ינואר 2022

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

הנדון:
Adempas 0.5 mg; 1mg; 1.5mg; 2mg; 2.5mg
אדמפס 0.5 מג, 1 מ"ג, 1.5 מ"ג, 2 מ"ג, 2.5 מ"ג
Film coated tablets
Riociguat 0.5 mg; 1mg; 1.5mg; 2mg; 2.5mg

אנו מבקשים להודיעכם שהעלון לרופא והעלון לצרכן של התכשיר עודכנו.

ההתוויה המאושרת לתכשיר:

Chronic thromboembolic pulmonary hypertension (CTEPH)
Adempas is indicated for the treatment of adult patients with WHO Functional Class (FC) II to III with
• inoperable CTEPH,
• persistent or recurrent CTEPH after surgical treatment, to improve exercise capacity.
Pulmonary arterial hypertension (PAH)
Adempas, as monotherapy or in combination with endothelin receptor antagonists, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III
to improve exercise capacity.
Efficacy has been shown in a PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

בהודעה זו כלולים העידכונים המהותיים בלבד. בפירוט שלהלן מופיע, רק המידע שהתעדכן. תוספת טקסט מסומנת בקו תחתון.

העדכונים בעלון לרופא:

4.2 Posology and method of administration

Renal impairment

Data in patients with severe renal impairment (creatinine clearance <30 mL/min) are limited and there are no data for patients on dialysis. Therefore, use of Adempas is not recommended in these patients (see section 4.4).

Patients with mild and moderate renal impairment (creatinine clearance < 80- 30 mL/min) showed a higher exposure to this medicinal product (see section 5.2). There is a higher risk of hypotension in patients with renal impairment, therefore particular care should be exercised during individual dose titration.

Patients on stable doses of strong multi pathway CYP / P glycoprotein (P-gp) and breast cancer resistance protein (BCRP) inhibitors

When initiating Adempas in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors, such as azole antimycotics (e.g. ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir), consider a starting dose of 0.5 mg, three times a day to mitigate the risk of hypotension. Monitor for signs and symptoms of hypotension on initiation and on treatment. Consider a dose reduction for patients on Adempas doses higher than or equal to 1.0 mg if the patient develops signs or symptoms of hypotension (see sections 4.4 and 4.5).

4.3 Contraindications

- Concomitant use with other soluble guanylate cyclase stimulators.

4.4 Special warnings and precautions for use

Concomitant use with other medicinal products

•The concomitant use of riociguat with strong multi pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp) / breast cancer resistance protein (BCRP) inhibitors such as azole antimycotics (e.g., ketoconazole, posaconazole, itraconazole) or HIV protease inhibitors (e.g. ritonavir) is not recommended, due to the results in a pronounced increase in riociguat exposure (see sections 4.5 and 5.2).

•Assess the benefit-risk for each patient individually before prescribing Adempas in patients on stable doses of strong multi pathway CYP and P-gp/BCRP inhibitors. To mitigate the risk of hypotension, consider dose reduction and monitoring for signs and symptoms of hypotension (see sections 4.2 and 4.5).

•In patients on stable doses of Adempas, the initiation of strong multi pathway CYP and P gp/BCRP inhibitors is not recommended as no dosage recommendation can be given due to limited data. Alternative treatments should be considered.

4.5 Interaction with other medicinal products and other forms of interaction

Soluble Guanylate Cyclase Stimulators
Concomitant use of riociguat with other soluble guanylate cyclase stimulators is contraindicated (see section 4.3).
Effects of other substances on riociguat

Concomitant use with strong multi pathway CYP and P-gp/BCRP inhibitors

Highly active antiretroviral therapy (HAART)

In *vitro*, abacavir, rilpivirine, efavirenz, ritonavir, cobicistat and elvitegravir inhibited CYP1A1 and the metabolism of riociguat in the order listed with abacavir as the strongest inhibitor. Cobicistat, ritonavir, atazanavir and darunavir are additionally classified as CYP3A inhibitors. In addition,

ritonavir showed inhibition of P-gp.

