective serotonin re-uptake inhibitors (SSRIs), serotonin norepinephrine re-uptake inhibitors (SNRIs) or tricyclic antidepressants as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Tramadol
Data from small studies indicate that ondansetron may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
Women of childbearing potential should consider the use of contraception.

Pregnancy
Based on human experience from epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during the first trimester of pregnancy.
In one cohort study including 1.8 million pregnancies, first trimester ondansetron use was associated with an increased risk of oral clefts (3 additional cases per 10 000 women treated; adjusted relative risk, 1.24, (95% CI 1.03-1.48)).
The available epidemiological studies on cardiac malformations show conflicting results.
Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity.
Ondansetron should not be used during the first trimester of pregnancy.

Breast-feeding
Studies have shown that ondansetron is excreted in the milk of lactating animals (see section 5.3). It is therefore recommended that mothers taking ondansetron should not breastfeed their infants.

4.7 Effects on ability to drive and use machines

In psychomotor testing ondansetron does not impair performance nor cause sedation. No detrimental effects on such activities are predicted from the pharmacology of ondansetron.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: 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) and very rare (<1/10,000).

Very common, common and uncommon events were generally determined from clinical trial data. The incidence in placebo was taken into account. Rare and very rare events were generally determined from postmarketing spontaneous data.

The following frequencies are estimated at the standard recommended doses of ondansetron.

Immune system disorders

Rare:	Immediate hypersensitivity reactions sometimes severe, including anaphylaxis.

Anaphylaxis can be life-threatening. Hypersensitivity reactions have been observed in patients who experienced the same reactions with other selective 5-HT_3 receptor antagonists.

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, acute, crisis-like oculomotor disorders with gaze apraxia [oculogyric crisis] and dyskinesias, but without any demonstrable permanent clinical sequelae)
Rare:	Dizziness predominantly during rapid IV administration.

Eye disorders

Rare:	Transient visual disturbances (e.g. blurred vision) predominantly during IV administration.
Very rare:	Transient blindness predominantly during IV administration.

In the majority of reported cases, blindness regressed within 20 minutes. Most patients were being treated with chemotherapeutic agents, including cisplatin. The cause of some of the reported cases of transient blindness was of cortical origin.

Cardiac disorders

Uncommon:	Arrhythmias, chest pain with or without ST segment depression, bradycardia.
Rare:	QTc prolongation (including Torsade de Pointes)

Vascular disorders

Common:	Sensation of warmth or flushing.
Uncommon:	Hypotension.

Respiratory, thoracic and mediastinal disorders

Uncommon:	Hiccups.

Gastrointestinal disorders

Common:	Constipation.

Hepatobiliary disorders

Uncommon: Asymptomatic increases in liver function tests.

These adverse reactions usually occurred in patients who had received chemotherapy with cisplatin.

Skin and subcutaneous tissue disorders
Very rare: Toxic skin eruption, including toxic epidermal necrolysis

Children and adolescents
The adverse reaction profile in children and adolescents was comparable to that observed in adults.

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

Symptoms and Signs
There is limited experience of ondansetron overdose. In the majority of cases, symptoms were similar to those already reported in patients receiving recommended doses (see section 4.8). Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second-degree AV block.

Ondansetron prolongs the QT interval in a dose-dependent fashion. ECG monitoring is recommended in cases of overdose.

Cases consistent with serotonin syndrome have been reported in young children following oral overdose.

Paediatric population
Paediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeded estimated ingestion of 4mg/kg) in infants and children aged 12 months to 2 years.

Treatment
There is no specific antidote for ondansetron, therefore in cases of suspected overdose, symptomatic and supportive therapy should be given as appropriate.

Further management should be as clinically indicated or as recommended by the national poisons centre, where available.

The use of ipecacuanha to treat overdose with ondansetron is not recommended as patients are unlikely to respond due to the anti-emetic action of ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: serotonin 5-HT_3 antagonists
ATC code: A04A A01

Mechanism of action
Ondansetron is a highly selective, competitive 5-HT_3 receptor antagonist.

The exact pharmacological mechanism of action in the control of nausea, retching and vomiting has not yet been elucidated in humans.

Animal studies show that both cytotoxic chemotherapy and radiation therapy cause a release of 5-hydroxytryptamine (5-HT, serotonin) in the small intestine. 5-HT stimulates 5- HT_3 receptors at neurons in the periphery (visceral afferent vagus) and in the central nervous system (area postrema), thereby inducing retching. Ondansetron antagonises the effect of 5-HT directly on 5-HT_3 receptors, thus inhibiting the biochemical/pharmacological process of vomiting.

Clinical efficacy and safety
In one pharmaco-psychological study in human subjects, ondansetron showed no sedative effect.

