**TECHNICAL SHEET**

## 1. NAME OF THE MEDICINAL PRODUCT

Ondansetron Normon 4 mg film-coated tablets EFG.
Ondansetron Normon 8 mg Film-coated tablets EFG.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Ondansetron Normon 8 mg tablet contains 8 mg of ondansetron as ondansetron hydrochloridedihydrate.

Each Ondansetron NORMON 4 mg tablet contains 4 mg of ondansetron as ondansetron hydrochloride dihydrate.

Excipient(s) with known effect Each
Ondansetron Normon 4 mg tablet contains 0.078 mg of lactose.
Each Ondansetron Normon 8 mg tablet contains 0.156 mg of lactose.For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.
Yellow, elongated, biconvex tablet.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic indications

*Adults*

Ondansetron is indicated for the control of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of postoperative nausea and vomiting.

*Pediatric population*

Ondansetron is indicated for the control of chemotherapy-induced nausea and vomiting in children aged 6 months and older.

There are no studies on the use of orally administered ondansetron in the prevention and treatment ofpostoperative nausea and vomiting. Injectable ondansetron is recommended for the treatment of postoperative nausea and vomiting in children 1 month of age and older.

### 4.2. Dosage and method of administration

Posology

Ondansetron tablets are administered orally.

**Chemotherapy- and radiotherapy-induced nausea and vomiting (CINV and RINV)**

The emetogenic potential of cancer treatment varies according to the doses and combinations of chemotherapy and radiotherapy regimens used. The choice of dosage regimen should be determined by the severity of emesis.

Adults

*Emetogenic chemotherapy and radiotherapy:*

It is recommended to use a dose of 8 mg orally, 1-2 hours before treatment with chemotherapy or radiotherapy, followed by8 mg administered orally 12 hours later for a maximum period of 5 days.

When highly emetogenic chemotherapy is used, a single dose of 24 mg ondansetron may be administered orally with 12 mgdexamethasone sodium phosphate orally, one to two hours before chemotherapy. After the first 24 hours, oral ondansetron may be continued, 8 mg twice daily, for 5 days after a treatment cycle.

Pediatric population

*Chemotherapy-induced nausea and vomiting in children ÿ 6 months and adolescents*

The dose for chemotherapy-induced nausea and vomiting may be calculated on a body surface area or weight basis – see below. If the dose is calculated on a weight basis, the total daily dose results in higher doses than if the dose is calculated ona body surface area basis (see sections 4.4 and 5.1).

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 nauseaand vomiting induced by radiotherapy in children.

*Calculation of dose per body surface area:*

Ondansetron should be administered immediately prior to chemotherapy as a single intravenous dose of 5 mg/m2 .

The intravenous dose should not exceed 8 mg.

Oral dosing may be started 12 hours later and may be continued for up to 5 days (see Table 1 below). The total daily doseshould not exceed the adult dose of 32 mg.

*Table 1: Dose per body surface area for chemotherapy-induced nausea and vomiting - Children ÿ6 months and adolescents*

| *Body surface area* | *Day 1(a,b)* | *Days 2-6 (b)* |
|---|---|---|
| *<0.6 m2* | *5 mg/ m2 intravenously plus 2 mg orallyafter 12 hours* | *2 mg orally every 12 hours (c)4 mg orally, every 12 hours(c)* |
| *ÿ 0.6 m2* | *5 mg/ m2 intravenously plus 4 mg orallyafter 12 hours* | |

a. The intravenous dose should not exceed 8 mg. b.
The total daily dose should not exceed the adult

dose of 32 mg.
c. The 2 mg dose cannot be obtained with the 4 mg tablets as these have not been manufactured to be broken into two equaltablets.

*Dosage calculation by body weight:*

If the dose is calculated on a weight basis, the results in total daily dose are higher than if it is calculated on a body surfacebasis (see sections 4.4 and 5.1).

Ondansetron should be administered immediately prior to chemotherapy as a single intravenous dose of 0.15 mg/kg. Theintravenous dose should not exceed 8 mg.
Two additional intravenous doses should be administered at 4-hour intervals. The total daily dose should not exceed the adult
dose of 32 mg.
Oral dosing may begin 12 hours later and may be continued for up to 5 days (see Table 2 below).

