אוגוסט 2022

**רופא /ה, רוקח/ת נכבד/ה**

**חברת טבע מודיעה על העדכונים הבאים בעלון <u>לרופא</u> של התכשיר הבא:**

**Irinotecan Teva** **אירינוטקן טבע**

**Contains:** 20 mg/ml irinotecan hydrochloride trihydrate

**עדכונים בעלון לרופא**

---

**<u>התוויה כפי שאושרה בתעודת הרישום:</u>**

for the treatment of patients with metastatic colorectal cancer:

- In combination with 5-fluorouracil and folinic acid in patients without prior chemotherapy for metastatic disease.
- As a single agent in patients who have failed an established 5-fluorouracil containing treatment regimen.
- For the treatment of patients with small cell lung cancer.
- For the treatment of patients with gastric cancer.
- Irinotecan in combination with leucovorin, Oxaliplatin and 5-fluorouracil for the first-line treatment of patients with metastatic pancreatic adenocarcinoma

**<u>ברצוננו להודיע שהעלון לצרכן עודכן, בפירוט שלהלן כלולים העדכונים העיקריים בלבד (תוספות מסומנות באדום והסרות מידע כטקסט מחוק):</u>**

**4.4 Special warnings and precautions for use**

[...]

**Haematology**

[...]

<u>Patients with reduced UGT1A1 activity</u>

Patients that are UGT1A1 poor metabolisers, such as patients with Gilbert's syndrome (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk for severe neutropenia and diarrhoea following irinotecan treatment.
This risk increases with the irinotecan dose level.
Although a precise dose reduction in starting dose has not been established, a reduced irinotecan starting dose should be considered for patients that are UGT1A1 poor metabolisers, especially patients who are administered doses > 180 mg/m$^2$ or frail patients. Consideration should be given to applicable clinical guidelines for dose recommendations in this patient population. Subsequent doses may be increased based on individual patient tolerance to treatment.

UGT1A1 genotyping can be used to identify patients at increased risk of severe neutropenia and diarrhoea, however the clinical utility of pre-treatment genotyping is uncertain, since UGT1A1 polymorphism does not account for all the toxicity seen from irinotecan therapy (see section 5.2).

**5.2 Pharmacokinetic properties**

[…]

Patients with reduced UGT1A1 activity

Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) is involved in the metabolic deactivation of SN-38, the active metabolite of irinotecan to inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities among individuals. ~~One specific variation of the~~ The most well-characterised UGT1A1 ~~gene includes a polymorphism in the promoter region known as the~~ genetic variants are UGT1A1*28 ~~variant. This variant~~ and UGT1A1*6. These variants and other congenital deficiencies in UGT1A1 expression (such as Gilbert's syndrome and Crigler-Najjar ~~and Gilbert's syndrome~~) are associated with reduced activity of this enzyme. ~~Data from a meta analysis indicate that individuals with Crigler-Najjar syndrome (types 1 and 2) or those who are homozygous for the UGT1A1*28 allele (Gilbert's syndrome) are at increased risk of haematological toxicity (Grades 3 and 4) following administration of irinotecan at moderate or high doses (>150 mg/m$^2$). A relationship between UGT1A1 genotype and the occurrence of irinotecan induced diarrhoea was not established. Patients known to be homozygous for UGT1A1*28 should be administered the normally indicated irinotecan starting dose. However, these patients should be monitored for haematologic toxicities. A reduced irinotecan starting dose should be considered for patients who have experienced prior haematologic toxicity with previous treatment. The exact reduction in starting dose in this patient population has not been established and any subsequent dose modifications should be based on a patient's tolerance of the treatment (see sections 4.2 and 4.4).~~

~~There is at present insufficient data to conclude on clinical utility of UGT1A1 genotyping.~~

Patients that are UGT1A1 poor metabolisers (e.g. homozygous for UGT1A1*28 or *6 variants) are at increased risk of severe adverse reactions such as neutropenia and diarrhoea following administration of irinotecan, as a consequence of SN-38 accumulation. According to data from several meta-analyses, the risk is higher for patients receiving irinotecan doses > 180 mg/m2 (see section 4.4).

In order to identify patients at increased risk of experiencing severe neutropenia and diarrhoea, UGT1A1 genotyping can be used. Homozygous UGT1A1*28 occurs with a frequency of 8-20% in the European, African, Near Eastern and Latino population. The *6 variant is nearly absent in these populations. In the East Asian population the frequency of *28/*28 is about 1-4%, 3-8% for *6/*28 and 2-6% for *6/*6. In the Central and South Asian population the frequency of *28/*28 is around 17%, 4% for *6/*28 and 0.2% for *6/*6.