

02.08.2022 DRUGS CONTAINING IRINOTECAN – URGENT SAFETY RESTRICTION _EN

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RESTRICTED

REPUBLIC OF TURKEY MINISTRY OF HEALTH Turkish Medicines and Medical Devices Agency
Number : E-24931227-510.01.04-826428 Subject : Drugs Containing Irinotecan - Urgent Safety Restriction

FILE Regarding drugs containing irinotecan; the warning published on the official website of the French National Agency for the Safety of Medicines and Health Products (ANSM) regarding "dose reduction of the initial dose in patients who are weak metabolizers for UGT1A1 and need >180 mg/m² dose of irinotecan or who are not in good health condition at any dose level" has been evaluated by our Agency, and it is necessary to add the statements included in the short product information of the mentioned drugs, attached hereto.

Applications for Product Information Updates (PIU) of the reference products reflecting these changes should be sent to the Pharmacological Evaluation Unit within 15 days from the date of announcement for review. Pharmacological Evaluation Unit should be contacted for other drugs containing irinotecan within 15 days after the publication of the PIU texts of the reference products on our official website. However, for drugs containing the active substance without a reference or with an inactive reference in the market; it is necessary to apply to the Pharmacological Evaluation Unit within 15 days from the date of announcement without waiting for the publication of any PIU text of a reference drug on our official website.

Your attention and action on this matter are kindly requested. Assoc. Prof. Tolga KARAKAN
Agency President

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PRODUCT SUMMARY 4.4. Special Warnings and Precautions [If there is a subsection titled "Patients with low UGT1A1 activity" in the existing product information section 4.4, all statements under this subsection should be removed and replaced with the following text.] Patients with low UGT1A1 activity Patients with weak metabolism for UGT1A1, such as those with Gilbert's syndrome (homozygous for UGT1A128 or UGT1A16 variants), are at high risk for severe neutropenia and diarrhea following irinotecan therapy. This risk increases with the dose level of irinotecan. Although the extent of reduction in the initial dose of irinotecan for patients with slow metabolism for UGT1A1 has not been clearly defined, a reduction in the initial dose of irinotecan should be considered, especially in patients who require a dose above 180 mg/m² or those who are fragile in health. Suitable clinical guidelines should be considered for dose recommendations in these patient populations. Subsequent doses of irinotecan can be increased depending on the individual treatment tolerance of the patient. UGT1A1 genotyping can be used to identify patients at high risk for severe neutropenia and diarrhea. However, the clinical benefit of genotyping before starting treatment remains uncertain due to UGT1A1 polymorphism not being the sole parameter responsible for toxicities observed with irinotecan therapy.

5.2. Pharmacokinetic Properties Patients with low UGT1A1 activity Uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1) plays a role in the metabolic deactivation of the active metabolite of irinotecan, SN-38, to the inactive SN-38 glucuronide (SN-38G). The UGT1A1 gene is highly polymorphic, resulting in variable metabolic capacities depending on the individual. The best characterized genetic variants of UGT1A1 are UGT1A128 and UGT1A16. Variants in UGT1A1 expression (such as Gilbert's syndrome and Crigler-Najjar syndrome) and other congenital deficiencies are associated with decreased activity of this enzyme.

In patients with slow metabolism of UGT1A1 (e.g., homozygous for UGT1A1*28 or *6 variants), the risk of serious adverse reactions such as neutropenia and diarrhea increases as a result of SN-38 accumulation following irinotecan administration. According to data from several meta-analyses, the risk is higher in patients receiving irinotecan doses >180 mg/m². (see section 4.4).

UGT1A1 genotyping can be used to identify patients at high risk for severe neutropenia and diarrhea. The homozygous UGT1A128 variant is observed in 8-20% frequency in European, African, Middle Eastern, and Latin populations. The UGT1A16 variant is almost absent in these populations. In East Asian populations, the frequency of UGT1A1 variants is approximately 1-4% for *28/*28, 3-8% for *6/*28, and 2-6% for *6/*6. In South and Central Asian populations, the frequency of UGT1A1 variants is 17% for *28/*28, 4% for *6/*28, and 0.2% for *6/*6.