SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ondansetron Aristo 4 mg film-coated tablets
Ondansetron Aristo 8 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

<Invented name> 4 mg film-coated tablets
One film-coated tablet contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipient with known effect:
One film-coated tablet contains 19.137 mg lactose.

<Invented name> 8 mg film-coated tablets
One film-coated tablet contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipient with known effect:
One film-coated tablet contains 38.274 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

<Invented name> 4 mg film-coated tablets
White to cream-coloured, oval-shaped film-coated tablets.

<Invented name> 8 mg film-coated tablets
Yellow, oval-shaped, film-coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

<Invented name> is used for the treatment of nausea and vomiting in therapy with cytotoxic agents and radiotherapy, as well as for the prevention of nausea and vomiting after surgery.

4.2 Posology and method of administration

Posology

Chemotherapy and radiotherapy-induced nausea and vomiting
The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. Selection of the dose and dosing regimen must therefore be guided by the emetogenic potential.

Adults
The recommended oral dose is 8 mg, taken 1-2 hours prior to chemotherapy or radiation, followed by 8 mg orally every 12 hours over a maximum of 5 days.

In highly emetogenic chemotherapy, a single oral dose up to a maximum of 24 mg ondansetron can be given orally together with 12 mg dexamethasone-21-dihydrogen phosphate disodium salt

or equivalent 1 to 2 hours prior to chemotherapy. After the first 24 hours, ondansetron treatment can be continued orally for up to 5 days after a course of treatment. The recommended dose is 8 mg, twice daily.

For the prevention of delayed or prolonged emesis, oral treatment is recommended.

Children and adolescents (aged 6 months to 17 years)
The dose for treatment of chemotherapy-induced nausea and vomiting can be calculated on the basis of body surface area (BSA) or based on body weight. In clinical studies with children and adolescents, ondansetron was given as an intravenous infusion, diluted in 25 to 50 mL saline solution or another compatible solution for infusion, over no less than 15 minutes. Posology based on body weight results in higher total daily doses compared with posology based on body surface area (see section 5.2).

No data are available from controlled clinical studies on the use of ondansetron for the prevention of prolonged (protracted) chemotherapy-induced nausea and vomiting. Similarly, no data are available from controlled clinical studies on the use of ondansetron in radiotherapy-induced nausea and vomiting in children.

Posology based on body surface area:
Ondansetron should be intravenously administered immediately prior to chemotherapy at an initial dose of 5 mg/m^2. The single IV dose must not exceed 8 mg. Administration of oral doses can proceed 12 hours later and can be continued over a period of up to 5 days (see Table 1). The total dose within 24 hours (as divided doses) must not exceed the adult dose of 32 mg.

Table 1: Posology based on body surface area in chemotherapy-induced nausea and vomiting (aged 6 months to 17 years)

Body surface area	**Day 1**	**Days 2-6**
< 0.6 m^2	**Initially** 5 mg/m^2 IV *plus* 2 mg ondansetron **after 12 hours**	**Every 12 hours:** 2 mg ondansetron
≥ 0.6 m^2 to ≤ 1.2 m^2	**Initially** 5 mg/m^2 IV *plus* 4 mg ondansetron **after 12 hours**	**Every 12 hours:** 4 mg ondansetron
> 1.2 m^2	**Initially** 5 mg/m^2 IV or 8 mg IV *plus* 8 mg ondansetron **after 12 hours**	**Every 12 hours:** 8 mg ondansetron

Posology based on body weight:
Posology based on body weight results in higher total daily doses compared to posology based on body surface area (see section 5.2).

Ondansetron should be administered immediately prior to chemotherapy as an intravenous single dose of 0.15 mg/kg body weight. The single IV dose must not exceed 8 mg. If needed, 2 further IV doses can be administered at a 4-hour interval.

Administration of oral doses can proceed 12 hours later and can be continued over a period of up to 5 days (see Table 2).

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

Table 2: Posology based on body weight in chemotherapy-induced nausea and vomiting (aged ≥ 6 months up to 17 years)

Body weight	**Day 1**	**Days 2-6**
≤ 10 kg	Up to 3 × 0.15 mg/kg doses IV every 4 hours	2 mg ondansetron every 12 hours
> 10 kg	Up to 3 × 0.15 mg/kg doses IV every 4 hours	4 mg ondansetron every 12 hours

Elderly patients
No dose adjustment or change in the dosing frequency is required.

