הודעה על החמרה (מידע בטיחות) בעלון לרופא

(מעודכן 05.2013)

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**
		Indication
		contraindications
Ethnic differences In clinical studies, no relevant differences in exposure or efficacy were observed between patients of different ethnic groups. A higher incidence of hand foot skin reaction (HFSR) / palmar-plantar erythrodysesthesia syndrome, severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga compared with Caucasians. The Asian patients treated with Stivarga in clinical studies were primarily from East Asia (~90%). There is limited data on regorafenib in the black patient population. No dose adjustment is necessary based on ethnicity (see section 5.2).	***Ethnic differences*** In clinical studies, no relevant differences in exposure, safety or efficacy were observed between patients of different ethnic groups. No dose adjustment is necessary based on ethnicity (see section 5.2). There is limited data on regorafenib in the black patient population.	**Posology, dosage & administration**
Hepatic effects Abnormalities of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with Stivarga. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations (including fatal outcomes) have been reported in a	***Hepatic effects*** Abnormalities of liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST] and bilirubin) have been frequently observed in patients treated with Stivarga. Severe liver function test abnormalities (Grade 3 to 4) and hepatic dysfunction with clinical manifestations	**Special Warnings and Special Precautions for Use**

small proportion of patients (see section 4.8). In clinical trials, a higher incidence of severe liver function test abnormalities and hepatic dysfunction was observed in Asian (in particular Japanese) patients treated with Stivarga as compared with Caucasians (see section 4.2). … ***Gastrointestinal perforation and fistula*** Gastrointestinal perforation (including fatal outcome) and fistulae have been reported in patients treated with Stivarga (see section 4.8). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula. … ***Dermatological toxicity*** Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with Stivarga. In clinical trials, a higher incidence of HFSR was observed in Asian (in particular Japanese) patients treated with Stivarga as compared with Caucasians (see section 4.2). Serious adverse reactions of erythema multiforme and Stevens Johnson Syndrome was higher in Stivarga-treated patients than in the placebo-treated patients. Toxic epidermal necrolysis occurred in 0.17% of 1200 Stivarga-treated patients across all clinical trials (see section 4.8). Measures for the prevention of HFSR include control of calluses and use of shoe cushions and	(including fatal outcomes) have been reported in a small proportion of patients (see section 4.8). …. ***Gastrointestinal perforation and fistu*** Gastrointestinal perforation and fistulae have been reported in patients treated with Stivarga (see section 4.8). These events are also known to be common disease-related complications in patients with intra-abdominal malignancies. Discontinuation of Stivarga is recommended in patients developing gastrointestinal perforation or fistula. ... ***Dermatological toxicity*** Hand-foot skin reaction (HFSR) or palmar-plantar erythrodysesthesia syndrome and rash represent the most frequently observed dermatological adverse reactions with Stivarga Serious adverse reactions of erythema multiforme and Stevens Johnson Syndrome was higher in Stivarga-treated patients than in the placebo-treated patients. Toxic epidermal necrolysis occurred in 0.17% of 1200 Stivarga-treated patients across all clinical trials (see section 4.8). Measures for the prevention of HFSR include control of calluses and use of shoe cushions and gloves to prevent pressure stress to soles and palms. Management	

gloves to prevent pressure stress to soles and palms. Management of HFSR may include the use of keratolytic creams (e.g. urea-, salicylic acid-, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of Stivarga, or in severe or persistent cases, permanent discontinuation of Stivarga should be considered (see section 4.2).	of HFSR may include the use of keratolytic creams (e.g. urea-, salicylic acid-, or alpha hydroxyl acid-based creams applied sparingly only on affected areas) and moisturizing creams (applied liberally) for symptomatic relief. Dose reduction and/or temporary interruption of Stivarga, or in severe or persistent cases, permanent discontinuation of Stivarga should be considered (see section 4.2).	
		Interaction with Other Medicaments and Other Forms of Interaction
		pregnancy Fertility, and Lactation
Compared to the global phase III CRC trial (CORRECT) with predominantly (~80%) Caucasian patients enrolled, a higher incidence of liver enzyme increases was observed in Stivarga-treated patients in the Asian phase III CRC trial (CONCUR) with predominantly (> 90%) East Asian patients enrolled. **Table 4a: Treatment emergent liver enzyme test abnormalities reported in placebo-controlled phase III trial in Asian patients with metastatic CRC (CONCUR)** ראו **Table 4a** כהמשך לטקסט זה בנספח מס. 1		**Adverse events**

מצ"ב העלון, שבו מסומנות ההחמרות המבוקשות על רקע צהוב.
שינויים שאינם בגדר החמרות סומנו (בעלון) בצבע שונה. יש לסמן רק תוכן מהותי ולא שינויים במיקום הטקסט.

הועבר בדואר אלקטרוני בתאריך.....

Laboratory parameter, (in % of samples investigated)	Stivarga plus BSC[§] (N=136)			Placebo plus BSC[§] (N=68)		
	All Grades *	Grade 3*	Grade 4*	All Grades *	Grade 3*	Grade 4*
Bilirubin increased	66.7	7.4	4.4	32.8	4.5	0.0
AST increased	69.6	10.4	0.7	47.8	3.0	0.0
ALT increased	54.1	8.9	0.0	29.9	1.5	0.0

[§] Best Supportive Care
* Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0