אפריל 2018

Zelboraf®
זלבוראף
vemurafenib 240mg
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 התכשיר זלבוראף. בהודעה זו מצוינים רק עדכונים מהותיים ועדכונים אשר מהווים החמרה.

ההתוויה הרשומה לתכשיר בישראל:
ZELBORAF is indicated for the treatment of $BRAF^{V600}$ mutation-positive unresectable or metastatic melanoma.

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,

בתאור צפרי-חגג
מחלקת רישום

מיכל קליין
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עדכונים מהותיים בעלון לרופא

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

Effects of vemurafenib on other medicinal products
Vemurafenib may increase the plasma exposure of medicinal products predominantly metabolised by CYP1A2 and decrease the plasma exposure of medicines predominantly metabolised by CYP3A4. Concomitant use of vemurafenib with agents metabolized by CYP1A2 and CYP3A4 with narrow therapeutic windows is not recommended. Dose adjustments for medicinal products predominantly metabolised via CYP1A2 or CYP3A4 should be considered based on their therapeutic windows before concomitantly treating with vemurafenib (see sections 4.5 and 4.6).
…
Concomitant administration of strong inducers of CYP3A4, P-gp and glucuronidation (e.g. rifampicin, rifabutin, carbamazepine, phenytoin or St John's Wort [hypericin]) might lead to decreased exposure of vemurafenib and should be avoided when possible (see section 4.5). Alternative treatment with less inducing potential should be considered to maintain the efficacy of vemurafenib.

בסעיף 4.5 Interaction with other medicinal products and other forms of interaction עודכן המידע הבא:

Effects of vemurafenib on Drug Metabolizing Enzymes
Results from an in vivo drug-drug interaction study in metastatic melanoma patients demonstrated that vemurafenib is a moderate CYP1A2 inhibitor and a CYP3A4 inducer.

Concomitant use of vemurafenib with agents metabolized by CYP1A2 with narrow therapeutic windows (e.g. agomelatine, alosetron, duloxetine, melatonin, ramelteon, tacrine, tizanidine, theophylline) is not recommended. If co-administration cannot be avoided, exercise caution, as vemurafenib may increase plasma exposure of CYP1A2 substrate drugs. Dose reduction of the concomitant CYP1A2 substrate drug may be considered, if clinically indicated.
Co-administration of vemurafenib increased the plasma exposure (AUC) of caffeine (CYP1A2 substrate) 2.6-fold. In another clinical trial, vemurafenib increased C_{max} and AUC of a single 2 mg dose of tizanidine (CYP1A2 substrate) approximately 2.2-fold and 4.7-fold, respectively.

Concomitant use of vemurafenib with agents metabolized by CYP3A4 with narrow therapeutic windows is not recommended. If co-administration cannot be avoided, it needs to be considered that vemurafenib may decrease plasma concentrations of CYP3A4 substrates and thereby their efficacy may be impaired.
…
Co-administration of vemurafenib resulted in an 18% increase in AUC of S-warfarin (CYP2C9 substrate). Exercise caution and consider additional INR (international normalized ratio) monitoring when vemurafenib is used concomitantly with warfarin (see section 4.4).

Vemurafenib moderately inhibited CYP2C8 *in vitro*. The *in vivo* relevance of this finding is unknown, but a risk for a clinically relevant effect on concomitantly administered CYP2C8 substrates cannot be excluded. Concomitant administration of CYP2C8 substrates with a narrow therapeutic window should be made with caution since vemurafenib may increase their concentrations.

Effects of concomitant medicines on vemurafenib
In vitro studies suggest that CYP3A4 metabolism and glucuronidation are responsible for the metabolism of vemurafenib. Biliary excretion appears to be another important elimination pathway. Concomitant administration of strong CYP3A4 inhibitors or inducers or inhibitors/inducer of transport protein activity may alter vemurafenib concentrations.
There are no clinical data available showing the effect of strong inhibitors of CYP3A4 and/or transport protein activity on vemurafenib exposure. Vemurafenib should be used with caution in combination with strong inhibitors of CYP3A4, glucuronidation and/or transport proteins (e.g. ritonavir, saquinavir, telithromycin, ketoconazole, itraconazole, voriconazole, posaconazole, nefazodone, atazanavir).

בסעיף 4.6 Fertility, pregnancy and lactation עודכן המידע הבא:

Pregnancy
There are no data regarding the use of vemurafenib in pregnant women.
Vemurafenib revealed no evidence of teratogenicity in rat or rabbit embryo/foetuses (see section 5.3). In animal studies, vemurafenib was found to cross the placenta. Based on its mechanism of action, vemurafenib could cause fetal harm when administered to a pregnant woman. Vemurafenib should not be administered to pregnant women unless the possible benefit to the mother outweighs the possible risk to the foetus.

בסעיף 4.8 Undesirable effects עודכן המידע הבא:

Summary of the safety profile
The most common adverse drug reactions (ADR) of any grade (> 30%) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, alopecia, nausea diarrhea, headache, pruritus, vomiting, skin papilloma and hyperkeratosis. The most common (≥ 5%) Grade 3 ADRs were cuSCC, keratoacanthoma, rash, arthralgia and gamma-glutamyltransferase (GGT) increased. CuSCC was most commonly treated by local excision.

Table 3: ADRs occurring in patients treated with vemurafenib in the phase II or phase III study and events originating from safety reports across all trials[(1)] and post-marketing sources[(2)].

Very common: keratoacanthoma, dizziness, palmar-plantar erythrodysaesthesia syndrome
Common: Neutropenia, neuropathy peripheral, Vasculitis, AST increased
Uncommon: iridocyclitis

עדכונים מהותיים בעלון לצרכן

בסעיף 4. תופעות לוואי עודכן המידע הבא:

תופעות לוואי שכיחות מאוד - תופעות שמופיעות ביותר ממשתמש אחד מעשרה

תסמונת יד ורגל (אדמומיות, קילוף בעור או שלפוחיות בכפות הידיים ובכפות הרגליים)

תופעות לוואי שכיחות - תופעות שמופיעות ב 1-10 משתמשים מתוך 100

דלקת בכלי הדם

בעיות עצביות העלולות לגרום לכאב, חוסר תחושה ו/או חולשה בשרירים (מחלת עצבים היקפיים)

הפחתה ברמות תאי הדם הלבנים (נויטרופניה)