*Table 2: Weight-Based Dosing for Chemotherapy-Induced Nausea and Vomiting (Children ÿ6 Months and Adolescents)*

| | Day 1(a,b) | Days 2-6 (b) |
|---|---|---|
| Weight ÿ10 kg | Up to 3 doses of 0.15 mg/kg IV every 4hours | 2 mg orally every 12 hours(c) |
| >10 kg | Up to 3 doses of 0.15 mg/kg IV every 4hours | 4 mg orally, every 12 hours(c) |

a. The intravenous dose should not exceed 8 mg. b. The total daily dose should not exceed the adult dose of 32 mg.
c. The 2 mg dose cannot be obtained with the 4 mg tablets as these have not been manufactured to be broken into two equaltablets.

Elderly patients

No modifications are required to the oral dose or frequency of administration.

Patients with renal failure

No variation in daily dose, frequency of dosing or route of administration is required.

Patients with hepatic impairment:

Ondansetron clearance is significantly reduced and the serum half-life significantly prolonged in subjects with moderate orsevere hepatic impairment. In such patients a total daily dose of 8 mg intravenously or orally should not be exceeded.

Patients who are slow metabolizers of sparteine/debrisoquine

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine.
Therefore, the levels of exposure to the drug after repeated administration in these patients do not differ from those achieved in the general population. Therefore, no modification of the daily dose or frequency of administration is required.

**Postoperative nausea and vomiting (PONV)**

Adults

For the prevention of postoperative nausea and vomiting, the recommended oral dose is 16 mg administered one hour before anesthesia.

For the treatment of established postoperative nausea and vomiting, the administration of ondansetron injectable is recommended (see SPC for ondansetron injectable solution).

Pediatric population

*Postoperative nausea and vomiting in children ÿ1 month and adolescents*

No studies have been performed on the use of orally administered ondansetron for the prevention or treatment of postoperative nausea and vomiting; slow intravenous injection is recommended (see SmPC for ondansetron solution for injection).

There are no data on the use of ondansetron in the treatment of postoperative nausea and vomiting in children under 2 years of age.

Elderly patients

There is little experience with the use of ondansetron in the prevention and treatment of postoperative nausea and vomiting in the elderly; however, ondansetron has been well tolerated in patients over 65 years of age receiving chemotherapy.

Patients with renal failure

No variation in daily dose, frequency of dosing or route of administration is required.

Patients with liver failure

Ondansetron clearance is significantly reduced and the serum half-life significantly prolonged in subjects with moderate or severe hepatic impairment. In such patients a total daily dose of 8 mg intravenously or orally should not be exceeded.

Patients who are slow metabolizers of sparteine/debrisoquine

The elimination half-life of ondansetron is not altered in subjects classified as poor metabolisers of sparteine and debrisoquine.
Therefore, the levels of exposure to the drug after repeated administration in these patients do not differ from those achieved in the general population. Therefore, no modification of the daily dose or frequency of administration is required.

Method of administration

Ondansetron Normon tablets are administered orally. The tablets are swallowed whole with a little water.

**4.3. Contraindications**

Hypersensitivity to the active substance, to other selective 5-HT3 receptor antagonists (e.g. granisetron, dolasetron) or to any of the excipients listed in section 6.1.

Based on reports of profound hypotension and loss of consciousness when administered ondansetron together with apomorphine hydrochloride, concomitant use of ondansetron and apomorphine is contraindicated (see section 4.5).

## 4.4. Special warnings and precautions for use

Hypersensitivity reactions have been reported in patients who have had hypersensitivity to other selective 5HT3 receptorantagonists.
Respiratory events should be treated symptomatically and physicians should pay particular attention to them as precursorsto hypersensitivity reactions.

Ondansetron prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases ofTorsade de Pointes have been reported in patients taking ondansetron.
Ondansetron should be avoided in patients with congenital long QT syndrome.
Ondansetron should be administered with caution in patients who have or may develop QTc prolongation, includingpatients with electrolyte disturbances, heart failure,

congestive, bradyarrhythmias or patients taking other drugs that cause QT interval prolongation or electrolyte disturbances.