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

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

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in patients categorised as poor sparteine/debrisoquine metabolisers. Consequently, no difference in exposure after repeated administration is expected in such patients compared with the general population. No change in the dose or dosing frequency is required.

Post-operative nausea and vomiting (PONV)

Adults
For the prevention of PONV, ondansetron can be administered orally or by slow intravenous injection.

For the prevention of PONV, the recommended dose is 16 mg ondansetron orally 1 hour prior to anaesthesia.

For the treatment of established PONV, treatment with ondansetron as a slow intravenous injection is recommended.

Children and adolescents (aged 1 month up to 17 years)
No studies are available on the oral administration of ondansetron for the prophylaxis or treatment of postoperative nausea and vomiting; in this case, a slowly administered intravenous injection (over no less than 30 seconds) is recommended.

For children under 2 years of age, only limited data are available on the use of ondansetron for the treatment of postoperative nausea, nausea and vomiting.

Elderly
There is limited experience in the use of ondansetron in the prevention and treatment of post-operative nausea and vomiting (PONV) in the elderly, however ondansetron is well tolerated in patients over 65 years receiving chemotherapy.

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

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

Patients with poor sparteine/debrisoquine metabolism
The elimination half-life of ondansetron is not altered in patients categorised as poor sparteine/debrisoquine metabolisers. Consequently, no difference in exposure after repeated administration is expected in such patients compared with the general population. No change in the dose or dosing frequency is required.

Method of administration

Oral use.

4.3 Contraindications

Concomitant use with apomorphine (see section 4.5).

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

<Invented name> 4 mg film-coated tablets 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 this patient group, more suitable dosage forms with a lower level of active substance are available.

<Invented name> 8 mg film-coated tablets must not be used in children. For this patient group, more suitable dosage forms with a lower level of active substance are available.

4.4 Special warnings and precautions for use

Hypersensitivity reactions have been observed in patients who have exhibited hypersensitivity to other selective 5-HT_3 receptor antagonists. If respiratory complaints occur, these should be treated symptomatically and monitored carefully by the physician, as respiratory complaints may be symptoms of an incipient hypersensitivity reaction.

Ondansetron dose-dependently prolongs the QT interval (see section 5.1). Furthermore, cases of torsade de pointes have been reported in post-marketing spontaneous reports among patients receiving ondansetron. In patients with congenital long QT syndrome, the use of ondansetron should be avoided. In patients with a prolonged QTc interval or who may develop a prolonged QTc interval, ondansetron should be used with caution. This group includes patients with electrolyte disturbances, congestive heart failure, bradyarrhythmias or patients taking other medicines that cause prolongation of the QT interval or electrolyte disturbances.

Cases of myocardial ischemia have been reported in patients treated with ondansetron. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Hypokalaemia or hypomagnesaemia should be corrected prior to administration of ondansetron.

Cases of serotonin syndrome, a potentially life-threatening condition, have been reported in concomitant use of ondansetron with other serotonergic agents (see section 4.5).
If concomitant treatment with ondansetron and other serotonergic agents (including selective serotonin reuptake inhibitors (SSRIs), noradrenaline reuptake inhibitors (SNRIs) and buprenorphine) is clinically warranted, careful observation of the patient is advised.
Symptoms of serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms.
If serotonin syndrome is suspected, discontinuation of therapy should be considered depending on the severity of the symptoms.

As ondansetron slows colonic transit, patients with signs of subacute intestinal obstruction should be monitored following the administration of ondansetron.

Prophylaxis of nausea and vomiting with ondansetron may mask occult bleeding after adenotonsillar surgery. Therefore, affected patients should be monitored carefully after administration of ondansetron.

Paediatric population
Children and adolescents receiving ondansetron together with hepatotoxic chemotherapy agents should be closely monitored for hepatic dysfunction.

<Invented name>contains lactose
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

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 medicinal products commonly co-administered with it. Specific studies have shown that ondansetron does not interact with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental and propofol.
Ondansetron is metabolised by multiple hepatic cytochrome P450 isoenzymes – CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of cytochrome P450 isoenzymes capable of metabolising ondansetron, inhibition or reduced activity of any one isoenzyme (e.g. CYP2D6 genetic deficiency) is normally compensated by other isoenzymes. Thus, no significant change in ondansetron clearance or dose requirement should arise.

Administration of ondansetron with QT interval-prolonging medicines may further prolong the QT interval. Concomitant use of ondansetron with cardiotoxic medicines (e.g. anthracyclines) may increase the risk for the onset of arrhythmias. Concomitant use of ondansetron with medicinal products that induce prolongation of the QT interval and/or electrolyte disturbances should proceed with caution (see section 4.4).

