הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

תאריך: 25/12/2017

שם תכשיר באנגלית ומספר הרישום **Adempas 0.5 mg 153-76-34132-00/01**

Adempas 1 mg 153-77-34137-00/01

Adempas 1.5 mg 153-78-34138-00/01

Adempas 2 mg 153-79-34139-00/01

Adempas 2.5 mg 135-80-34150-00/01

שם בעל הרישום באייר ישראל בע"מ

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**

Special populations *Renal impairment* Patients with moderate renal impairment (creatinine clearance <50 - 30 mL/min) showed a higher exposure to this medicine	*Special populations* *Renal impairment* Patients with moderate renal impairment (creatinine clearance 80 - 30 mL/min) showed a higher exposure to this medicine	**4.2 Posology and method of administration**
Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers'	Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form	**4.3 Contraindications**
In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form including recreational drugs called 'poppers'	In a clinical study the highest dose of Adempas (2.5 mg tablets three times daily) potentiated the blood pressure lowering effect of sublingual nitroglycerin (0.4 mg) taken 4 and 8 hours after intake. Therefore co-administration of Adempas with nitrates or nitric oxide donors (such as amyl nitrite) in any form	**4.5 Interaction with other medicinal products and other forms of interaction** Pharmacodynamic interactions
Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, CYP3A5, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of unchanged riociguat and renal excretion of unchanged riociguat via glomerular filtration.	Riociguat is cleared mainly via cytochrome P450-mediated (CYP1A1, CYP3A4, ~~CYP2C8~~, CYP2J2) oxidative metabolism, direct biliary/faecal excretion of unchanged riociguat and renal excretion of unchanged riociguat via glomerular filtration.	Effects of other substances on riociguat
Patients must not get pregnant during Adempas therapy (see section 4.3). Riociguat (2.5 mg three times per day) did not have a clinically meaningful effect on the plasma levels of combined oral contraceptives containing levonorgestrel and ethinyl estradiol when concomitantly administered to healthy female subjects. Based on this study and as riociguat is not an inducer of any of the relevant metabolic enzymes, also no pharmacokinetic interaction is expected with other hormonal contraceptives.		Effects of riociguat on other substances
An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In	An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. In	**5.1 Pharmacodynamic Properties**

CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change in 6MWD from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 57 m in the former 1.0–2.5 mg riociguat group and 43 m in the former placebo group. Improvements in 6MWD persisted at 2 years in CHEST-2. Mean change from baseline for the overall population (N=237) was 57 m at 6 months (n=218), 51 m at 9 months (n=219), 52 m at 12 months (n=209) and 48 m at 24 months (n=193). The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 89%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 90% respectively, and for patients of WHO functional class III at baseline was 97%, 93% and 88% respectively.	CHEST-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in CHEST-2 (28 weeks on-study for CHEST-1 + CHEST-2) was 63 m in the former 1.0–2.5 mg riociguat group and 35 m in the former placebo group. The probability of survival at 1 year was 97%, at 2 years 94% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 97%, 94% and 88% respectively, and for patients of WHO functional class III at baseline was 97%, 94% and 87% respectively.	Clinical efficacy and safety *Efficacy in patients with CTEPH* Long-term treatment
An open-label extension study (PATENT-2) included 396 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change in 6MWD from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 52 m in the former 1.0–2.5 mg riociguat group, 45 m in the former placebo group and 52 m in the former 1.0–1.5 mg riociguat group. Improvements in 6MWD persisted at 2 years in	An open-label extension study (PATENT-2) included 363 patients who had completed PATENT-1 at the cut-off-date. In PATENT-2, all patients received an individualised riociguat dose up to 2.5 mg three times daily. The mean change from baseline to week 12 (last observation until week 12) in PATENT-2 (24 weeks on-study for PATENT-1 + PATENT-2) was 53 m in the former 1.0–2.5 mg riociguat group, 42 m in the former placebo group and 54 m in the former 1.0–1.5 mg riociguat group.	*Efficacy in patients with PAH* Long-term treatment