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

Hypokalemia and hypomagnesemia should be corrected before administration of ondansetron.

Cases of serotonin syndrome have been reported following concomitant administration of ondansetron with other serotonergic medicinal products (see section 4.5). If concomitant treatment with ondansetron and serotonergic medicinal products is clinicallywarranted, patient monitoring is recommended.

Since ondansetron is known to increase intestinal transit time, patients should be monitored for signs of subacuteintestinal obstruction after its administration.

In patients who have undergone adenotonsillectomy, prevention of nausea and vomiting with ondansetron may mask occultbleeding. Therefore, such patients should be carefully monitored after receiving ondansetron.

In patients who have undergone adenotonsillectomy, prevention of nausea and vomiting with ondansetron may mask occultbleeding. Therefore, such patients should be carefully monitored after receiving ondansetron.

~~Pediatric population~~

Pediatric patients receiving ondansetron in conjunction with hepatotoxic chemotherapy should be monitored for changesin liver function.

Chemotherapy-induced vomiting and nausea: When the dose is calculated on a mg/kg body weight basis and three doses areadministered at 4-hour intervals, the total daily dose will be higher than if a single dose of 5 mg/m2 is administered followedby an oral dose. The comparative efficacy of these two dosing regimens has not been investigated in clinical trials.
Comparison between trials indicates similar efficacy of both regimens – see section 5.1.

Warnings on excipients

This medicine 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 induces or inhibits the metabolism of other drugs with which it is commonly co-administered. Specific studies indicate that there is no interaction when ondansetron is administered with alcohol, temazepam, furosemide, alfentanil, tramadol, morphine, lidocaine, thiopental or propofol.

Ondansetron is metabolized by multiple hepatic cytochrome P-450 enzymes: CYP3A4, CYP2D6, and CYP1A2. Because of the large number of metabolic enzymes capable of metabolizing ondansetron, inhibition or reduced activity of one enzyme (e.g., genetic deficiency of CYP2D6) is usually compensated for by other enzymes and should result in little or no significant change in overall ondansetron clearance or dosage requirements.

Caution should be exercised when co-administering ondansetron with drugs that prolong the QT interval and/or drugs that cause electrolyte disturbances (see section 4.4).

*Apomorphine*

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

*Phenytoin, carbamazepine and rifampicin*

In patients treated with potent CYP3A4 inducers (e.g., phenytoin, carbamazepine, and rifampin), oral clearance of ondansetronwas increased and plasma concentrations were reduced.

*Serotonergic medications (SSRIs, SNRIs)*

Cases of serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) have beenreported following concomitant administration of ondansetron with other serotonergic medicinal products including selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) (see section 4.4).

*Tramadol*

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

The use of ondansetron with drugs that prolong the QT interval may result in further prolongation of the QT interval. Concomitant use of ondansetron with cardiotoxic drugs (e.g. anthracyclines) may increase the risk of arrhythmias (seesections 4.4 and 4.8).

**4.6. Fertility, pregnancy and lactation**

Pregnancy

A pregnancy test should be performed in women of childbearing potential before starting treatment with Ondansetron.

Women of childbearing potential should be warned that Ondansetron Normon may cause harm to the developing fetus. It is recommended that sexually active women of childbearing potential use effective contraception (a method that results in pregnancy rates less than 1%) during treatment with Ondansetron Normon and for two days after stopping treatment with Ondansetron Normon.

Based on human experience gained from epidemiological studies, ondansetron is suspected of causing orofacial malformations ifadministered during the first trimester of pregnancy.
In a cohort study of 1.8 million pregnancies, first-trimester use of ondansetron was associated with an increased risk of oral clefts (3additional cases per 10,000 treated women; adjusted relative risk, 1.24 [95% CI, 1.03-1.48].

Available epidemiological studies on cardiac malformations show contradictory results.

Reproduction studies in rats and rabbits showed no evidence of harm to the fetus when ondansetron was administeredduring organogenesis at doses approximately 6 and 24 times, respectively, the maximum recommended human
oral dose of 24 mg/day, calculated on a body surface area basis.

Safety data for ondansetron during pregnancy are limited and findings from available pharmacoepidemiological studies areinconsistent.