Apomorphine
Due to reports of severe hypotension and loss of consciousness when ondansetron is used together 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), oral ondansetron clearance was increased and ondansetron blood concentrations were decreased.

Serotonergic medicinal products (e.g. SSRIs, SNRIs and buprenorphine)
<Invented name> should be used cautiously when co-administered with serotonergic medicinal products such as selective serotonin reuptake inhibitors (SSRIs), serotonin noradrenaline reuptake inhibitors (SNRIs) and buprenorphine as the risk of serotonin syndrome, a potentially life-threatening condition, is increased (see section 4.4).

Tramadol
Data from smaller 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
Tests have shown that ondansetron passes into the milk of lactating animals (see section 5.3). It is therefore recommended that mothers receiving ondansetron should not breast-feed their babies.

4.7 Effects on ability to drive and use machines

Ondansetron has no or negligible influence on the ability to drive and use machines. In psychomotor tests, it showed no performance-impairing or sedative effect. No adverse effect on these skills can be inferred from the pharmacological properties of the active substance ondansetron.

4.8 Undesirable effects

Adverse events are listed below by system organ class and absolute frequency (all reported events). Frequencies are defined as:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
not known	(cannot be estimated from the available data)

Very common, common and uncommon adverse reactions were generally determined from clinical trial data. The incidence of adverse reactions with placebo was taken into account. Rare and very rare adverse events were generally determined from post-marketing spontaneous data.

The following frequencies were determined with standard ondansetron dosing.

Immune system disorders

Rare:	Immediate hypersensitivity reactions (sometimes severe), including anaphylaxis.

Anaphylaxis can be life-threatening. Hypersensitivity reactions have also been observed in patients who have shown such phenomena with other selective 5-HT_3 antagonists.

Nervous system disorders

Very common:	Headache
Uncommon:	Seizures, movement disorders (including extrapyramidal reactions such as dystonic reactions, acute spasmodic oculomotor disorders with gaze deviation [oculogyric crisis] and dyskinesias), but without demonstrable long-term clinical sequelae
Rare:	Light-headedness, mainly with rapid IV administration

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

The majority of the blindness cases reported resolved within 20 minutes. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.

Cardiac disorders
Uncommon: Arrhythmias, chest pain with or without ST-segment depression on the ECG, bradycardia
Rare: QTc prolongation (including torsade de pointes)
Not known: Myocardial ischemia (see section 4.4)

Vascular disorders
Common: Sensation of warmth or flushing
Uncommon: Hypotension (fall in blood pressure)

Respiratory, thoracic and mediastinal disorders
Uncommon: Hiccups

Gastrointestinal disorders
Common: Constipation

Hepatobiliary disorders
Uncommon: Asymptomatic increases in liver function tests*

*These events were observed commonly in patients receiving chemotherapy with cisplatin.

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

Children and adolescents
The adverse reaction profile in children and adolescents was comparable to the adverse reaction profile 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 Appendix V.

4.9 Overdose

Symptoms and signs
There is insufficient experience with ondansetron overdose. Symptoms were similar to those reported in patients after the recommended dosage (see section 4.8). Manifestations of an overdose included visual disturbances, severe constipation, low blood pressure and a vasovagal episode with transient second-degree AV block.

Ondansetron dose-dependently prolongs the QT interval. In the event of an overdose, ECG monitoring is recommended.

Paediatric population

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

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

The further course of action should be as clinically indicated or in accordance with national poison centre recommendations.

The use of ipecac (ipecacuanha) to treat an overdose with ondansetron is not recommended, as patients are unlikely to respond due to the antiemetic action of ondansetron itself.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: serotonin 5-HT_3 antagonists,
ATC code: A04AA01

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 and vomiting in humans is not yet elucidated. Animal studies show that both cytotoxic chemotherapy and radiotherapy elicit the release of 5-hydroxytryptamine (5-HT, serotonin) in the small intestine. 5-HT stimulates 5-HT_3 receptors on neurons in the periphery (visceral afferent vagus) and in the central nervous system (area postrema), thereby resulting in retching. Ondansetron antagonises the action of 5-HT directly at 5-HT_3 receptors and thus inhibits the biochemical/pharmacological process of emesis.

Clinical efficacy and safety
In a pharmaco-psychological study in volunteers ondansetron has not shown a sedative effect.

