הודעה על החמרה (מידע בטיחות) בעלון לרופא
(מעודכן 3102.50)

תאריך: **7.7.2015**

שם תכשיר באנגלית ומספר הרישום: **Ondansetron – Fresenius Reg. No. 148.94.33550.00**

שם בעל הרישום: **Medic-Trim Healthcare Ltd**

ההחמרות המבוקשות

טקסט חדש	טקסט נוכחי	פרק בעלון
Highly emetogenic chemotherapy: For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ONDANSETRON - FRESENIUS can be given by intravenous administration. Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy: • A single dose of 8mg by slow intravenous injection (in not less than 30 seconds) immediately before chemotherapy. • A dose of 8mg by slow intravenous injection immediately before chemotherapy in not less than 30 seconds, followed by two further intravenous doses (in not less than 30 seconds) of 8mg ~~two to~~ four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours. • ~~A single~~ A maximum initial intravenous dose of 16mg diluted in 50-100ml of saline or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy.The initial dose of ondansetron may be followed by two additional 8mg intravenous doses (in not less than 30 seconds) four hours apart.	*Highly emetogenic chemotherapy*: For patients receiving highly emetogenic chemotherapy, e.g. high-dose cisplatin, ONDANSETRON - FRESENIUS can be given by intravenous administration. Ondansetron has been shown to be equally effective in the following dose schedules over the first 24 hours of chemotherapy: A single dose of 8mg by slow intravenous injection immediately before chemotherapy. or A dose of 8mg by slow intravenous injection immediately before chemotherapy in not less than 30 seconds, followed by two further intravenous doses of 8mg two to four hours apart, or by a constant infusion of 1mg/hour for up to 24 hours. or A single intravenous dose of 16mg diluted in 50-100ml of saline or other compatible infusion fluid (see section 6.6) and infused over not less than 15 minutes immediately before chemotherapy.	**Posology, dosage& administration - Adult**

Dosing by BSA: ONDANSETRON – FRESENIUS should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The single intravenous dose must not exceed 8 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 1). The total ~~daily~~ dose over 24 hours (given as divided doses) must not exceed adult dose of 32 mg. Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents BSA | Day 1 [a,b] | Days 2-6[b] < 0.6 m^2 | 5 mg/m^2 i.v. plus 2 mg p.o.-after 12 hrs | 2 mg p.o. e 12 hrs ≥0.6 m^2 | 5 mg/m^2 i.v. plus 4 mg p.o. after 12 hrs | 4 mg p.o. every 12 hr a The intravenous dose must not exceed 8mg. b The total ~~daily~~ dose over 24 hours must not exceed adult dose of 32 mg Dosing by bodyweight: Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4. and 5.1). ONDANSETRON – FRESENIUS 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. ~~The total daily dose must not exceed adult dose of 32 mg.~~ Oral dosing can commence twelve 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.	Dosing by BSA: ONDANSETRON – FRESENIUS should be administered immediately before chemotherapy as a single intravenous dose of 5 mg/m^2. The intravenous dose must not exceed 8 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 1). The total daily dose must not exceed adult dose of 32 mg. Table 1: BSA-based dosing for Chemotherapy - Children aged ≥6 months and adolescents BSA | Day 1 [a,b] | Days 2-6[b] < 0.6 m^2 | 5 mg/m^2 i.v. plus 2 mg p.o.-after 12 hrs | 2 mg p.o. e 12 hrs ≥0.6 m^2 | 5 mg/m^2 i.v. plus 4 mg p.o. after 12 hrs | 4 mg p.o. every 12 hr a The intravenous dose must not exceed 8mg. b The total daily dose must not exceed adult dose of 32 mg Dosing by bodyweight: Weight-based dosing results in higher total daily doses compared to BSA-based dosing (sections 4.4. and 5.1). ONDANSETRON – FRESENIUS should be administered immediately before chemotherapy as a single intravenous dose of 0.15 mg/kg. The intravenous dose must not exceed 8 mg. Two further intravenous doses may be given in 4-hourly intervals. The total daily dose must not exceed adult dose of 32 mg. Oral dosing can commence twelve hours later and may be continued for up to 5 days (Table 2).	**Posology, dosage & administration - Paediatric Population**

Table 2: Weight-based dosing for Chemotherapy - Children aged ≥6 months and adolescents | Weight	Day 1 [a,b]	Days 2-6[b]
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≤ 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	2 mg p.o. every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg p.o. every 12 hrs | a The intravenous dose must not exceed 8mg. b The total ~~daily~~ dose over 24 hours must not exceed adult dose of 32 mg.	Table 2: Weight-based dosing for Chemotherapy - Children aged ≥6 months and adolescents | Weight	Day 1 [a,b]	Days 2-6[b]
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≤ 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	2 mg p.o. every 12 hrs
> 10 kg	Up to 3 doses of 0.15 mg/kg every 4 hrs	4 mg p.o. every 12 hrs	 a The intravenous dose must not exceed 8mg. b The total daily dose must not exceed adult dose of 32 mg.	
In patients 65 to 74 years of age, the dose schedule for adults can be followed. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. **In patients 75 years of age or older**, the initial intravenous dose of ondansetron should not exceed 8 mg. All intravenous doses should be diluted in 50-100 ml of saline or other compatible infusion fluid (see section 6.6) and infused over 15 minutes. The initial dose of 8 mg may be followed by two further intravenous doses of 8 mg, infused over 15 minutes and given no less than four hours apart. (see section 5.2)	Ondansetron is well tolerated by patients over 65 years and no alteration of dosage, dosing frequency or route of administration are required.	**Posology, dosage& administration - Elderly:**
~~Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron.~~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~~. These conditions include~~, including patients with electrolyte abnormalities, ~~with congenital long QT syndrome~~	Rarely, transient ECG changes including QT interval prolongation have been reported in patients receiving ondansetron. Ondansetron prolongs the QT interval in a dose-dependent manner. 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. These conditions include patients with electrolyte abnormalities, with congenital long QT syndrome, congestive heart failure, bradyarrhythmias or	**Special Warning and special Precautions for use**