PATENT-2. Mean change from baseline for the overall population (N=396) was 53 m at 6 months (n=366), 52 m at 9 months (n=354), 50 m at 12 months (n=351) and 46 m at 24 months (n=316). The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 88%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 93% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 84% respectively. *Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP):* A randomised, double blind, placebo-controlled phase II study (RISE-IIP) to evaluate the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) was terminated early due to an increased risk of mortality and serious adverse events in in patients treated with riociguat and a lack of efficacy More patients taking riociguat died (11% vs. 4%) and had serious adverse events (37% vs. 23%) during the main phase. In the long-term extension, more patients who switched from the placebo group to riociguat (21%) died than those who continued in the riociguat group (3%).	The probability of survival at 1 year was 97%, at 2 years 93% and at 3 years 91%. Survival in patients of WHO functional class II at baseline at 1, 2 and 3 years was 98%, 96% and 96% respectively, and for patients of WHO functional class III at baseline was 96%, 91% and 87% respectively. *Patients with pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP):* A randomised, double blind, placebo-controlled phase II study (RISE-IIP) to evaluate the efficacy and safety of riociguat in patients with symptomatic pulmonary hypertension associated with idiopathic interstitial pneumonias (PH-IIP) was terminated early. Interim results showed an increased risk of mortality and serious adverse events in subjects receiving riociguat compared to those receiving placebo. The available data do not indicate a clinically significant benefit from riociguat treatment in these patients.	
N-demethylation, catalysed by CYP1A1, CYP3A4, CYP3A5 and CYP2J2 is the major biotransformation pathway of riociguat leading	N-demethylation, catalysed by CYP1A1, CYP3A4, ~~CYP2C8~~ and CYP2J2 is the major biotransformation pathway of riociguat leading	**5.2 Pharmacokinetic Properties** Metabolism

to its major circulating active metabolite M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.	to its major circulating active metabolite M-1 (pharmacological activity: 1/10th to 1/3rd of riociguat) which is further metabolised to the pharmacologically inactive N-glucuronide.	

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ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
2) לפני השימוש בתרופה	**אין להשתמש בתרופה אם:** • הנך נוטל תרופות לטיפול ביתר לחץ-דם, בכאבים בחזה או במחלת לב הנקראות ניטרטים או תורמי תחמוצת חנקן (ניטריק אוקסיד) בכל צורה שהיא (כגון אמיל ניטריט).	**אין להשתמש בתרופה אם:** • הנך נוטל תרופות לטיפול ביתר לחץ-דם, בכאבים בחזה או במחלת לב הנקראות ניטרטים או תורמי תחמוצת חנקן (ניטריק אוקסיד) בכל צורה שהיא (כגון אמיל ניטריט). זה כולל גם תכשירים שנועדו לשינוי המצב התודעתי (recreational drugs) המכונים פופרס.
3) כיצד תשתמש בתרופה? אם נטלת בטעות מינון גבוה יותר	**אם נטלת בטעות מינון גבוה יותר** ואתה חווה תופעות לוואי כלשהן (ראה סעיף 4 "תופעות לוואי") עליך לפנות לרופא. במידה ולחץ הדם שלך צונח (מה שיכול לגרום לך לתחושת סחרחורת) עליך לפנות לקבלת טיפול רפואי מיידי.	**אם נטלת בטעות מינון גבוה יותר** ואתה חווה תופעות לוואי כלשהן (ראה סעיף 4 "תופעות לוואי") עליך לפנות לרופא. במידה ולחץ הדם שלך צונח (מה שיכול לגרום לך לתחושת סחרחורת) עליך לפנות לקבלת טיפול רפואי מיידי.
4) תופעות לוואי	**תופעות הלוואי החמורות ביותר הינן:** דימום חמור מהריאות (תופעת לוואי שאינה שכיחה), יכול לגרום לשיעול דמי	**תופעות הלוואי החמורות ביותר הינן:** דימום חמור מהריאות, יכול לגרום לשיעול דמי , נצפו מקרים שהסתיימו במוות (תופעת לוואי שאינה שכיחה).