דצמבר 2019

Esbriet® 267 mg	Esbriet® 267 mg Tablets	Esbriet® 801 mg Tablets
אסברייט 267 מ"ג	אסברייט 267 מ"ג טבליות	אסברייט 267 מ"ג טבליות
Pirfenidone	Pirfenidone	Pirfenidone
Hard Capsules	**Film coated tablets**	**Film coated tablets**

רופא/ה יקר/ה, רוקח/ת יקר/ה,

חברת רוש פרמצבטיקה (ישראל) בע"מ מבקשת להודיעכם על מספר עדכונים בעלון לרופא ובעלון לצרכן של התכשירים המצוינים מעלה. בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויה הרשומה לתכשירים בישראל:

Esbriet is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF).

הסבר:
טקסט עם קו תחתי מציין טקסט שהוסף לעלון.
~~טקסט עם קו חוצה~~ מציין טקסט שהוסר מן העלון.

למידע נוסף יש לעיין בעלון לרופא ובעלון לצרכן כפי שאושרו ע"י משרד הבריאות.

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פנייה לבעל הרישום: רוש פרמצבטיקה (ישראל) בע"מ, ת.ד 6391 , הוד השרון 4524079 טלפון 09-9737777. כתובתנו באינטרנט: www.roche.co.il.

ב ב ר כ ה,

בת אל כהן
רוקחת ממונה

לביא עמי-עד
רוקח ממונה

עדכונים מהותיים בעלון לרופא

בסעיף 4.2 Posology and method of administration עודכן המידע הבא:

[…]

Renal impairment

No dose adjustment is necessary in patients with mild ~~to moderate~~ renal impairment.
Esbriet should be used with caution in patients with moderate (CrCl 30-50 ml/min) renal impairment.
Esbriet therapy should not be used in patients with severe renal impairment (CrCl <30 ml/min) or end stage renal disease requiring dialysis (see sections 4.3 and 5.2).

[…]

בסעיף 4.4 Special warnings and precautions for use עודכן המידע הבא:

[…]

Angioedema/ Anaphylaxis

Reports of angioedema (some serious) such as swelling of the face, lips and/or tongue which may be associated with difficulty breathing or wheezing have been received in association with use of Esbriet in the post-marketing setting.
Reports of anaphylactic reactions have also been received.
Therefore, patients who develop signs or symptoms of angioedema or severe allergic reactions following administration of Esbriet should immediately discontinue treatment. Patients with angioedema or severe allergic reactions should be managed according to standard of care. Esbriet must not be used in patients with a history of angioedema or hypersensitivity due to Esbriet (see section 4.3).

[…]

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

[…]

Immune system disorders: Anaphylaxis was added as an adverse reaction at Not known (cannot be estimated from the available data) frequency.
Anaphylaxis was identified through post-marketing surveillance.

[…]

בסעיף 5.2 Pharmacokinetic properties עודכן המידע הבא:

Absorption

Administration of Esbriet capsules with food results in a large reduction in Cmax (by 50%) and a smaller effect on AUC, compared to the fasted state. Following oral administration of a single dose of 801 mg to healthy older adult volunteers (50-66 years of age) in the fed state, the rate of pirfenidone absorption slowed, while the AUC in the fed state was approximately 80-85% of the AUC observed in the fasted state.
Bioequivalence was demonstrated in the fasted state when comparing the 801 mg tablet to three 267 mg capsules. In the fed state, the 801 mg tablet met bioequivalence criteria based on the AUC measurements compared to the capsules, while the 90% confidence intervals for Cmax (108.26% - 125.60%) slightly exceeded the upper bound of standard bioequivalence limit (90% CI: 80.00% - 125.00%). The effect of food on pirfenidone oral AUC was consistent between the tablet and capsule formulations. Compared to the fasted state, administration of either formulation with food reduced pirfenidone Cmax, with Esbriet tablet reducing the Cmax slightly less (by 40%) than Esbriet capsules (by 50%).
A reduced incidence of adverse events (nausea and dizziness) was observed in fed subjects when compared to the fasted group. Therefore, it is recommended that Esbriet be administered with food to reduce the incidence of nausea and dizziness.
The absolute bioavailability of pirfenidone has not been determined in humans.