congestive heart failure, bradyarrhythmias or patients taking other medicinal products that lead to QT prolongation or electrolyte abnormalities. ~~Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances.~~ .... 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 and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs), monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol, and intravenous methylene blue). Some of the reported cases were fatal. Serotonin syndrome occurring with overdose of ondansetron alone has also been reported. The majority of reports of serotonin syndrome related to 5-HT receptor antagonist use occurred in a post-anesthesia care unit or an infusion center	patients taking other medicinal products that lead to QT prolongation . Therefore, caution should be exercised in patients with cardiac rhythm or conduction disturbances, in patients treated with anti-arrhythmic agents or beta-adrenergic blocking agents and in patients with significant electrolyte disturbances. ... 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 and other serotonergic drugs (including selective serotonin reuptake inhibitors (SSRI) and serotonin noradrenaline reuptake inhibitors (SNRIs)	
Caution should be exercised when ondansetron is coadministered with drugs that prolong the QT interval and/or cause electrolyte abnormalities. (see section 4.4) Use of Ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of Ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin) antifungals (such as ~~or~~ ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias (section 4.4).	Use of Ondansetron with QT prolonging drugs may result in additional QT prolongation. Concomitant use of Ondansetron with cardiotoxic drugs (e.g. anthracyclines such as doxorubicin, daunorubicin or trastuzimab), antibiotics (such as erythromycin or ketoconazole), antiarrhythmics (such as amiodarone) and beta blockers (such as atenolol or timolol) may increase the risk of arrhythmias (section 4.4).	**Interaction with other Medicaments and other Form of Interaction**

Eye disorders **...** Very rare: Transient blindness predominantly during intravenous administration.(2) Cases of transient blindness, have been reported. These cases of transient blindness were reported to resolve within a few minutes up to 48 hours. Transient blurred vision, in some cases associated with abnormalities of accommodation, have also been reported **…** **Additional data from post marketing experience** Cardiovascular Arrhythmias (including ventricular and supraventricular tachycardia, premature ventricular contractions, and atrial fibrillation), bradycardia, electrocardiographic alterations (including second-degree heart block, QT/QTc interval prolongation, and ST segment depression), palpitations, and syncope. General Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylactic reactions, angioedema, bronchospasm, cardiopulmonary arrest, hypotension, laryngeal edema, laryngospasm, shock, shortness of breath, stridor) have also been reported. A positive lymphocyte transformation test to ondansetron has been reported, which suggests immunologic sensitivity to ondansetron. Hepatobiliary Liver enzyme abnormalities have been reported. Liver failure and death have been reported in patients with cancer receiving concurrent medications including potentially hepatotoxic cytotoxic chemotherapy and antibiotics.	**Eye disorders** **...** Very rare: Transient blindness predominantly during intravenous administration.(2)	**Undesirable** **Effects**

Neurological Oculogyric crisis, appearing alone, as well as with other dystonic reactions. Skin Urticaria , Stevens-Johnson syndrome Toxic skin eruption, including toxic epidermal necrolysis Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form. (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).		
~~Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses~~ 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 QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose. ~~In all instances, the events resolved completely~~ Pediatric cases consistent with serotonin syndrome have been reported after inadvertent oral overdoses of ondansetron (exceeding estimated ingestion of 5 mg/kg) in young children. Reported symptoms included somnolence, agitation, tachycardia, tachypnea, hypertension, flushing, mydriasis, diaphoresis, myoclonic movements, horizontal nystagmus, hyperreflexia, and seizure. Patients required supportive care, including intubation in some cases, with complete recovery without sequelae within 1 to 2 days	Little is known at present about overdosage with ondansetron, however, a limited number of patients received overdoses Manifestations that have been reported include visual disturbances, severe constipation, hypotension and a vasovagal episode with transient second degree AV block.Ondansetron prolongs QT interval in a dose-dependent manner. ECG monitoring is recommended in cases of overdose.In all instances, the events resolved completely	**Overdose**

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 (see section 4.2).	***Elderly*** Specific studies in the elderly or patients with renal impairment have been limited to intravenous and oral administration. However, it is anticipated that the half-life of ondansetron after rectal administration in these populations will be similar to that seen in healthy volunteers, since the rate of elimination of ondansetron following rectal administration is not determined by systemic clearance. Studies in healthy elderly volunteers have shown slight age-related increases in half-life (5 hours).	**Pharmacokinetic** **Properties**

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.

שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה.יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך.....

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