Prolongation of the QT interval
The effect of ondansetron on the QT interval was investigated 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 the QTcF interval (Fridericia correction) 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 the QTcF interval (Fridericia correction) versus placebo after baseline correction was 5.8 msec (7.8 msec). In this study, there were no QTcF intervals above 480 msec and no prolongation of the QTcF interval above 60 msec was measured. No significant changes occurred in PR- and QRS intervals, as measured by electrocardiogram.

Children and adolescents

Chemotherapy-induced nausea and vomiting:
The efficacy of ondansetron in the control of chemotherapy-induced vomiting and nausea was investigated in a double-blind, randomised clinical study with 415 patients aged 1 to 18 years (S3AB3006). On treatment days, patients received either 5 mg/m^2 ondansetron intravenously and 4 mg ondansetron orally after 8 to12 hours or 0.45 mg/kg body weight (BW) of ondansetron intravenously and an oral placebo dose after 8 to 12 hours. Complete control of emesis on the treatment day with the most severe symptoms was 49% (5 mg/m^2 IV and ondansetron 4 mg p.o.)

and 41% (0.45 mg/kg IV and placebo p.o.). Following chemotherapy, both groups received 4 mg ondansetron as a solution twice daily for three days. No difference was observed in the overall incidence or nature of adverse reactions between both treatment groups.

A double-blind, randomised and placebo-controlled clinical study (S3AB4003) with 438 patients aged 1 to 17 years demonstrated, on the treatment day with the most severe 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 as a solution with 2 to 4 mg dexamethasone orally on treatment days.

Following chemotherapy, both groups received 4 mg ondansetron as a solution twice daily for two days. No difference was observed in the overall incidence or nature of adverse events between both treatment groups.

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

Another open-label, uncontrolled, single-arm study (S3A239) with 28 children investigated the efficacy of an intravenous dose of 0.15 mg/kg BW ondansetron, followed by two oral doses with 4 mg ondansetron for children under 12 years or with 8 mg ondansetron for children aged 12 years and older. 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 prophylaxis of postoperative nausea and vomiting was investigated in a randomised, double-blind and placebo-controlled study with 670 children aged 1 to 24 months (post-conceptional age ≥ 44 weeks, weight ≥ 3 kg). Elective surgery under general anaesthesia was scheduled for enrolled patients with an ASA status of ≤ III. After induction of anaesthesia, a single dose of 0.1 mg/kg BW ondansetron was administered within 5 minutes. The proportion of patients experiencing at least one emetogenic episode during the 24-hour observation phase (ITT) was greater in the placebo group than for patients receiving ondansetron (28% vs. 11%, $p < 0.0001$).

Four randomised, double-blind and placebo-controlled studies have been performed with 1,469 male and female patients aged 2 to 12 years undergoing general anaesthesia. Patients were randomised either to treatment with a single dose of ondansetron IV (0.1 mg/kg for children with a body weight of 40 kg or less, 4 mg for children with a body weight over 40 kg; number of patients = 735) or to treatment with placebo (number of patients = 734). The study medication was administered over at least 30 seconds shortly before or after induction of anaesthesia. The efficacy of ondansetron in the prophylaxis of postoperative nausea and vomiting was significantly greater compared with placebo. The results of these studies are summarised in Table 3.

Table 3: Prophylaxis and treatment of postoperative nausea and vomiting in paediatric patients – 24-hour response to treatment

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 discontinuation

5.2 Pharmacokinetic properties

Absorption
Peak plasma concentrations of about 30 ng/ml are attained approximately 1.5 hours after an 8 mg oral dose. Mean bioavailability in healthy volunteers, after administration of a single 8 mg tablet, is about 55 to 60%. There is no direct correlation between plasma levels and antiemetic 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
The clearance of ondansetron mainly occurs via its hepatic metabolism. The metabolites are excreted in the urine and faeces. The elimination half-life is approximately 3 hours.

Special patient populations

Paediatric population
In paediatric patients aged 1 to 4 months (n = 19) undergoing surgery, weight-normalised clearance was approximately 30% slower compared to clearance in patients aged between 5 and 24 months (n = 22), but was comparable to that in patients aged 3 to 12 years. The mean half-life in the patient population aged 1 to 4 months was 6.7 hours versus 2.9 hours in patients aged 5 to 24 months and 3 to 12 years, respectively. The differences in pharmacokinetic parameters in the 1- to 4-month-old patient population can be explained in part by the higher proportion of body water in newborns and infants and by the higher volume of distribution for water-soluble active substances such as ondansetron.

