מרץ 2018
KS038

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה ,

הנדון: התכשיר - Ulceron

Powder for solution for injection

ברצוננו להודיע על עדכון בעלון לרופא של התכשיר שבנדון.

הודעה זו מתייחסת רק לסעיפים בהם נעשה שינוי המהווה החמרה: טקסט מודגש בצהוב משמעו החמרה.

קיימים עדכונים מינוריים נוספים.

ההתוויה המאושרת:

- Duodenal ulcer
- Gastric ulcer
- Moderate and severe forms of reflux oesophagitis
- Zollinger-Ellison-Syndrome

העדכונים המהותיים שנעשו בעלון לרופא הינם:

4.2 Posology and method of administration

Patients with hepatic Impairment
A daily dose of 20 mg pantoprazole (half a vial of 40 mg pantoprazole) should not be exceeded in patients with severe liver impairment (see section 4.4).
Patients with renal Impairment
No dose adjustment is necessary in patients with impaired renal function (see section 5.2).
Older people
No dose adjustment is necessary in older patients (see section 5.2).

4.4 Special warnings and precautions for use
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Gastric malignancy
Symptomatic response to pantoprazole may mask the symptoms of gastric malignancy and may delay diagnosis

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Co-administration with HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir, due to significant reduction in their bioavailability (see section 4.5).

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Gastrointestinal infections caused by bacteria
Treatment with pantoprazole may lead to a slightly increased risk of gastrointestinal infections caused by bacteria such as *Salmonella* and *Campylobacter* or *C. difficile*.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. is essentially 'sodiumfree'.

Hypomagnesemia
Severe hypomagnesaemia has been reported in patients treated with PPIs like pantoprazole for at least three months and in most cases for a year. Serious manifestations of hypomagnesaemia such as fatigue, tetany, delirium, convulsions, dizziness and ventricular arrhythmia can occur but they may begin insidiously and be overlooked. In most affected patients, hypomagnesaemia improved after magnesium replacement and discontinuation of the PPI.

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Subacute cutaneous lupus erythematosus (SCLE)
Proton pump inhibitors are associated with very infrequent cases of SCLE. If lesions occur, especially in sun exposed areas of the skin, and if accompanied by arthralgia, the patient should seek medical help promptly and the healthcare professional should consider stopping Ulceron. SCLE after previous treatment with a proton pump inhibitor may increase the risk of SCLE with other proton pump inhibitors.

Interference with Laboratory Tests
Increased Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid this interference, Ulceron. treatment should be stopped for at least 5 days before CgA measurements (see section 5.1). If CgA and gastrin levels have not returned to reference range after initial measurement, measurements should be repeated 14 days after cessation of proton pump inhibitor treatment.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products with pH Dependent Absorption Pharmacokinetics
Because of profound and long lasting inhibition of gastric acid secretion, pantoprazole may interfere with the absorption of other medicinal products where gastric pH is an important determinant of oral bioavailability, e.g. some azole antifungals such as ketoconazole, itraconazole, posaconazole and other medicine such as erlotinib.

HIV protease inhibitors
Co-administration of pantoprazole is not recommended with HIV protease inhibitors for which absorption is dependent on acidic intragastric pH such as atazanavir due to significant reduction in their bioavailability (see section 4.4).

If the combination of HIV protease inhibitors with a proton pump inhibitor is judged unavoidable, close clinical monitoring (e.g. virus load) is recommended. A pantoprazole dose of 20 mg per day should not be exceeded. Dosage of the HIV protease inhibitor may need to be adjusted.

Coumarin anticoagulants (phenprocoumon or warfarin)
Co-administration of pantoprazole with warfarin or phenprocoumon did not affect the pharmacokinetics of warfarin, phenoprocoumon or INR. However, there have been reports of increased INR and prothrombin time in patients receiving PPIs and warfarin or phenoprocoumon concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding, and even death.
Patients treated with pantoprazole and warfarin or phenprocoumon may need to be monitored for increase in INR and prothrombin time.

Methotrexate
Concomitant use of high dose methotrexate (e.g. 300 mg) and proton-pump inhibitors has been reported to increase methotrexate levels in some patients. Therefore in settings where high-dose methotrexate is used, for example cancer and psoriasis, a temporary withdrawal of pantoprazole may need to be considered.

Other interactions studies
Pantoprazole is extensively metabolized in the liver via the cytochrome P450 enzyme system. The main metabolic pathway is demethylation by CYP2C19 and other metabolic pathways include oxidation by CYP3A4.

Interaction studies with medicinal products also metabolized with these pathways, like carbamazepine, diazepam, glibenclamide, nifedipine, and an oral contraceptive containing levonorgestrel and ethinyl oestradiol did not reveal clinically significant interactions.

An interaction of pantoprazole with other medicinal products or compounds, which are metabolized using the same enzyme system, cannot be excluded.

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Medicinal products that inhibit or induce CYP2C19:

Inhibitors of CYP2C19 such as fluvoxamine could increase the systemic exposure of pantoprazole. A dose reduction may be considered for patients treated long-term with high doses of pantoprazole, or those with hepatic impairment.