Prolongation of the QT interval
The effect of ondansetron on the QT interval was evaluated in a double-blind, randomised, placebo- and positive- (moxifloxacin) controlled crossover study with 58 healthy adult men and women. Doses of 8 mg and 32 mg ondansetron were infused intravenously over 15 minutes. At the highest tested dose of 32 mg, the maximum mean change (upper limit of 90% CI) in QTcF interval (Fridericia-corrected) versus placebo after baseline correction was 19.6 msec (21.5 msec). At the lower tested dose of 8 mg, the maximum mean change (upper limit of 90% CI) in QTcF interval (Fridericia-corrected) versus placebo after baseline correction was 5.8 msec (7.8 msec). In this study, no QTcF intervals exceeding 480 msec and no prolongation of the QTcF interval exceeding 60 msec were measured. No significant changes occurred in PR or QRS intervals as measured via an electrocardiogram.

Paediatric population
Chemotherapy-induced nausea, retching and vomiting
The efficacy of ondansetron in the control of chemotherapy-induced nausea and vomiting was investigated in a double-blind, randomised clinical study with 415 patients aged from 1 to 18 years (S3AB3006). On treatment days, the patients were given either 5 mg/m^2 ondansetron intravenously and 4 mg ondansetron orally after 8 to 12 hours, or 0.45 mg/kg BW ondansetron intravenously and an oral placebo dose after 8 to 12 hours. Complete control of emesis on the treatment day with the most violent symptoms was 49% (5 mg/m^2 IV and 4 mg ondansetron p.o.) vs. 41% (0.45 mg/kg IV and placebo p.o.). After chemotherapy, both groups received 4 mg ondansetron solution twice daily for three days. There was no difference in the overall incidence or in the type of adverse reactions observed between both treatment groups.

A double-blind, randomised and placebo-controlled clinical study (S3AB4003) with 438 patients aged from 1 to 17 years showed, on the treatment day with the most violent symptoms, complete control of emesis in

- 73% of patients receiving an intravenous dose of 5 mg/m^2 ondansetron with 2 to 4 mg dexamethasone orally and in
- 71% of patients receiving 8 mg ondansetron solution with 2 to 4 mg dexamethasone orally on treatment days.

Post-chemotherapy both groups received 4 mg ondansetron syrup twice daily for 2 days. There was no difference in the overall incidence or nature of adverse events between the two treatment groups.

The efficacy of ondansetron in 75 children aged 6 to 48 months was investigated in an open-label, non-comparative, single-arm study (S3A40320). All children received three 0.15 mg/kg doses of intravenous ondansetron, administered 30 minutes before the start of chemotherapy and then at 4 and 8 hours after the first dose. Complete control of emesis was achieved in 56% of patients.

Another open-label, non-comparative, single-arm study (S3A239) investigated the efficacy of one intravenous dose of 0.15 mg/kg ondansetron followed by two oral ondansetron doses of 4 mg for children aged < 12 years and 8 mg for children aged ≥ 12 years (total no. of children n = 28). Complete control of emesis was achieved in 42% of patients.

Prophylaxis of postoperative nausea and vomiting
The efficacy of a single dose of ondansetron in the prevention of post-operative nausea and vomiting was investigated in a randomised, double-blind, placebo-controlled study in 670 children aged 1 to 24 months (postconceptual age ≥44 weeks, weight ≥ 3 kg). Included subjects were scheduled to undergo elective surgery under general anaesthesia and had an ASA status ≤ III. A single dose of ondansetron 0.1 mg/kg was administered within five minutes following induction of anaesthesia. The proportion of subjects who experienced at least one emetic episode during the 24-hour assessment period (ITT) was greater for patients on placebo than those receiving ondansetron (28% vs. 11%, p <0.0001).

Four double-blind, placebo-controlled studies have been performed in 1469 male and female patients (2 to 12 years of age) undergoing general anaesthesia. Patients were randomised to either single intravenous doses of ondansetron (0.1 mg/kg for paediatric patients weighing 40 kg or less, 4 mg for paediatric patients weighing more than 40 kg; number of patients = 735) or placebo (number of patients = 734). Study drug was administered over at least 30 seconds, immediately prior to or following anaesthesia induction. Ondansetron was significantly more effective than placebo in preventing nausea and vomiting. The results of these studies are summarised in Table 3.

Table 3: Prevention and treatment of postoperative nausea and vomiting in paediatric patients – treatment response over 24 hours

Study	**Endpoint**	**Ondansetron %**	**Placebo %**	**p-value**
S3A380	CR	68	39	≤ 0.001
S3GT09	CR	61	35	≤ 0.001
S3A381	CR	53	17	≤ 0.001
S3GT11	No nausea	64	51	0.004
S3GT11	No vomiting	60	47	0.004

CR = no emetogenic episodes, emergency care or study termination

5.2 Pharmacokinetic properties

Mean pharmacokinetic parameter values:

	8 mg orally	8 mg IV
Time to peak plasma concentration (t_{max}):	1.6 h	0.12 h
Elimination half-life ($t_{½}$):	approximately 3 h	approximately 3 h
	(in elderly patients up to 5 h)	

Absorption
Mean bioavailability in healthy male subjects, following the administration of a single 8 mg tablet, is approximately 55 to 60%. There is no direct correlation of plasma concentration and anti-emetic effect.

Distribution
Plasma protein binding (*in vitro*) is 70 to 76%.