In paediatric patients aged 3 to 12 years undergoing elective surgery under general anaesthesia, the absolute values both for the clearance and volume of distribution of ondansetron were reduced in comparison to values in adult patients. Both parameters increased linearly in relation to body weight and, at 12 years of age, were close to those in young adults. After adjustment of clearance and volume of distribution for body weight, the values for these parameters were similar between the different age groups. Use of a weight-based dosage takes age-related changes into account and brings about normalisation of systemic exposure in paediatric patients.

The pharmacokinetic analysis was performed in a population of 428 patients (cancer patients, surgery patients and healthy volunteers) aged 1 month to 44 years after intravenous administration of ondansetron. Based on this analysis, systemic exposure (AUC) of ondansetron after oral or intravenous administration in children and adolescents was comparable to that in adults, with the exception of children aged 1 to 4 months. The volume was age-related and was lower in adults than in infants and children. Clearance was dependent on weight, but not on age, with the exception of children aged 1 to 4 months. It is difficult to conclude whether children aged 1 to 4 months underwent an additional reduction in age-related clearance or whether the cause is simply due to innate variability, owing to the low number of patients studied in this age group.

As patients under 6 months of age receive only a single dose of ondansetron in postoperative nausea and vomiting, decreased clearance is deemed not to be clinically relevant.

Elderly patients
Early phase I studies in healthy elderly volunteers showed an age-related decrease in clearance and an increase in the half-life of ondansetron. However, wide interindividual variability led to a considerable overlap in pharmacokinetic parameters between younger (< 65 years) and elderly subjects (> 65 years) and, in the clinical studies on chemotherapy-induced nausea and vomiting, there were no overall differences in the safety or efficacy observed between younger and elderly cancer patients to support different dosage recommendations for elderly patients.

Patients with renal impairment
In patients with moderate renal impairment (creatinine clearance 15 to 60 mL/min), both systemic clearance and volume of distribution are reduced after intravenous administration of ondansetron, resulting in a slight, but clinically insignificant increase in the elimination half-life (to 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 following IV administration.

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

5.3 Preclinical safety data

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

Reproductive toxicology studies
Reproductive toxicology studies with rats and rabbits revealed no indications of a harmful effect for the foetus when ondansetron was respectively administered during organogenesis at approximately 6-fold and 24-fold the maximum recommended human oral dose of 24 mg/day, based on body surface area.

In studies with rats and rabbits on embryofoetal development, pregnant animals received ondansetron at oral doses of up to 15 mg/kg/day and 30 mg/kg/day, respectively, during organogenesis. With the exception of a slight decrease in maternal body weight in rabbits, there were no significant effects of ondansetron on the mother animals or development of the offspring. Dosages of 15 mg/kg/day in rats and 30 mg/kg/day in rabbits were respectively equivalent to approximately 6-fold and 24-fold the maximum recommended human oral dose of 24 mg/day, based on body surface area.

In toxicity studies on pre- and postnatal development, pregnant rats received oral ondansetron doses of up to 15 mg/kg/day from day 17 of pregnancy up to parturition on day 21. With the exception of a slight decrease in maternal body weight, there were no toxic effects of ondansetron on the pregnant rats or on pre- and postnatal development of their offspring, including reproductive behaviour of the associated F1 generation. Dosages of 15 mg/kg/day in rats were equivalent to approximately 6-fold the maximum recommended human oral dose of 24 mg/day, based on body surface area.

Ondansetron and its metabolites accumulate in the milk of rats at a milk/plasma ratio of 5.2:1.

A study on cloned human cardiac ion channels has shown that ondansetron has the potential to affect cardiac repolarisation via blockade of hERG potassium channels. In a thorough QT study with healthy subjects, a dose-dependent prolongation of the QT interval was observed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Lactose
Cellulose, microcrystalline
Starch, pregelatinised (maize)
Magnesium stearate (Ph. Eur.)

Film-coating:
Hypromellose
Triacetin
Titanium dioxide (E 171)
Iron oxide yellow (for 8 mg tablets only)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister (PVC/Aluminium) Pack size:
4 mg: 4, 6, 7, 10, 14, 15, 28, 30, 49, 50and 100 tablets.
8 mg: 4, 5, 6, 10, 15, 30, 49, 50 and 100 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

[To be completed nationally]

8. MARKETING AUTHORISATION NUMBER

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD/MM/YYYY

[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

02/06/2022