The impact of HAART (including different combinations of abacavir, atazanavir, cobicistat, darunavir, dolutegravir, efavirenz, elvitegravir, emtricitabine, lamivudine, rilpivirine, ritonavir, and tenofovir) on riociguat exposure was investigated in a dedicated study in HIV patients. Concomitant administration of HAART combinations led to an increase in riociguat mean AUC of up to about 160% and to an approximate 30% increase in mean C_{max}. The safety profile observed in HIV patients taking a single dose of 0.5 mg riociguat together with different combinations of HIV drugs used in HAART was generally comparable to other patient populations.

To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, e.g. as contained in HAART, consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).

Antifungals

To mitigate the risk of hypotension when Adempas is initiated in patients on stable doses of strong multi pathway CYP (especially CYP1A1 and CYP3A4) and P-gp/BCRP inhibitors, e.g. ketoconazole, Posaconazole or itraconazole consider a reduced starting dose. It is recommended to monitor these patients for signs and symptoms of hypotension (see sections 4.2 and 4.4).

Concomitant use with other CYP and P-gp/BCRP inhibitors

Inhibitors for the UDP-Glycosyltransferases (UGT) 1A1 and 1A9 may potentially increase the exposure of the riociguat metabolite M1, which is pharmacologically active (pharmacological activity: $1/10^{th}$ to $1/3^{rd}$ of riociguat). For co-administration with these substances follow the recommendation on dose titration (see section 4.2).

Concomitant use with CYP3A4 inducers

Bosentan, reported to be a moderate inducer of CYP3A4, led to a decrease of riociguat steady-state plasma concentrations in PAH patients by 27% (see sections 4.1 and 5.1). For co-administration with bosentan follow the recommendation on dose titration (see section 4.2).

The concomitant use of riociguat with strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to decreased riociguat plasma concentration. For co-administration with strong CYP3A4 inducers follow the recommendation on dose titration (see section 4.2).

4.8 Undesirable effects

Summary of the safety profile

The safety of Adempas has been evaluated in phase III studies of 681 patients with CTEPH and PAH receiving at least one dose of riociguat (see section 5.1). With longer observation in uncontrolled long term extension studies the safety profile was similar to that observed in the placebo controlled phase III trials.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Clinical efficacy and safety

Efficacy in patients with CTEPH

Long-term treatment of CTEPH

An open-label extension study (CHEST-2) included 237 patients who had completed CHEST-1. At the end of the study, mean (SD) treatment duration in the total group was 1285 (709) days and median duration was 1174 days (ranging from15 to 3512 days). In total, 221 patients (93.2%) had a treatment duration of approximately 1 year (at least 48 weeks), 205 patients (86.5%) of approximately 2 years (at least 96 weeks) and 142 patients (59.9%) of approximately 3 years (at least 144 weeks). Treatment exposure was 834 person years in total.
The safety profile in CHEST-2 was similar to that observed in pivotal trials. After treatment with riociguat, the mean 6MWD improved in the overall population by 53 m at 12 months (n=208), 48 m at 24 months (n=182), and 49 m at 36 months (n=117) compared to baseline. Improvements in 6MWD persisted until the end of the study.
Table 4 shows the proportion of patients* with changes in WHO functional class during riociguat treatment compared to baseline.

Table 4: CHEST-2: Changes in WHO Functional Class

	Changes in WHO Functional Class (n (%) of patients)		
Treatment duration in CHEST-2	Improved	Stable	Worsened
1 years (n=217)	100 (46%)	109 (50%)	6 (3%)
2 years (n=193)	76 (39%)	111 (58%)	5 (3%)
3 years (n=128)	48 (38%)	65 (51%)	14 (11%)
*Patients participated in the study until the drug was approved and commercially available in their countries.			

The probability of survival was 97% after 1 year, 93% after 2 years and 89% after 3 years of riociguat treatment.

