PROFESSIONAL INFORMATION

SCHEDULING STATUS S4

1. NAME OF THE MEDICINE

ONDANSETRON 4 ODF PHARMA-Q, orodispersible films

ONDANSETRON 8 ODF PHARMA-Q, orodispersible films

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ONDANSETRON 4 ODF PHARMA-Q: Each orodispersible film contains 4 mg ondansetron (as ondansetron hydrochloride dihydrate).

ONDANSETRON 8 ODF PHARMA-Q: Each orodispersible film contains 8 mg ondansetron (as ondansetron hydrochloride dihydrate).

Excipients with known effect:

Contains sweetener (ONDANSETRON 4 ODF PHARMA-Q contains 4 mg and ONDANSETRON 8 ODF PHARMA-Q contains 8 mg sucralose).

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Orodispersible films.

ONDANSETRON 4 ODF PHARMA-Q: White to off white opaque rectangular shape strip with matte finish on one side and other side is smooth.

ONDANSETRON 8 ODF PHARMA-Q: White to off white opaque rectangular shape strip with matte finish on one side and other side is smooth.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ONDANSETRON ODF PHARMA-Q is indicated for:

- the management of nausea and vomiting induced by cytotoxic cancer chemotherapy and radiotherapy.
- the prevention and treatment of post-operative nausea and vomiting (PONV).

Routine prophylaxis is not recommended for patients in whom there is little expectation that nausea and vomiting will occur.

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. The selection of dose regimen should be determined by the severity of the emetogenic challenge.

Adults:

Emetogenic chemotherapy and radiotherapy:

For most patients receiving emetogenic chemotherapy or radiotherapy, ONDANSETRON ODF PHARMA-Q can be taken orally 1 – 2 hours before treatment, followed by 8 mg orally twelve hourly. In circumstances where delayed or prolonged emesis is expected after the first 24 hours, ONDANSETRON ODF PHARMA-Q may be continued orally, 8 mg twice daily for up to five days after a course of treatment.

Highly emetogenic chemotherapy:

To protect against delayed or prolonged emesis after the first 24 hours, treatment with

ONDANSETRON ODF PHARMA-Q may be continued orally, with 8 mg twice daily for up to 5 days after a course of treatment.

Children:

Experience is currently limited, but ondansetron was effective and well tolerated in children over the age of 4 years, when given intravenously at a dose of 5 mg/m^2 over 15 minutes, immediately before cancer chemotherapy, followed by oral therapy at doses of ONDANSETRON ODF PHARMA-Q every 12 hours for up to 5 days.

Elderly patients:

Based on more recent ondansetron, as in ONDANSETRON ODF PHARMA-Q, plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults.

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 ODF PHARMA-Q 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 should not be exceeded and therefore parenteral or oral administration is recommended.

Prevention and treatment of post-operative nausea and vomiting:

Adults:

For treatment of established PONV, administration by injection is recommended. Alternatively, for the prevention of post-operative nausea and vomiting, 16 mg may be given orally one hour prior to induction of anaesthesia.

Elderly:

Based on more recent ondansetron, as in ONDANSETRON ODF PHARMA-Q, plasma concentrations and exposure-response modelling, a greater effect on QTcF is predicted in patients ≥ 75 years of age compared to young adults.

A slight age-related decrease in clearance, and an increase in the half-life of ondansetron, as in ONDANSETRON ODF PHARMA-Q, is predicted, presenting as slight, clinically insignificant age-related increases in both oral bioavailability (65 %) and a prolonged elimination half-life (5 hours) of ondansetron.

Patients with renal impairment:

No alteration of daily dosage or frequency of dosing, or route of administration are required for mild or moderate renal impairment. There is limited information available for daily dosage or frequency of dosing, or route of administration for severe renal impairment.

Patients with hepatic impairment:

Clearance of ONDANSETRON ODF PHARMA-Q 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 should not be exceeded.

Method of administration:

Oral.

Place ONDANSETRON ODF PHARMA-Q on top of the tongue, where it will disperse within seconds, then swallow.

4.3 Contraindications

- Hypersensitivity to ondansetron or to any of the excipients listed in section 6.1.
- Concomitant use with apomorphine (see section 4.5).
- ONDANSETRON ODF PHARMA-Q use is contraindicated during the first 12 weeks of pregnancy irrespective of the indication, due to an increased risk of developing oral cleft palate and/or lip to the foetus (see section 4.4).
- The use of ONDANSETRON ODF PHARMA-Q for post-operative nausea and vomiting is contraindicated in pregnancy (see section 4.6).
- Congenital long QT syndrome.