Biotransformation
Ondansetron is metabolised via several hepatic cytochrome P450 isoenzymes - CYP3A4, CYP2D6 and CYP1A2. Deficiency of the CYP2D6 enzyme (debrisoquine polymorphism) does not affect the pharmacokinetic behaviour of ondansetron. The pharmacokinetic properties of ondansetron are unchanged with repeated administration.

Elimination
Ondansetron is primarily eliminated via hepatic metabolism. Metabolites are excreted with urine and faeces.

Special Patient Populations

Paediatric population (aged 1 month to 17 years)
In paediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight normalised clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to the patients aged 3 to 12 years. The half-life in the patient population aged 1 to 4 month was reported to average 6.7 hours compared to 2.9 hours for patients in the 5 to 24 month and 3 to 12 year age range. The differences in pharmacokinetic parameters in the 1 to 4 month patient population can be explained in part by the higher percentage of total body water in neonates and infants and a higher volume of distribution for water soluble drugs like ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery with general anaesthesia, the absolute values for both the clearance and volume of distribution of ondansetron were reduced in comparison to values with adult patients. Both parameters increased in a linear fashion with weight and by 12 years of age, the values were approaching those of young adults. When clearance and volume of distribution values were normalised by body weight, the values for these parameters were similar between the different age group populations. Use of weight based dosing compensates for age-related changes and is effective in normalising systemic exposure in paediatric patients.

Population pharmacokinetic analysis was performed on 428 subjects (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years following intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron following oral or IV dosing in Paediatric population was comparable to adults, with the exception of infants aged 1 to 4 months. Volume was related to age and was lower in adults than in infants and children. Clearance was related to weight but not to age with the exception of infants aged 1 to 4 months.
It is difficult to conclude whether there was an additional reduction in clearance related to age in infants 1 to 4 months or simply inherent variability due to the low number of subjects studied in this age group. Since patients less than 6 months of age will only receive a single dose of ondansetron in post operative nausea and vomiting a decreased clearance is not likely to be clinically relevant.

Elderly
Early Phase I studies in healthy elderly volunteers showed a slight age-related decrease in clearance, and an increase in half-life of ondansetron. However, wide inter-subject variability resulted in considerable overlap in pharmacokinetic parameters between young (< 65 years of age) and elderly subjects (≥ 65 years of age) and there were no overall differences in safety or efficacy observed between young and elderly cancer patients enrolled in CINV clinical trials to support a different dosing recommendation for the elderly.
Based on more recent ondansetron plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥75 years of age compared to young adults. Specific dosing information is provided for patients over 65 years of age and over 75 years of age for intravenous dosing (see section 4.2).

Patients with renal impairment
In patients with renal impairment (creatinine clearance 15-60 mL/min), both systemic clearance and volume of distribution are reduced following IV administration of ondansetron, resulting in a slight, but clinically insignificant increase in elimination half-life (5.4 hours). A study in patients with severe renal impairment who required regular haemodialysis (studied between dialyses) showed ondansetron's pharmacokinetics to be essentially unchanged.

Patients with hepatic impairment

In patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15-32 hours) and an oral bioavailability approaching 100% because of reduced pre-systemic metabolism.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential.

Reproductive studies in rats and rabbits did not show evidence of harm to the foetus when ondansetron was administered during organogenesis at approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, based on body surface area, respectively.

In embryo-foetal development studies in rats and rabbits, pregnant animals received oral doses of ondansetron up to 15 mg/kg/day and 30 mg/kg/day, respectively, during the period of organogenesis. With the exception of a slight decrease in maternal body weight gain in the rabbits, there were no significant effects of ondansetron on the maternal animals or the development of the offspring. At doses of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal dose was approximately 6 and 24 times the maximum recommended human oral dose of 24 mg/day, respectively, based on body surface area.

In a pre- and postnatal developmental toxicity study, pregnant rats received oral doses of ondansetron up to 15 mg/kg/day from Day 17 of pregnancy to litter Day 21. With the exception of a slight reduction in maternal body weight gain, there were no effects upon the pregnant rats and the pre- and postnatal development of their offspring, including reproductive performance of the mated F1 generation. At a dose of 15 mg/kg/day in rats, the maternal dose was approximately 6 times the maximum recommended human oral dose of 24 mg/day based on BSA.

Ondansetron and its metabolites accumulate in the milk of rats with a milk plasma ratio of 5.2:1.
A study in cloned human cardiac ion channels has shown that ondansetron has the potential to affect cardiac repolarisation by blocking the hERG potassium channels.

In one thorough QT study in healthy subjects, a dose-dependent prolongation of the QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sorbitol
Crospovidone
Colloidal silicon dioxide
Microcrystalline cellulose
Aspartame
Strawberry flavouring
Sodium stearyl fumarate
Magnesium stearate [vegetable]

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

Aluminium/aluminium blisters.
Pack size: 6 orodispersible tablets

6.6 Special precautions for disposal and other handling

No special requirements

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER(S) IN GERMANY

4 mg: 68302.00.00
8 mg: 68303.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

27.8.2010

10. DATE OF REVISION OF THE TEXT

02/2021

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.