Efficacy in patients with PAH

Long-term treatment of PAH

An open label extension study (PATENT-2) included 396 patients who had completed PATENT-1.
In PATENT-2, mean (SD) treatment duration in the total group (not including exposure in PATENT-1) was 1375 (772) days and median duration was 1331 days (ranging from 1 to 3565 days). In total, treatment exposure was approximately 1 year (at least 48 weeks) for 90%, 2 years (at least 96 weeks) for 85%, and 3 years (at least 144 weeks) for 70% of patients. Treatment exposure was 1491 person years in total.
The safety profile in PATENT-2 was similar to that observed in pivotal trials. After treatment with riociguat, the mean 6MWD improved in the overall population by 50 m at 12 months (n=347), 46 m at

24 months (n=311) and 46 m at 36 months (n=238) compared to baseline. Improvements in 6MWD persisted until the end of the study.

Table 8 shows the proportion of patients* with changes in WHO functional class during riociguat treatment compared to baseline.

Table 8: PATENT-2: Changes in WHO Functional Class

	Changes in WHO Functional Class (n(%) of patients)		
Treatment duration in PATENT-2	Improved	Stable	Worsened
1 years (n=358)	116 (32%)	222 (62%)	20 (6%)
2 years (n=321)	106 (33%)	189 (59%)	26 (8%)
3 years (n=257)	88 (34%)	147 (57%)	22 (9%)
*Patients participated in the study until the study drug was approved and commercially available in their countries.			

The probability of survival was 97% after 1 year, 93% after 2 years and 88% after 3 years of riociguat treatment.

עידכונים בעלון לצרכן:

2)לפני השימוש בתרופה

אין להשתמש בתרופה אם:

- הנך נוטל **ממריצים מסיסים** אחרים **של גואנילט ציקלאז (**soluble guanylate cyclase stimulators). שאל את הרופא אם אינך בטוח.

אזהרות מיוחדות הנוגעות לשימוש בתרופה:
לפני השימוש באדמפאס ספר לרופא אם:

- אתה נוטל תרופות **לטיפול בזיהומים פטרתיים** (כגון, קטוקונזול, פוסקונזול, איטראקונזול) או תרופות לטיפול בזיהום בנגיף הכשל החיסוני האנושי HIV (כגון: אבאקויר, אטאזנביר, קוביסיסטאט, דרונאביר, דולוטגראביר, אפאבירנז, אלביטגראביר, אמטריציטבין, לאמיבודין, רילפיבירין, ריטונאביר וטנופוביר). הרופא שלך יעקוב אחר מצבך הבריאותי וישקול מינון התחלתי מופחת עבור אדמפס.

אינטראקציות/תגובות בין תרופתיות
אם אתה לוקח, אם לקחת לאחרונה או אם אתה עשוי לקחת, תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח. במיוחד יש ליידע את הרופא או הרוקח אם אתה לוקח:

-תרופות לטיפול ביתר לחץ דם או במחלת לב (כגון ניטרטים ואמיל ניטריט בכל צורה שהיא או ממריצים מסיסים אחרים של גואנילט ציקלאז). אין להשתמש בהן יחד עם אדמפאס.

-תרופות לטיפול בזיהומים פטרייתיים (כגון קטוקונאזול, פוסאקונאזול, איטראקונאזול). או תרופות לטיפול בזיהום נגיף הכשל החיסוני האנושי HIV (כגון: אבאקויר, אטאזנביר, קוביסיסטאט, דרונאביר, דולוטגראביר, אפאבירנז, אלביטגראביר, אמטריציטבין רילפיבירין או ריטונאביר) מכיון שיש לשקול אלטרנטיביות טיפול חלופיות. במידה והנך כבר נוטל אחת מהתרופות הללו ומתחיל טיפול עם אדמפס, הרופא שלך יעקוב אחר מצבך הבריאותי וישקול מינון התחלתי מופחת עבור אדמפס.

אם יש לך שאלות נוספות בנוגע לשימוש בתרופה, היוועץ ברופא או ברוקח.
https://data.health.gov.il/drugs/index.html#!/byDrug
ניתן לקבלם מודפסים ע"י פניה לחברת באייר ישראל, רח' החרש 36 הוד השרון, טלפון: 09-7626700

בברכה
באייר ישראל