Post-marketing reports describe cases of congenital malformations with the use of Ondansetron during pregnancy; however, thereports are insufficient to establish a causal relationship.

Ondansetron should not be used during the first trimester of pregnancy.

Lactation

It is not known whether Ondansetron Normon is excreted in human milk. There are no data on adverse reactions in nursing infants oreffects on breast milk production. However, ondansetron has been shown to pass into the milk of lactating animals. It is therefore recommended that nursing mothers do not breast-feed their infants while taking ondansetron.

Fertility
Women of childbearing age should consider using contraception.

**4.7. Effects on ability to drive and use machines**

Ondansetron has no influence on the ability to drive and use machines.

**4.8. Adverse reactions**

The adverse reactions described below have been classified by organ, system and frequency.
Frequencies have been defined asfollows: very common (ÿ1/10), common (ÿ1/100, <1/10), uncommon (ÿ1/1,000, <1/100), rare (ÿ1/10,000, <1/1,000), very rare (<1/10,000), including isolated reports.

Data from clinical trials were used to determine the frequency of adverse reactions classified from very common to uncommon. The incidence in patients treated with placebo was taken into account. Adverse reactions classified as rare and very rare were generallydetermined from post-marketing data.

The following frequencies are determined at the standard recommended doses of ondansetron, according to the indication andformulation.

**Immune system disorders**
*Rare:* immediate hypersensitivity reactions, sometimes severe, including anaphylaxis. May cause cross-sensitivity with other selective5-HT3 antagonists.

**Nervous system disorders**
*Very common:* headache.

*Uncommon:* convulsions, movement disorders (including extrapyramidal reactions such as dystonic reactions, oculogyric crises anddyskinesia)(1) .
Rare: vertigo, predominantly during rapid intravenous administration.

**Eye disorders**
*Rare:* transient visual disturbances (e.g. blurred vision) mainly during intravenous administration.

*Very rare:* transient blindness, mainly during intravenous administration(2).

**Heart disorders**
*Uncommon:* arrhythmias, chest pain with or without ST segment depression, bradycardia.

*Rare:* QTc interval prolongation (including Torsade de Pointes).
*Not known:* myocardial ischemia (see section 4.4).

**Vascular disorders**
*Common:* sensation of redness or heat.
*Uncommon:* hypotension.

**Respiratory, thoracic and mediastinal disorders**
*Uncommon:* hiccups.

**Gastrointestinal disorders**
*Common:* constipation

**Hepatobiliary disorders**
*Uncommon:* asymptomatic increases in liver function tests(3)

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

(1) Observed without conclusive evidence of persistent clinical sequelae.
(2) Most reported cases of blindness resolved within 20 minutes. Most patients had received chemotherapeutic agents, including cisplatin. Some cases of transient blindness were reported to be of cortical origin.
(3) These reactions were frequently observed in patients receiving cisplatin chemotherapy.

Pediatric population

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

~~Reporting suspected allergic reactions~~

It is important to report suspected allergic reactions after authorisation of the medicinal product. This allows continued monitoringof the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Spanish System of Pharmacovigilance of Medicinal Products for Human Use: www.notificaRAM.es.

**4.9. Overdose**

*Symptoms and signs*
Little is currently known about ondansetron overdosage, however, a limited number of patients have received overdoses. Reported manifestations of overdose include visual disturbances, severe constipation, hypotension (and fainting), and a vasovagal episode with transient second-degree atrioventricular block. In all cases, the events resolved completely.

Ondansetron prolongs the QT interval in a dose-dependent manner. In case of overdose, electrocardiogram monitoring is recommended.

Pediatric population

Cases of serotonin syndrome have been reported in children following accidental oral overdose of ondansetron(estimated excess ingestion of 4 mg/kg) in infants and children 12 months to 2 years of age.

*Treatment*

There is no specific antidote for ondansetron; therefore, in case of suspected overdose, appropriate symptomatic and supportive treatment should be provided.

Administration of ipecac to treat ondansetron overdose is not recommended as patients are unlikely to respond due to the antiemetic action of ondansetron.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1. Pharmacodynamic properties

Pharmacotherapeutic group: antiemetics and antinauseants, serotonin receptor antagonists (5 – HT3).
ATC code: A04AA01.

