הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

אושר – 5.16

תאריך _____

שם תכשיר באנגלית ומספר הרישום **150-87-33823-00 Stivarga**

שם בעל הרישום באייר ישראל בע"מ

טופס זה מיועד לפרוט ההחמרות בלבד !

ההחמרות המבוקשות		
טקסט חדש	**טקסט נוכחי**	**פרק בעלון**
Antibiotics The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see section 5.2). Co-administration with neomycin, a poorly absorbed antimicrobial agent used for eradicating the gastrointestinal microflora (which may interfere with the enterohepatic circulation of regorafenib) had no effect on the regorafenib exposure, but there was an approximately 80% decrease in the exposure of the active metabolites M-2 and M-5 which showed in vitro and in vivo comparable pharmacological activity as regorafenib. The clinical significance of this neomycin interaction is unknown, but may result in a decreased efficacy of regorafenib. Pharmacokinetic interactions of other antibiotics have not been studied.	*Antibiotics* The concentration-time profile indicates that regorafenib and its metabolites may undergo enterohepatic circulation (see section 5.2). Co-administration of antibiotics that affect the flora of the gastrointestinal tract may interfere with the enterohepatic circulation of regorafenib and may result in a decreased regorafenib exposure. The clinical significance of these potential interactions is unknown, but may result in a decreased efficacy of regorafenib.	**Interaction with Other Medicaments and Other Forms of Interaction**
Description of selected adverse reactions In most cases of severe liver injury, liver dysfunction had an onset within the first 2 months of therapy, and was characterized by a hepatocellular pattern of injury with transaminase elevations >20xULN, followed by bilirubin increase. In clinical trials, a higher incidence of severe liver injury with fatal outcome was observed in Japanese patients (~1.5%) treated with Stivarga	***Description of selected adverse reactions*** Severe drug-induced liver injury (DILI) with fatal outcome occurred in 3 patients out of more than 1,200 Stivarga-treated patients across all clinical trials (0.25%). Two of the patients had liver metastases. Liver dysfunction in these patients had an onset within the first 2 months of therapy, and was characterised by a hepatocellular pattern of injury with transaminase elevations >20xULN,	**Adverse events**

compared with non-Japanese patients (<0.1%).	followed by bilirubin increase. Liver biopsies in 2 patients revealed hepatocellular necrosis with inflammatory cell infiltration.	