אפריל 2025

Rezurock

200mg, film-coated tablets

חברת סאנופי ישראל מבקשת להודיע על עדכון העלונים לרופא ולצרכן.

ההתוויה המאושרת:

Rezurock is indicated for the treatment of patients aged 12 years and older with chronic graft versus host disease (chronic GVHD) who have received at least two prior lines of systemic therapy.

העדכונים העיקריים בעלונים הינם:

בעלון לרופא:

4.2 Posology and method of administration

…..

Renal impairment

No dose modification of Rezurock is required in patients with mild or moderate renal impairment (creatinine ~~creatine~~ clearance ≥ 30 mL/min).

No data are available for patients with severe renal impairment (creatinine ~~creatine~~ clearance < 30 mL/min) or for patients with end-stage renal disease on dialysis (see sections 5.1 and 5.2). Use with caution.

…..

4.5 Interaction with other medicinal products and other forms of interaction

…..

Transporters

Avoid coadministration of belumosudil with P-gp (e.g. dabigatran), OATP1B1, and BCRP substrates (e.g. rosuvastatin), for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the P-gp, OATP1B1, and BCRP substrates dosage(s) in accordance with the respective Prescribing Information.

Belumosudil is a an inhibitor~~substrate~~ of P-gp. , OATP1B1, and BCRP. Coadministration of belumosudil with P- gp, OATP1B1, and BCRP substrates increased their plasma concentrations (see section 5.2), which

Greenwork Park, Yakum, Building E, 1st floor, 6097600, Israel
Tel.: +972-9-8633081 - Fax: +972-9-8851444 - www.sanofi.co.il

~~Belumosudil inhibits BCRP, P-gp, and OATP1B1. The co-administration of oral BCRP, P-gp and OATP1B1 substrates with belumosudil~~ may increase the risk of adverse reactions related to these substrates.
~~concentrations of the substrate drugs (such as digoxin and docetaxel).~~

4.6 Fertility, pregnancy and lactation

…..

Fertility

There are no human data on the effect of belumosudil on fertility. ~~Based on findings from animal studies, belumosudil may impair male and female fertility at dose levels above the recommended clinical dose. The effects on fertility are reversible (see section 5.3).~~

Belumosudil repeat dose toxicity studies in rats demonstrated effects of general toxicity manifesting low body weight that may lead to impairment of female fertility (see section 5.3).

Based on testicular findings from rats and dogs, belumosudil may impair male fertility (see section 5.3).

…..

5.2 Pharmacokinetic properties

…..

Drug Interaction Studies

Effects of Other Drugs on Belumosudil

Strong Cytochrome P450 (CYP) 3A Inhibitors: There was no clinically meaningful effect on belumosudil exposure when co-administered with itraconazole in healthy subjects.

Strong CYP3A4 Inducers: Coadministration of rifampin decreased belumosudil C_{max} by 59% and AUC by 72% in healthy subjects.

Moderate CYP3A Inducers: Coadministration of efavirenz is predicted to decrease belumosudil C_{max} by 19% and AUC by 35% in healthy subjects.

Proton Pump Inhibitors: Coadministration of rabeprazole decreased belumosudil C_{max} by 87% and AUC by 80%, and coadministration of omeprazole decreased belumosudil C_{max} by 68% and AUC by 47% in healthy subjects.

Effects of Belumosudil on Other Drugs

Enzyme Systems

CYP3A Substrates: Coadministration of belumosudil is predicted to increase midazolam (a sensitive CYP3A substrate) C_{max} and AUC approximately 1.26- and 1.47-fold, respectively.

CYP2C9 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C9 substrates (such as warfarin).

CYP2C8 Substrates: Coadministration of belumosudil is not expected to have clinically meaningful effect on the exposure of CYP2C8 substrates that are not an OATP1B1 substrate.

CYP1A2 Substrates with a Narrow Therapeutic Index: Belumosudil is predicted to increase theophylline AUC by 40%. Caution should be advised when co-administering belumosudil with CYP1A2 substrates with a narrow therapeutic index (e.g., theophylline, warfarin, tizanidine or pomalidomide).

Transporter systems
OATP1B1/BCRP substrates: Coadministration of belumosudil increases rosuvastatin C_{max} and AUC by 3.6 and 4.6-fold, respectively (see section 4.5).

P-glycoprotein (P-gp) substrates: Coadministration of belumosudil increased the exposure of dabigatran by 2-fold.

In Vitro Studies
Enzymes Systems: Belumosudil is an inhibitor of CYP1A2, CYP2C19, CYP2D6, UGT1A1 and UGT1A9.

Transporter Systems: Belumosudil is a substrate of P-glycoprotein (P-gp). Belumosudil inhibits BCRP, P-gp, and OATP1B1 at clinically relevant concentrations.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, genotoxicity, carcinogenic potential.

Belumosudil did not result in any carcinogenic effect in a 6-month CByB6F1-Tg (HRAS)2Jic hemizygous mouse study.
~~Carcinogenicity studies have not been conducted with belumosudil.~~

Belumosudil was not mutagenic in an in vitro bacterial mutagenicity (Ames) assay. Belumosudil was not clastogenic in either an in vitro chromosome aberration assay in mammalian (CHO) cells or an in vivo mouse bone marrow micronucleus assay.

Belumosudil repeat dose toxicity studies in rats demonstrated effects of general toxicity manifesting low body weight that may lead to impairment of female fertility. Based on testicular findings from rats and dogs, belumosudil may impair male fertility.

