DIRECT HEALTHCARE PROFESSIONAL COMMUNICATION IN AGREEMENT WITH EUROPEAN MEDICINES AGENCY (EMA) AND AGENZIA ITALIANA DEL FARMACO (AIFA)

31st January, 2022

Irinotecan medicinal products: reduction in the starting dose to reduce the risk of irinotecan induced neutropenia and diarrhea in patients with UGT1A1 *28 and *6 variant

Dear Healthcare Professional,

The Marketing Authorisation Holders for irinotecan medicinal products, in agreement with AIFA, would like to inform you about important information on the safety of irinotecan medicinal products:

Summary

- **Patients with reduced UGT1A1 activity (e.g., homozygous for UGT1A1*28 or *6 variants, such as in Gilbert's syndrome) are at increased risk for severe neutropenia and diarrhea following irinotecan treatment. This risk increases with the irinotecan dose level.**

- **A reduced irinotecan starting dose should be considered for patients that are UGT1A1 poor metabolisers, although a precise dose reduction in starting dose has not been established, especially patients who are administered doses >180 mg/m² 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 diarrhea, however the clinical utility of pre-treatment genotyping is uncertain, since UGT1A1 polymorphism does not account for all the toxicity seen from irinotecan therapy.**

Background on the safety concern

Irinotecan is indicated for single-agent or combination treatment of patients with metastatic carcinoma of the colon or rectum that has recurred or progressed following 5-fluorouracil (5-FU)-based therapy; previously untreated metastatic carcinoma of the colon or rectum.
Irinotecan in combination with cetuximab is indicated for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, KRAS wild-type metastatic colorectal cancer, who had not received prior treatment for metastatic disease or after failure of irinotecan-including cytotoxic therapy.

Uridine diphosphate-glucuronosyl transferase 1A1 enzyme (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. The most well-characterized UGT1A1 genetic variants are UGT1A1*28 and UGT1A1*6. These variants and other congenital deficiencies in UGT1A1 expression are associated with reduced activity of this enzyme.

Patients with reduced UGT1A1 activity (e.g., homozygous for UGT1A1*28 or *6 variants, such as in Gilbert's syndrome) are at increased risk for severe neutropenia and diarrhea following irinotecan treatment. This risk increases with the irinotecan dose level.
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.

The Summary of Product Characteristics (sections 4.4 and 5.2) and Package Leaflet (section 2) are being updated according to the above information.

Call for reporting
Healthcare professionals are reminded to continue to report suspected adverse reactions associated to irinotecan in accordance with the national spontaneous reporting system, via Agenzia Italiana del Farmaco website:
https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

AIFA takes this opportunity to remind all Healthcare Professionals of the importance of reporting suspected adverse drug reactions, as an indispensable tool to confirm a favorable benefit / risk ratio in real conditions of use.
Reports of Suspected Adverse Reaction from drugs must be sent to the Head of Pharmacovigilance of the Facility the Healthcare Professional belongs to.
This direct healthcare professional communication is also published on the AIFA website (http://www.aifa.gov.it) whose regular consultation is recommended for the best professional information and citizen service.