הודעה על החמרה (מידע בטיחות) בעלון לרופא

תאריך:	**10.2016**	
שם תכשיר ומספר רישום:	**VARGATEF 100MG 154 76 34336 00** **VARGATEF 150MG 154 77 34338 00**	
שם בעל רישום:	**בורינגר אינגלהיים ישראל בע"מ**	

טופס זה מיועד לפרוט ההחמרות בלבד!

ההחמרות המבוקשות

פרק בעלון	טקסט נוכחי	טקסט חדש
4.2 Posology and method of administration	… *Hepatic impairment* Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %; see section 5.2*)*. No adjustment of the starting dose is needed for patients with mild hepatic impairment based on clinical data (Child Pugh A; see section 4.4). The safety, efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B and C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Vargatef is not recommended. …	… *Hepatic impairment* Nintedanib is predominantly eliminated via biliary/faecal excretion (> 90 %). Exposure increased in patients with hepatic impairment (Child Pugh A, Child Pugh B; see section 5.2). No adjustment of the starting dose is needed for patients with mild hepatic impairment (Child Pugh A) based on clinical data.. Limited safety data available from 9 patients with moderate hepatic impairment (Child Pugh B) are insufficient to characterize this population. The safety efficacy, and pharmacokinetics of nintedanib have not been investigated in patients with severe hepatic impairment (Child Pugh C. Treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with Vargatef is not recommended (see section 4.4 and 5.2).

<table>
<tr>
<td>Based on increased exposure, the risk for adverse events may be increased in patients with mild hepatic impairment (Child Pugh A; see sections 4.2 and 5.2). Limited safety data are available in 9 patients with hepatocellular carcinoma and moderate hepatic impairment classified as Child Pugh B. Although no unexpected safety findings were reported in these patients, the data are insufficient to support a recommendation for treatment of patients with moderate hepatic impairment. The efficacy of nintedanib has not been investigated in patients with moderate hepatic impairment (Child Pugh B). The safety, efficacy and pharmacokinetics of nintedanib have not been studied in patients with severe hepatic impairment (Child Pugh C). Treatment with Vargatef is not recommended in patients with moderate or severe hepatic impairment (see section 4.2).
….</td>
<td>Hepatic function
The safety and efficacy of nintedanib has not been studied in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. Therefore treatment with Vargatef is not recommended in such patients (see sections 5.2).

Administration of nintedanib was associated with an elevation of liver enzymes (ALT, AST, ALKP) or bilirubin, with a potentially higher risk for female patients. These increases were reversible in the majority of cases.
….</td>
<td>4.4 Special warnings and precautions for use</td>
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<table>
<tr><th>System Organ Class</th><th>Very common (≥ 1/10)</th><th>Common (≥ 1/100 < 1/10)</th><th>Uncommon (≥ 1/1,000 < 1/100)</th></tr>
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Gamma-glutamyltransferase increased</td><td></td></tr>
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<td>4.8Undesirable effects</td>
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<td>Reproduction toxicity
A study of male fertility and early embryonic development to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, embryofoetal lethality and teratogenic effects were observed at exposure levels below human exposure, at the maximum recommended human dose (MRHD) of 200 mg b.i.d. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.</td>
<td>Reproduction toxicity
A study of male fertility and early embryonic development to implantation in rats did not reveal effects on the male reproductive tract and male fertility.

In rats, embryofoetal lethality and teratogenic effects were observed at exposure levels below human exposure, at the maximum recommended human dose (MRHD) of 250 mg b.i.d. Effects on the development of the axial skeleton and on the development of the great arteries were also noted at subtherapeutic exposure levels.</td>
<td>5.3Preclinical safety data</td>
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</table>

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.

הודעה על החמרה (מידע בטיחות) בעלון לצרכן

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ההחמרות המבוקשות		
פרק בעלון	**טקסט נוכחי**	**טקסט חדש**
4. תופעות לוואי	.... תופעות לוואי שכיחות מאד: תופעות שעלולות להופיע ביותר מ- 1 משתמשים מתוך 10 ..... • עליה בערכי אנזימי כבד בבדיקות דם תופעות לוואי שכיחות: תופעות שעלולות להופיע באחד עד 10 משתמשים מתוך 100 (לא קיים)	.... תופעות לוואי שכיחות מאד: תופעות שעלולות להופיע ביותר מ- 1 משתמשים מתוך 10 ..... • עליה בערכי אנזימי כבד (alanine aminotransferase, aspartate aminotransferase, blood alkaline phosphatase) בבדיקות דם תופעות לוואי שכיחות: תופעות שעלולות להופיע באחד עד 10 משתמשים מתוך 100 (תוספת חדשה) • עלייה בערכי אנזימי כבד (gamma-glutamyltransferase) בבדיקות דם