4.4 Special warnings and precautions for use

Cross-hypersensitivity reactions have been reported in patients who have exhibited hypersensitivity to other selective $5HT_3$ receptor antagonists.

Respiratory events should be treated symptomatically and medical practitioners should pay particular attention to them as precursors of hypersensitivity reactions.

Ondansetron, as in ONDANSETRON ODF PHARMA-Q prolongs the QT interval in a dose-dependent manner (see section 5.1). In addition, post-marketing cases of torsades de pointes have been reported in patients using ONDANSETRON ODF PHARMA-Q.

Avoid ONDANSETRON ODF PHARMA-Q in patients with congenital long QT syndrome (see section 4.3). ONDANSETRON ODF PHARMA-Q should be administered with caution to patients who have or may develop prolongation of QTc, including patients with electrolyte abnormalities, congestive

heart failure, bradydysrhythmias or patients taking other medicines that lead to QT prolongation or electrolyte abnormalities.

Myocardial ischemia has been reported in patients treated with ondansetron, as in ONDANSETRON ODF PHARMA-Q. In some patients, especially in the case of intravenous administration, symptoms appeared immediately after administration of ondansetron, as in ONDANSETRON ODF PHARMA-Q. Patients should be alerted to the signs and symptoms of myocardial ischaemia.

Hypokalaemia and hypomagnesaemia should be corrected prior to ONDANSETRON ODF PHARMA-Q administration.

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ONDANSETRON ODF PHARMA-Q and other serotonergic medicines (including selective serotonin reuptake inhibitors (SSRIs) and serotonin noradrenaline reuptake inhibitors (SNRIs)). If concomitant treatment with ONDANSETRON ODF PHARMA-Q and buprenorphine/opioids or other serotonergic medicines is clinically warranted, appropriate close observation of the patient is advised, particularly during treatment initiation and dose increases.

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

As ONDANSETRON ODF PHARMA-Q is known to increase large bowel transit time, patients with signs of intestinal obstructions should be closely monitored following administration.

In patients with adeno-tonsillar surgery prevention of nausea and vomiting with ONDANSETRON ODF PHARMA-Q may

mask occult bleeding. Therefore, such patients should be carefully monitored after ONDANSETRON ODF PHARMA-Q.

The use of ONDANSETRON ODF PHARMA-Q during the first 12 weeks of pregnancy increases the risk of developing oral cleft palate and or lip to the fetus (see section 4.3).

Special populations:

Patients with hepatic impairment:

Adult: Clearance of ONDANSETRON ODF PHARMA-Q 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 should not be exceeded.

Paediatric population:

The daily dose for children should not exceed 4 mg.

Paediatric patients receiving ondansetron, as in ONDANSETRON ODF PHARMA-Q with hepatotoxic chemo-therapeutic medicines should be monitored closely for impaired hepatic function.

4.5 Interactions with other medicines and other forms of interaction

The concomitant use with apomorphine is contraindicated (see section 4.3). Profound hypotension and loss of consciousness was reported when ONDANSETRON ODF PHARMA-Q was taken concomitantly with apomorphine hydrochloride.

There is no evidence that ONDANSETRON ODF PHARMA-Q either induces or inhibits the

metabolism of other medicines commonly co-administered with it. Specific studies have shown that there are no interactions when ONDANSETRON ODF PHARMA-Q is taken with alcohol, temazepam, furosemide, alfentanil, morphine, lidocaine, thiopental, or propofol.

Ondansetron, as in ONDANSETRON ODF PHARMA-Q is metabolised by multiple hepatic cytochrome P450 enzymes CYP3A4, CYP2D6 and CYP1A2. Due to the multiplicity of metabolic enzymes capable of metabolising ondansetron, as in ONDANSETRON ODF PHARMA-Q, enzyme inhibition or reduced activity of one enzyme (e.g. CYP2D6 genetic deficiency) is normally compensated for by other enzymes and should result in little or no significant change in overall ONDANSETRON ODF PHARMA-Q clearance or dose requirement.

Caution must be exercised when ONDANSETRON ODF PHARMA-Q is co-administered with other medicines that prolong the QT interval and/or cause electrolyte abnormalities (see section 4.4).

Use of ONDANSETRON ODF PHARMA-Q with QT prolonging medicines may result in additional QT prolongation. Concomitant use of ONDANSETRON ODF PHARMA-Q with cardiotoxic medicines (e.g. anthracyclines [e.g. doxorubicin, daunorubicin] or trastuzumab), antibiotics (e.g. erythromycin), antifungals (e.g. ketoconazole), antidysrhythmics (e.g. amiodarone) and beta-blockers (e.g. atenolol or timolol) may increase the risk of dysrhythmias (see section 4.4).