Enzyme inducers affecting CYP2C19 and CYP3A4 such as rifampicin and St John´s wort (Hypericum perforatum) may reduce the plasma concentrations of PPIs that are metabolized through these enzyme systems.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of Ulceron.
Animal studies have shown reproductive toxicity (see section 5.3).

As a precautionary measure, it is preferable to avoid the use of Ulceron during pregnancy.

Breast-feeding
Animal studies have shown excretion of pantoprazole in breast milk. There is insufficient information on the excretion of pantoprazole in human milk but excretion into human milk has been reported. A risk to the newborns/infants cannot be excluded. Therefore a decision on whether to discontinue breast-feeding or to discontinue/abstain from Ulceron therapy should take into account the benefit of breast-feeding for the child, and the benefit of Ulceron therapy for the women.

Fertility
There was no evidence of impaired fertility following the administration of pantoprazole in animal studies (see section 5.3).

4.7 Effects on ability to drive and use of machines
Pantoprazole has no or negligible influence on the ability to drive and use machines.

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4.8 Undesirable effects

Approximately 5 % of patients can be expected to experience adverse drug reactions (ADRs). The most commonly reported ADRs is injection site thrombophlebitis. Diarrhoea and headache occurred in approximately 1 % of patients.
The table below lists adverse reactions reported with pantoprazole, ranked under the following frequency classification:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 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).
For all adverse reactions reported from post-marketing experience, it is not possible to apply any Adverse Reaction frequency and therefore they are mentioned with a “not known” frequency.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.
Table 1. Adverse reactions with pantoprazole in clinical trials and post-marketing experience

Frequency/ System Organ Class	Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders			Agranulocytosis	Thrombocytopenia ; Leukopenia Pancytopenia	
Immune system disorders			Hypersensitivity (including anaphylactic reactions and anaphylactic shock)		
Metabolism and nutrition disorders			Hyperlipidaemias and lipid increases (triglycerides, cholesterol); Weight changes		Hyponatraemia Hypomagnesaem-ia (see section 4.4); Hypocalcaemia[(1)]; Hypokalaemia
Psychiatric disorders		Sleep disorders	Depression (and all aggravations)	Disorientation (and all aggravations)	Hallucination; Confusion (especially in pre-disposed patients, as well as the aggravation of these symptoms in case of pre-existence)
Nervous system disorders	~~Headache;~~	Headache; Dizziness ~~Disturbances in vision (blurred vision)~~	Taste disorders		Parasthesia
Eye disorders			Disturbances in vision/ blurred vision		
Gastrointestinal disorders	~~Upper abdominal pain, Diarrhoea, Constipation, Flatulence~~ Fundic gland polyps	Diarrhoea; Nausea/ vomiting Abdominal distension and	~~Dry mouth~~		

	(benign)	bloating; Constipation; Dry mouth; abdominal pain and discomfort;			
Hepatobiliary disorders		Liver enzymes increased (transaminases, γ -GT);	Bilirubin increased	~~Severe hepatocellular Damage leading to jaundice with or without hepatic failure~~	Hepatocellular injury; jaundice; Hepatocellular failure
Skin and subcutaneous tissue disorders		Rash /exanthema/ eruption; Pruritus ~~Allergic reactions such as pruritus and skin rash~~	Urticaria; Angioedema	~~Urticaria; Angioedema Severe skin reactions such as Stevens-Johnson Syndrome, Erythema multiforme, Lyell-Syndrome~~	Stevens-Johnson syndrome, Lyell-syndrome; Erythema multiforme; Photosensitivity; Subacute cutaneous lupus erythematosus (see section 4.4)
Musculoskeletal and connective tissue disorders		Fracture of the hip, wrist or spine (see section 4.4)	Arthralgia; Myalgia		Muscle spasm [2]
Renal and urinary disorders					Interstitial nephritis (with possible progression to renal failure)
Reproductive system and breast disorders			Gynaecomastia		
General disorders and administration site conditions	Injection site thrombophlebitis;	Asthenia, fatigue and malaise	Body temperature increased; Oedema peripheral		
~~Investigations~~				~~Increased liver enzymes (transaminases, γ-GT); elevated triglycerides; increased body temperature~~	

1. Hypocalcemia in association with hypomagnesemia
2. Muscle spasm as a consequence of electrolyte disturbance

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4.9 Overdose

There are no known symptoms of ~~overdosage~~ over dosage in man.

~~Doses~~ Systemic exposure with up to 240 mg ~~i.v. were~~ administered intravenously over ~~two~~ 2 minutes ~~and~~ were well tolerated. As pantoprazole is extensively protein bound, it is not readily dialysable.

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העלון לרופא מפורסם במלואו באתר האינטרנט של משרד הבריאות, להלן הקישור:

https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h

ניתן לקבל את העלון המודפס במלואו באמצעות פניה לבעלת הרישום קיי.אס. קים אינטרנשיונל בע"מ,
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