Mechanism of action

Ondansetron is a potent and highly selective 5HT3 receptor antagonist. Its precise mode of action in the control of nausea and vomiting is unknown.
Chemotherapeutic and radiotherapy agents can cause the release of 5HT in the small intestine, initiating the vomiting reflex by activating 5HT3 receptors on the vagal afferent pathways.
Ondansetron blocks the onset of this reflex.

Activation of vagal afferent pathways may also produce the release of 5HT in the area postrema, located in the floor of the fourth ventricle, and this may also promote emesis through a central mechanism. Thus, the effect of ondansetron on the mechanism of nausea and vomiting induced by cytotoxic radiotherapy and chemotherapy is probably due to antagonism of 5HT3 receptors.
on neurons located in both the Central and Peripheral Nervous Systems.

The mechanisms of action of ondansetron in postoperative nausea and vomiting are unknown, but there may be common pathways with vomiting and nausea induced by cytotoxic agents.

Pharmacodynamic effects

Ondansetron does not alter plasma prolactin concentrations.

*QT interval prolongation*

The effect of ondansetron on the QTc interval has been evaluated in a double-blind, randomized, placebo- and positive-controlled (moxifloxacin)-controlled, crossover study in 58 healthy adult men and women. Ondansetron doses included 8 mg and 32 mg administered by intravenous infusion over 15 minutes. For the highest dose studied of 32 mg, the maximum mean difference (upper bound of the 90% CI) in QTcF from placebo after baseline correction was 19.6 (21.5) msec. For the lowest dose studied of 8 mg, the maximum mean difference (upper bound of the 90% CI) in QTcF from placebo afterbaseline correction was 5.8 (7.8) msec. There were no QTcF measurements greater than 480 msec in this study and QTcF prolongations were not greater than 60 msec. No significant changes were observed in electrocardiographic measures in PR or QRS intervals.

Pediatric population

Chemotherapy-induced nausea and vomiting

In a double-blind, randomized trial in 415 patients aged 1 to 18 years (S3AB3006), the efficacy of ondansetron in controllingchemotherapy-induced emesis and nausea was evaluated. On chemotherapy days, patients received either ondansetron 5 mg/m2 intravenously plus ondansetron 4 mg orally 8-12 hours later or ondansetron 0.45 mg/kg intravenously plus placebo given orally 8-12 hours later. After chemotherapy, both groups received ondansetron 4 mg orally twice daily for 3 days. Complete control of emesis on the worst day of chemotherapy was 49% (5 mg/m2 intravenously + ondansetron 4 mg orally) and 41% (0.45 mg/kg intravenously + placebo orally). Following chemotherapy administration, both groups received 4 mgof ondansetron orally twice daily for 3 days.

A double-blind, randomized, placebo-controlled clinical trial (S3AB4003), in 438 patients aged 1 to 17 years, demonstratedcomplete control of emesis on the worst day of chemotherapy in:

- 73% of patients received intravenous ondansetron at a dose of 5 mg/m2 , together with 2-4 mg of oral dexamethasone.
- 71% of patients received oral ondansetron at a dose of 8 mg + 2-4 mg oral dexamethasone on chemotherapy days.

Following chemotherapy, both groups received 4 mg of ondansetron orally twice daily for 2 days. There were no differences in theincidence or nature of adverse reactions between the two treatment groups.

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

In another open-label, non-comparative, single-arm clinical trial (S3A239), the efficacy of an intravenous dose of 0.15 mg/kg of ondansetron followed by two oral doses of 4 mg of ondansetron for children less than 12 years of age and 8 mg for children ÿ12 years of age was evaluated (total number of children n=28). Complete control of emesis was achieved in 42% of patients.

Postoperative nausea and vomiting

The efficacy of a single dose of ondansetron in preventing postoperative nausea and vomiting was evaluated in a randomized, double-blind, placebo-controlled trial in 670 children aged 1 to 24 months (post-fertilization age ÿ44 weeks, weight ÿ3 kg). Patients were scheduled to undergo surgery under general anesthesia and had ASA status ÿIII. A single doseof 0.1 mg/kg ondansetron was administered within 5 minutes of induction of anesthesia. The proportion of patients experiencing at least one episode of vomiting during the 24-hour evaluation period (ITT) was higher in the placebo group than inpatients receiving ondansetron (28% vs. 11%; $p<0.0001$).