Serotonergic medicines (e.g. SSRIs and SNRIs):

There have been post-marketing reports describing patients with serotonin syndrome (including altered mental status, autonomic instability and neuromuscular abnormalities) following the concomitant use of ONDANSETRON ODF PHARMA-Q and buprenorphine/opioids or other serotonergic medicines (including SSRIs and SNRIs) (see section 4.4).

Phenytoin, carbamazepine and rifampicin:

In patients treated with potent inducers of CYP3A4 (i.e. phenytoin, carbamazepine and rifampicin), the clearance of ONDANSETRON ODF PHARMA-Q was increased and blood concentrations of ondansetron were decreased causing a reduced antiemetic efficacy.

Tramadol:

ONDANSETRON ODF PHARMA-Q may reduce the analgesic effect of tramadol.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

Women of childbearing potential being treated with ONDANSETRON ODF PHARMA-Q should not become pregnant and should consider the use of contraception while taking ONDANSETRON ODF PHARMA-Q, as well as for two days after stopping treatment with ONDANSETRON ODF PHARMA-Q.

Pregnancy:

ONDANSETRON ODF PHARMA-Q is contraindicated for post-operative nausea and vomiting during pregnancy, as well as during the first 12 weeks of pregnancy irrespective of the indication due to the risk (see section 4.3).

Use during the first 12 weeks of pregnancy can be associated with an increased risk of developing oral cleft palate and/or lip to the fetus.

Breastfeeding:

Mothers receiving ONDANSETRON ODF PHARMA-Q should not breastfeed their babies.

Fertility:

There is no information on the effects of ondansetron on human fertility.

4.7 Effects on ability to drive and use machines

ONDANSETRON ODF PHARMA-Q causes nervous system and eye disorders which may adversely affect the ability of patients to drive a vehicle or operate machines. Patients taking ONDANSETRON ODF PHARMA-Q should therefore not drive a vehicle or use machines until the effects of ONDANSETRON ODF PHARMA-Q treatment are known (see section 4.8).

4.8 Undesirable effects

Summary of adverse reactions:

Immune system disorders:

Less frequent: Immediate hypersensitivity reactions, including cross-sensitivity reactions which are sometimes severe (e.g. anaphylaxis, bronchospasm, shortness of breath, hypotension, shock, angioedema, urticaria) have been reported.

Nervous system disorders:

Frequent: Headache.

Less frequent: Seizures, movement disorders (including extrapyramidal reactions such as oculogyric crisis, dystonic reactions and dyskinesia have been observed without definitive evidence of persistent clinical sequelae).

Eye disorders:

Less frequent: Transient visual disturbances (e.g. blurred vision) predominantly during intravenous administration.

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

Cardiac disorders:

Less frequent: Dysrhythmias, bradycardia and chest pains with or without ST segment depression, QTc prolongation (including torsades de pointes), myocardial ischaemia.

Vascular disorders:

Frequent: Sensation of warmth or flushing.

Less frequent: Hypotension.

Respiratory, thoracic and mediastinal disorders:

Less frequent: Hiccups.

Respiratory events should be treated symptomatically and medical practitioners should pay particular attention to them as precursors of hypersensitivity reactions.

Gastrointestinal disorders:

Frequent: Increase in large bowel transit time is known to be caused by ONDANSETRON ODF PHARMA-Q which cause constipation in some patients.

Hepato-biliary disorders:

Less frequent: Asymptomatic increases in liver function tests.

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

Skin and subcutaneous tissue disorders:

Less frequent: Toxic skin eruption, including toxic epidermal necrolysis.

Paediatric Population:

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

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of ONDANSETRON ODF PHARMA-Q is important. It allows continued monitoring of the benefit/risk balance of ONDANSETRON ODF PHARMA-Q. Health care providers are asked to report any suspected adverse reactions via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

Symptoms:

In the majority of cases symptoms were similar to or an extension of those already reported in patients receiving the 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 atrioventricular (AV) block.

Ondansetron prolongs the QT interval in a dose-dependent manner. Electrocardiogram (ECG) monitoring is recommended in cases of overdose.

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.