Repeated oral dose studies with belumosudil of up to 6-months in rats and 3-months in the dog were conducted. The No-Observed-Adverse-Effect-Level (NOAEL) in the 6-month rat study with 4-weeks recovery was < 50 mg/kg/day [male] /125 mg/kg/day [female] (<1.1- to 7.4-fold the AUC at the human recommended dose). In a 3-month dog study, belumosudil was administered at 35, 70, and 125 mg/kg/day with 4 weeks of recovery, the NOAEL was <35 mg/kg/day [male] and 35 mg/kg/day[female] (~1-fold human AUC).

Following administration of belumosudil to rats and/or dogs, the adverse effects observed in one or both species included toxicities in the gastrointestinal (GI) tract (emesis, loose stools, and/or abnormal black contents, increase in salivation), liver (elevated liver enzymes, hypertrophy/increased organ weight, and cholestasis/inflammation), kidney (increased blood urea nitrogen [BUN], tubular changes, pigmentation, intracellular protein droplets in the epithelium), hemolymphoid system (regenerative anemia), and reproductive system.

Adverse changes in male and female reproductive organs also occurred in general 3-month and 6- month toxicology studies. In males, findings included spermatozoa degeneration at a belumosudil dose of ≥50 mg/kg/day in rats and ≥35 mg/kg/day in dogs. The exposure (AUC) at the doses of 50 mg/kg/day in male rats and 35 mg/kg/day in male dogs is 1.1-fold the clinical exposure at the recommended human dose of 200 mg/day. Changes were reversible in dogs but not fully reversible in rats. In female rats, changes included lower uterine weights that correlated with uterine/cervical hypoplasia and decreased follicular development in ovaries related to adverse body weight reduction due to lower food consumption at 275 mg/kg/day in rats. Changes were fully reversed during the 4- week recovery period.

In a female rat fertility and early emrbyonic development
~~In a female rat fertility~~ study, belumosudil was administered to female rats 14 days prior to mating and up to gestation day 7. Belumosudil had no effect on fertility or reproductive function of female rats at doses of 50, 150 or 275 mg/kg/day. However, in female rats at a dose of 275 mg/kg/day resulted in maternal toxicity and increased post-implantation loss/resorptions and decrease in the number of viable foetuses. The exposure (AUC) at the dose of 275 mg/kg/day is approximately 9.4 times the clinical exposure (AUC) at the maximum recommended dose of 200 mg daily.

In a male rat fertility and early embryonic development study, belumosudil was administered to male rats 70 days prior to and throughout mating to non-treated female rats. Belumosudil had no effects on fertility or reproductive function in male rats at doses

of 50 and 150 mg/kg/day. However, a dose of 275 mg/kg/day resulted in generalized toxicity, reduced male fertility, abnormal sperm findings (reduced motility, reduced concentration and increased percentage of abnormal sperm), and testes/epididymis organ changes. The exposure (AUC) at the dose of 275 mg/kg/day is approximately 8.6 times the clinical exposure at the maximum recommended dose of 200 mg daily.

Embryo-foetal~~Adverse changes in male and female reproductive organs also occurred in general toxicology studies; findings included spermatozoa degeneration at a belumosudil dose of 35 mg/kg/day in dogs and decreased follicular~~ development studies were conducted~~in ovaries at 275 mg/kg/day~~ in rats with administration of belumosudil to pregnant animals~~. Changes were partially or fully reversed~~ during the ~~recovery~~ period~~.~~ of organogenesis at oral doses of 25, 50, 150, and 300 mg/kg/day in an exploratory pilot study and doses of 15, 50, and 150 mg/kg/day in a pivotal study. In the exploratory study, maternal toxicity and embryo-foetal developmental effects were observed. Maternal toxicity (reduced body weight gain) occurred at 150 and 300 mg/kg/day doses. Increased post-implantation loss occurred at 50 and 300 mg/kg/day. Foetal external malformations were observed at ≥50 mg/kg/day and included absence of anus and tail, omphalocele, and dome shaped head. The exposure (AUC) at ~~the doses of 35 mg/kg/day in dogs, and 275~~50 mg/kg/day in rats is approximately 1.4-fold~~0.5 times and 8-9 times, respectively,~~ the human~~clinical~~ exposure at the recommended dose of 200 mg daily.

In pregnant rabbits~~rats~~, oral administration of belumosudil during the period of organogenesis resulted in maternal toxicity (~~reduced body weight gain and low food consumption) at doses ≥ 50 mg/kg/day. Foetal effects included decreased foetal weight at ≥ 150 mg/kg/day (approximately 3.9 times the human exposure at the recommended dose based on AUC).~~

~~In pregnant rabbits, oral administration of belumosudil during the peroid of organogenesis resulted in maternal toxicity (~~body weight loss, reduced body weight gain, low food consumption and mortality) at doses ≥ 125 mg/kg/day. Foetal effects included abortions, increased post-implantation loss, decreased percentage of live foetuses, decreased foetal body weight, and skeletal/external malformations in foetuses at doses ≥ 50 mg/kg/day (approximately 0.08-fold~~07 times~~ the human exposure at the recommended dose based on AUC).

בעלון לצרכן:

2. לפני השימוש בתרופה

.....

אינטראקציות/תגובות בין תרופתיות

.....

תרופה	מטרת התרופה	השפעה פוטנציאלית
.....	.....	.....

סטטינים כגון אטורבסטטין או רוזובסטטין	להפחתת כולסטרול	בלומוסודיל עשוי להגביר את הריכוז של תרופות אלו מאחר שהוא מאט את הפירוק שלהן בגוף.
.....	.....	

העלונים המעודכנים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות וניתן לקבלם מודפסים על ידי פנייה לבעל הרישום- סאנופי ישראל בע"מ, Greenwork Park, מתחם העסקים בקיבוץ יקום, בניין E (קומה 1), 6097600, יקום או בטלפון: 09-8633081.

להלן הקישור לאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug

בברכה,
חברת סאנופי ישראל בע"מ