אוגוסט 2022

הנדון: וולִיבריס 5 מ"ג ו- 10 מ"ג טבליות מצופות
Volibris 5 mg and 10 mg Film Coated Tablets

רופא/ה נכבד/ה
רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשירים **Volibris 5mg &** **Volibris 10 mg.**

בהודעה זו כלולים השינויים המהותיים בעלון לרופא ובעלון לצרכן. בעלונים ישנם שינויים נוספים.

מרכיב פעיל וחוזקו:

Volibris 5mg: Ambrisentan – 5 mg
Volibris 10mg: Ambrisentan – 10 mg

התוויה הרשומה לתכשיר בישראל:

Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment with tadalafil.
Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.

עדכונים מהותיים נעשו בסעיפים הבאים בעלון לרופא :

4.8 Undesirable effects

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Summary of the safety profile

~~The safety of ambrisentan has been evaluated as monotherapy and/or in combination in clinical trials of more than 1200 patients with PAH (see section 5.1). Adverse reactions identified from 12 week placebo controlled clinical trial data are included below by system organ class and frequency. Information from longer term non-placebo controlled studies (ARIES-E and AMBITION (combination with tadalafil)) is also included below. No previously unknown adverse reactions were identified with long-term treatment or for ambrisentan in combination with tadalafil. With longer observation in uncontrolled studies (mean observation of 79 weeks), the safety profile was similar to that observed in the short term studies. Routine pharmacovigilance data are also presented.~~

Peripheral oedema (37%)~~, fluid retention~~ and headache (28%) ~~(including sinus headache, migraine)~~ were the most common adverse reactions observed with ambrisentan. The higher dose (10 mg) was associated with a higher incidence of these adverse reactions, and peripheral oedema tended to be more severe in patients ≥65 years in short-term clinical studies (see section 4.4).

Serious adverse reactions associated with ambrisentan use include anaemia (decreased haemoglobin, decreased haematocrit) and hepatotoxicity.

Reductions in haemoglobin concentrations and haematocrit (10%) have been associated with ERAs including ambrisentan. Most of these decreases were detected during the first 4 weeks of treatment and haemoglobin generally stabilised thereafter (see section 4.4).

Hepatic enzyme elevations (2%), hepatic injury and autoimmune hepatitis (including exacerbation of underlying disease) have been observed with ambrisentan (see sections 4.4 and 5.1).

Tabulated list of adverse reactions

Frequencies are defined as: 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) and not known (cannot be estimated from available data). For dose-related adverse reactions the frequency category reflects the higher dose of ambrisentan. ~~Frequency categories do not account for other factors including varying study duration, pre-existing conditions and baseline patient characteristics. Adverse reaction frequency categories assigned based on clinical trial experience may not reflect the frequency of adverse events occurring during normal clinical practice.~~ Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class	Frequency	Adverse reaction(s)
Blood and lymphatic system disorders	Very common	Anaemia (decreased haemoglobin, decreased haematocrit)[1]
Immune system disorders	Common	Hypersensitivity reactions (e.g. angioedema, rash, pruritus)
Nervous system disorders	Very common	Headache (including sinus headache, migraine)[2], dizziness
Eye disorders	Common	Blurred vision, visual impairment
Ear and labyrinth disorders	Common	Tinnitus[3]
	Uncommon	Sudden hearing loss[3]
Cardiac disorders	Very common	Palpitation
	Common	Cardiac failure[4]
Vascular disorders	Very common	Flushing[5]
	Common	Hypotension, syncope
Respiratory, thoracic and mediastinal disorders	~~Common~~ Very common	upper respiratory (e.g. nasal, sinus) congestion[7]
	Very common	Dyspnoea[6], nasopharyngitis[7]
	Common	Epistaxis, rhinitis[7], sinusitis[7]
Gastrointestinal disorders	Very common	Nausea, diarrhoea, vomiting[5]
	Common	Abdominal pain, constipation
Hepatobiliary disorders	Common	Hepatic transaminases increased
	Uncommon	Hepatic injury (see section 4.4), autoimmune hepatitis (see section 4.4)
Skin and subcutaneous tissue disorders	Common	Rash[8]
General disorders and administration site conditions	Very common	Peripheral oedema, fluid retention, chest pain/discomfort[5], fatigue
	Common	Asthenia

~~NR – not reported~~

[1] See section '*Description of selected adverse reactions*'.

[2] The frequency of headache appeared higher with 10 mg ambrisentan.

[3] Cases were only observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil.~~Data derived from routine pharmacovigilance surveillance and frequencies based on placebo-controlled clinical trial experience.~~

[4] Most of the reported cases of cardiac failure were associated with fluid retention.~~Data derived from routine pharmacovigilance surveillance~~

[5] Frequencies were observed in a placebo-controlled clinical study of ambrisentan in combination with tadalafil. Lower incidence was observed with ambrisentan monotherapy.~~Most of the reported cases of cardiac failure were associated with fluid retention. Data derived from routine pharmacovigilance surveillance, frequencies based on statistical modelling of placebo-controlled clinical trial data~~.

[6] Cases of worsening dyspnoea of unclear aetiology have been reported shortly after starting ambrisentan therapy.

[7] The incidence of nasal congestion was dose related during ambrisentan therapy.

[8] ~~Cases of autoimmune hepatitis, including cases of exacerbation of autoimmune hepatitis, and hepatic injury have been reported during ambrisentan therapy.~~
[9] [8] Rash includes rash erythematous, rash generalised, rash papular and rash pruritic.

מקרא לעדכונים המסומנים :
מידע שהוסר – מסומן בקו אדום חוצה ~~XXX~~
תוספת – כתב **כחול**
תוספת החמרה - כתב **כחול** – מסומן בצהוב מרקר

העלונים לרופא ולצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://data.health.gov.il/drugs/index.html#/byDrug וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
טניה רשקובן
רוקחת ממונה