Four double-blind, placebo-controlled studies have been conducted in 1,469 patients (boys and girls aged 2 to 12 years) undergoing general anesthesia. Patients were randomized to a single dose of intravenous ondansetron (0.1 mg/kg in pediatric patients weighing 40 kg or less; 4 mg in pediatric patients weighing more than 40 kg; number of patients=735) orplacebo (number of patients=734). The study drug was administered over at least 30 seconds, immediately before or after induction of anesthesia. Ondansetron was significantly more effective in preventing nausea and vomiting than placebo. Theresults of these studies are summarized in Table 3.

*Table 3. Prevention and treatment of PONV in pediatric patients – Response to treatment at 24 hours*

| Study | Variable | Ondansetron (%) | Placebo (%) | p value |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| S3A380 | RC | 68 | 39 | ÿ0.001 |
| S3GT09 | RC | 61 | 35 | ÿ0.001 |
| S3S381 | RC | 53 | 17 | ÿ0.001 |
| S3GT11 | No nausea | 64 | 51 | 0.004 |
| S3GT11 | No vomiting | 60 | 47 | 0.004 |
| | | | | |
| | | | | |
| | | | | |

RC= Complete response (no emetic episodes, rescue or withdrawal)

**5.2. Pharmacokinetic properties**

Absorption

Following oral administration, ondansetron is passively and completely absorbed from the gastrointestinal tract, undergoing first-pass metabolism. Peak plasma concentrations are reached approximately 1.5 hours after dosing. For doses greater than 8 mg, the dose-related increase in ondansetron systemic exposure is greater than proportional; this may reflect some reduction in first-pass metabolism at higher oral doses.

The mean bioavailability in healthy men, after administration of an 8 mg tablet, is approximately 55% to 60%.

Bioavailability is slightly enhanced by the presence of food, but not by antacids.

Distribution

The disposition of ondansetron after oral, intramuscular and intravenous administration is similar, with an elimination half-life of approximately 3 hours and a steady-state volume of distribution of approximately 140 litres. The systemic exposure achieved after administration of ondansetron by the intramuscular and intravenous routes is equivalent. Ondansetron is not highly bound to plasma proteins (70-76%).

Elimination

Ondansetron is eliminated from the systemic circulation predominantly by hepatic metabolism via multiple enzymatic pathways.Less than 5% of the absorbed dose is excreted unchanged in urine. The absence of the CYP2D6 enzyme (debrisoquine polymorphism) has no effect on the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron are not altered by repeated administration.

*Children and adolescents (from 1 month to 17 years)*

In pediatric patients aged 1 to 4 months (n=19) undergoing surgery, weight-normalized clearance was approximately 30% slower than in patients aged 5 to 24 months (n=22) but comparable to patients aged 3 to 12 years. The reported half-life in the 1- to 4 month population was a mean of 6.7 hours, compared with 2.9 hours in patients 5 to 24 months and 3 to 12 years. The differencesin pharmacokinetic parameters in the 1- to 4 month population may be explained in part by the higher percentage of total body water in neonates and infants and a larger volume of distribution for water-soluble drugs such as

ondansetron.

In pediatric patients aged 3 to 12 years undergoing elective surgery under general anesthesia, absolute values for ondansetron clearance and volume of distribution were reduced compared with values in adult patients. Both parameters increased in a linearfashion with weight and up to 12 years of age, values were similar.

were approaching those of young adults. When clearance and volume of distribution values were normalized by body weight, values for these parameters were similar across age groups. The use of weight-based dosing compensates for these age-related changes and is effective in normalizing systemic exposure in pediatric patients.