[…]

Biotransformation

Approximately 70–80% of pirfenidone is metabolised via CYP1A2 with minor contributions from other CYP isoenzymes including CYP2C9, 2C19, 2D6, and 2E1.
In vitro data indicate some pharmacologically relevant activity of the major metabolite (5-carboxy-pirfenidone) at concentrations in excess of peak plasma concentrations in IPF patients. This may become clinically relevant in patients with moderate renal impairment where plasma exposure to 5-carboxy-pirfenidone is increased.
~~*In vitro* and *in vivo* studies to date have not detected any activity of the major metabolite (5-carboxy-pirfenidone), even at concentrations or doses greatly above those associated with activity of pirfenidone itself.~~

[…]

Renal impairment

No clinically relevant differences in the pharmacokinetics of pirfenidone were observed in subjects with mild to severe renal impairment compared with subjects with normal renal function. The parent substance is predominantly metabolised to 5-carboxy-pirfenidone.

The mean (SD) $AUC_{0-\infty}$ of 5-carboxy-pirfenidone was significantly higher in the moderate ($p = 0.009$) and severe ($p < 0.0001$) renal impairment groups than in the group with normal renal function; 100 (26.3) mg•h/L and 168 (67.4) mg•h/L compared to 28.7 (4.99) mg•h/L respectively.

Renal Impairment	**Statistics**	**$AUC_{0-\infty}$ (mg•hr/L)**	
		Pirfenidone	**5-Carboxy-Pirfenidone**
Normal n=6	Mean (SD) Median (25^{th}–75^{th})	42.6 (17.9) 42.0 (33.1–55.6)	28.7 (4.99) 30.8 (24.1–32.1)
Mild n=6	Mean (SD) Median (25^{th}–75^{th})	59.1 (21.5) 51.6 (43.7–80.3)	49.3[a] (14.6) 43.0 (38.8–56.8)
Moderate n=6	Mean (SD) Median (25^{th}–75^{th})	63.5 (19.5) 66.7 (47.7–76.7)	100[b] (26.3) 96.3 (75.2–123)
Severe n=6	Mean (SD) Median (25^{th}–75^{th})	46.7 (10.9) 49.4 (40.7–55.8)	168[c] (67.4) 150 (123–248)

$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity.

[a] p-value versus Normal = 1.00 (pair-wise comparison with Bonferroni)

[b] p-value versus Normal = 0.009 (pair-wise comparison with Bonferroni)

[c] p-value versus Normal < 0.0001 (pair-wise comparison with Bonferroni)

Exposure to 5-carboxy-pirfenidone increases 3.5 fold or more in patients with moderate renal impairment. Clinically relevant pharmacodynamic activity of the metabolite in patients with moderate renal impairment cannot be excluded. No dose adjustment is required in patients with mild renal impairment who are receiving pirfenidone. Pirfenidone should be used with caution in patients with moderate renal impairment.

~~, and the pharmacokinetics of this metabolite is altered in subjects with moderate to severe renal impairment. However, the predicted amount of metabolite accumulation at steady state is not pharmacodynamically important because the terminal elimination half-life is only 1–2 hours in these subjects. No dose adjustment is required in patients with mild to moderate renal impairment who are receiving pirfenidone.~~

The use of pirfenidone is contraindicated in patients with severe renal impairment (CrCl <30ml/min) or end stage renal disease requiring dialysis (see sections 4.2 and 4.3).
Population pharmacokinetic analyses from 4 studies in healthy subjects or subjects with renal impairment and one study in patients with IPF showed no clinically relevant effect of age, gender or body size on the pharmacokinetics of pirfenidone.

עדכונים מהותיים בעלון לצרכן

בסעיף 2. אזהרות מיוחדות הנוגעות לשימוש בתרופה עודכן המידע הבא:

[...]

- יש ליידע את הרופא שלך אם אתה סובל מבעיות בכליה

[...]

בסעיף 4. תופעות לוואי עודכן המידע הבא:

[...]

הפסק ליטול אסברייט וידע את הרופא באופן מיידי אם אתה סובל מהתופעות הבאות:

- נפיחות בפנים, בשפתיים ו/או בלשון, גרד, סרפדת, קשיי נשימה או צפצופים, או תחושת עלפון, אשר הם סימנים לאנגיואדמה, תגובה אלרגית חמורה או אנפילקסיס. ~~זהו תופעת לוואי שאינה שכיחה~~.
- הצהבה של העיניים או של העור, שתן כהה, שייתכן וילוו גם בגירוד בעור והנם סימנים לתפקוד כבדי לקוי. אלה תופעות לוואי נדירות.

[...]