Treatment:

There is no specific antidote for ondansetron, as in ONDANSETRON ODF PHARMA-Q. Therefore, in all cases of suspected overdose, treatment is symptomatic and supportive as appropriate.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.10 Serotonin antagonists

Pharmacotherapeutic group: Anti-emetics and anti-nauseants, Serotonin (5-HT_3) antagonist.

ATC code: A04AA01.

Mechanism of Action:

Ondansetron is a potent, highly selective $5HT_3$ receptor-antagonist. Its precise mode of action in the control of nausea and vomiting is not known. Chemotherapeutic medicines and radiotherapy may cause release of 5HT in the small intestine, initiating a vomiting reflex by activating vagal afferents via $5HT_3$ receptors. Ondansetron blocks the initiation of this reflex.

Activation of vagal afferents may also cause a release of 5HT in the area postrema, located on the floor of the fourth ventricle, and this may also promote emesis through a central mechanism.

Thus, the effect of ondansetron in the management of the nausea and vomiting induced by cytotoxic cancer chemotherapy and radiotherapy is due to antagonism of $5HT_3$ receptors on neurons located in both the peripheral and central nervous systems.

The mechanisms of action in post-operative nausea and vomiting are not known but there may be common pathways with cytotoxically-induced nausea and vomiting.

Ondansetron does not alter plasma prolactin concentrations.

The role of ondansetron in opiate-induced emesis is not yet established.

5.2 Pharmacokinetic properties

Absorption:

ONDANSETRON ODF PHARMA-Q is an orodispersible film. Once in contact with saliva, it disintegrates in a few seconds.

Following oral administration ondansetron is passively and completely absorbed from the gastrointestinal tract and undergoes first pass metabolism. Peak plasma concentrations of about 30 ng/mL being attained approximately 1,6 hours after an 8 mg dose. For doses above 8 mg the increase in ondansetron systemic exposure with dose is greater than proportional; this may reflect some reduction in first pass metabolism at higher oral doses.

The mean bioavailability in healthy male subjects, following the oral administration of a single 8 mg tablet, is approximately 55 to 60 %.

Bioavailability, following oral administration, is slightly enhanced by the presence of food but unaffected by antacids.

Distribution:

Ondansetron is not highly protein bound (70 – 76 %).

Biotransformation:

Ondansetron is cleared from the systemic circulation predominantly by hepatic metabolism through multiple enzymatic pathways.

Elimination:

The disposition of ondansetron following oral, intramuscular (IM) and intravenous (IV) dosing is

similar with a terminal elimination half-life of about 3 hours and steady state volume of distribution of about 140 L.

Less than 5 % of the absorbed dose is excreted unchanged in the urine. The absence of the enzyme CYP2D6 (the debrisoquine polymorphism) has no effect on the pharmacokinetics of ondansetron. The pharmacokinetic properties of ondansetron are unchanged on repeat dosing.

Special patient populations:

Gender:

Gender differences were shown in the disposition of ondansetron, with females having a greater rate and extent of absorption following an oral dose and reduced systemic clearance and volume of distribution (adjusted for weight).

Children and Adolescents:

The differences in pharmacokinetic parameters in the 1 – 4 month-old 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 medicines like ondansetron.

Elderly:

Specific dosing information is provided for intravenous dosing patients over 65 years of age and over 75 years of age.

Renal impairment:

In patients with renal impairment (creatinine clearance 15 – 60 mL/min), systemic clearance and volume of distribution are reduced, 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.

Hepatic impairment:

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Banana flavour powder (spray dried 0473070)

Glycerine

Hydroxypropyl methylcellulose (hypromellose Methocel E15 premium LV)

Polacrilin potassium (Kyron T-134)

Polysorbate 80

Povidone and hypromellose solution

Povidone (Kollidon 30)

Purified water

Sucralose

Titanium dioxide (1171.E171)

Vanilla flavour powder (0473072).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months.

Store at or below 25 °C.

6.4 Special precautions for storage

Protect from direct sunlight.

6.5 Nature and contents of container

4-Ply laminated pouch containing 1 orodispersible film. The pouch material is composed of peelable LDPE, aluminium foil, polyethylene terephthalate (PET) and paper (opaque laminating base).

Pack size: 10 pouches are packed in an outer carton.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

50 Commando Road

Industria West 2093

Johannesburg

South Africa

info@pharmaq.co.za

Tel: 011 247 1600

8. REGISTRATION NUMBERS

ONDANSETRON 4 ODF PHARMA-Q: 58/5.10/0039

ONDANSETRON 8 ODF PHARMA-Q: 58/5.10/0040

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20 January 2026

10. DATE OF REVISION OF THE TEXT

To follow