A population pharmacokinetic analysis was performed following intravenous administration of ondansetron in 428 subjects (cancer patients, patients undergoing surgery, and healthy volunteers)aged 1 month to 44 years. Based on this analysis, the systemic exposure (AUC) of ondansetron following oral or intravenous administration in children and adolescents was comparable to that in adults, with the exception of infants aged 1 to 4 months. The volume of distribution was age-relatedand 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 age-related reduction in clearance in infants aged 1 to 4 months or it is simply inherent tovariability due to the small number of subjects studied in this age group. Because patients younger than 6 months will only receive a single dose for postoperative nausea and vomiting, decreased clearance is not expected to be clinically relevant.

*Elderly patients*

In Phase I studies in healthy elderly volunteers, slight decreases in clearance and an increase in elimination half-life of ondansetron were observed. However, despite wide intersubject variability, therewas considerable overlap in pharmacokinetic parameters between young (<65 years) and elderly (<65years) subjects, and no overall differences in efficacy and safety were observed between young and elderly cancer patients enrolled in the CINV clinical trials, supporting the recommendation for the use of different dosages in elderly patients.

Based on more recent data on ondansetron plasma concentrations and data on drug-response modelling, a greater effect on the QTc interval is expected in patients ÿ 75 years of age compared to younger adults. Specific information on the dosage regimen for intravenous administration is availablein patients aged 65 years and older and also for patients aged 75 years and older (see SmPC for ondansetron solution for injection, section 4.2 - Chemotherapy- and radiotherapy-induced nausea andvomiting - elderly).

*Gender*

The disposition of ondansetron varies according to sex, such that in women the rate and speed of oral absorption is higher and the systemic clearance and volume of distribution (adjusted for weight) are reduced.

*Patients with renal failure*

In patients with moderate renal impairment (creatinine clearance 15-60 ml/min), both systemic clearance and volume of distributionare reduced, resulting in a slight, but clinically insignificant, increase in elimination half-life (5.4 h). A study in patients with severe renal impairment regularly undergoing haemodialysis (assessed in the inter-dialysis period) showed that the pharmacokinetics of ondansetron were essentially the same after intravenous administration.

*Patients with liver failure*

In patients with severe hepatic impairment, systemic clearance of ondansetron is markedly reduced, with increased elimination half-lives (15-32 hours) and oral bioavailability close to 100% due to reduced

presystemic metabolism.

**5.3. Preclinical safety data**

Nonclinical data reveal no special hazard for humans based on conventional studies of genotoxicity, carcinogenic potential,and toxicity to reproduction and development.

In a study with cloned human cardiac ion channels, ondansetron at clinically relevant concentrations has been shown to affect cardiac repolarisation by blocking HERG potassium channels. In a QT interval study in healthy volunteers, ondansetron was shown to prolong the QT interval in a dose-dependent manner (see section 5.1 QT prolongation).

**6. PHARMACEUTICAL DATA**

**6.1. List of excipients**

Microcrystalline cellulose, pregelatinized corn starch (gluten free), lactose, stearate magnesium, hypromellose, titanium dioxide (E-171) and yellow iron oxide (E-172).

**6.2. Incompatibilities**

They have not been described.

**6.3. Shelf Life**

36 Months.

**6.4. Special precautions for storage**

No special storage conditions required. Store in original packaging.

**6.5. Nature and contents of the container**

Ondansetron Normon is packaged in white aluminum/PVC blister packs.

Ondansetron Normon 4 mg Film-coated tablets: 6, 15 and 500 (clinical packaging)film-coated tablets.

Ondansetron Normon 8 mg Film-coated tablets: 6, 15 and 500 (clinical packaging)film-coated tablets.

**6.6. Special precautions for disposal and other handling**

None special.

**7. MARKETING AUTHORIZATION HOLDER**

Merixil Pharma
Office No 28, 2nd Floor, Rose Plaza
I-8 Markaz, Islamabad.

**MANUFACTURED BY**

NORMON LABORATORIES SA
Valdecarrizo Roundabout, 6
28760 Tres Cantos - Madrid
SPAIN

**8.REGISTRATION NUMBER / MARKETING AUTHORISATION NUMBER.**

081802

**9.DATE OF FIRST MARKET AUTHORIZATION / RENEWAL OF REGISTRATION**

Date of first Registration / Market Authorization:15th Sep 2016
Date of latest renewal: 14th Sep 2026

**10. DATE OF TEXT REVISION**