NOVARTIS

אפריל 2020

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון: **Zofran injection 2mg/ml, solution for injection**

זופרן זריקות 2מג"/מ"ל

התכשיר שבנדון רשום בישראל להתוויות הבאות:

Adults:

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

Paediatric Population:

Zofran is indicated for the management of chemotherapy-induced nausea and vomiting (CINV) in children aged ≥6 months, and for the prevention and treatment of PONV in children aged ≥ 1 month.

המרכיב הפעיל: ONDANSETRON (AS HYDROCHLORIDE DIHYDRATE) 2MG/ML

ברצוננו להודיעכם על עדכונים בעלון לרופא של התכשיר שבנדון.

העדכונים מפורטים להלן (קו תחתי משמעו תוספת טקסט, ~~קו חוצה~~ משמעו מחיקת טקסט, החמרות מודגשות בצהוב):

4.4 Special warnings and precautions for use

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Zofran Injection contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium-free”.

4.6. Fertillity, pregnancy and lactation

Pregnancy

~~The safety of ondansetron for use in human pregnancy has not been established. Evaluation of experimental animal studies does not indicate direct or indirect harmful effects with respect to the development of the embryo, or foetus, the course of gestation and peri- and post-natal development. However as animal studies are not always predictive of human response the use of ondansetron in pregnancy is not recommended.~~

Based on human experience of epidemiological studies, ondansetron is suspected to cause orofacial malformations when administered during first trimester of pregnancy.

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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 to 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.

The use of ondansetron in pregnancy is not recommended.

Breast-feeding
Tests have shown that ondansetron passes into the milk of lactating animals. It is therefore recommended that mothers receiving Zofran should not breast-feed their babies.

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

4.8. Undesirable effects

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Eye disorders: very rare:

~~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.~~

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~~**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.~~

~~**Neurological**~~
~~Oculogyric crisis, appearing alone, as well as with other dystonic reactions.~~
~~**Skin**~~

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~~Urticaria, Stevens-Johnson syndrome Toxic skin eruption, including toxic epidermal necrolysis.~~

1. Observed without definitive evidence of persistent clinical sequelae.
2. The majority of the blindness cases reported resolved within ~~-~~20 minutes ~~48 hours~~. Most patients had received chemotherapeutic agents, which included cisplatin. Some cases of transient blindness were reported as cortical in origin.
3. These events were observed commonly in patients receiving chemotherapy with cisplatin.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
~~https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il~~
https://sideeffects.health.gov.il

4.9. Overdose

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

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

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

5.2. Pharmacokinetic properties

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~~Following administration of ondansetron suppository, plasma ondansetron concentrations become detectable between 15 and 60 minutes after dosing. Concentrations rise in an essentially linear fashion, until peak concentrations of 20-30 ng/mL are attained, typically 6 hours after dosing. Plasma concentrations then fall, but at a slower rate than observed following oral dosing due to continued absorption of ondansetron. The absolute bioavailability of ondansetron from the suppository is approximately 60% and is not affected by gender. The half-life of the elimination phase following suppository administration is determined by the rate of ondansetron absorption, not systemic clearance and is approximately 6 hours. Females show a small, clinically insignificant, increase in half-life in comparison with males.~~

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Hepatic Impairment

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Following oral, intravenous or intramuscular dosing in patients with severe hepatic impairment, ondansetron's systemic clearance is markedly reduced with prolonged elimination half-lives (15- 32 hours) and an oral bioavailability approaching 100% due to reduced pre-systemic metabolism. ~~The pharmacokinetics of ondansetron following administration as a suppository have not been evaluated in patients with hepatic impairment.~~

העלון לרופא כולל שינויי עריכה / שינויים נוספים שאינם החמרות.

כמן כן עודכנה כתובת בעל הרישום לכתובת: ת.ד 7126, תל-אביב.

העלון נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלו מודפס על-ידי פניה לבעל הרישום.

בברכה,
לנה גיטלין
רוקחת ממונה

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