

Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for vincristine, the scientific conclusions are as follows:

In view of available data on drug-drug interaction from a signal, a cumulative review including literature, spontaneous reports including a close temporal relationship, positive de-challenges and in view of a plausible mechanism of action, the PRAC considers a causal relationship for an interaction between vincristine and azole antifungals is at least a reasonable possibility. The PRAC concluded that the product information of products containing vincristine should be amended accordingly.

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)

On the basis of the scientific conclusions for vincristine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing vincristine is unchanged subject to the proposed changes to the product information

The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Interaction with azole antifungals

Concomitant administration of azole antifungals with vincristine has been associated with neurotoxicity and other serious adverse reactions, including seizures, peripheral neuropathy, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and paralytic ileus. Reserve azole antifungals for patients receiving vincristine who have no alternative antifungal treatment options (see section 4.5).

- Section 4.5

(An) interaction(s) should be amended/added as follows:

Add to the listed inhibitors of cytochrome P450 isoenzymes (CYP3A4) and P-glycoprotein:

ketoconazole

Concomitant administration of azole antifungals (e.g., itraconazole, voriconazole, posaconazole, isavuconazole and fluconazole) with vincristine may increase the plasma concentrations of vincristine, which can lead to an early onset and/or increased severity of neurotoxicity and other side effects (see section 4.4). Therefore, azole antifungals should be used with caution in patients receiving vincristine and should only be used when there are no alternative antifungal treatment options available or when the potential benefits outweigh the risks of the combination. Patients should be closely monitored for adverse effects with concomitant use.

Package Leaflet

Other medicines and Vincristine Sulfate

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

Use of the following medicines may make the side effects of vincristine worse:

- **azole antifungals (a group of medicines used to treat fungal infections e.g. itraconazole, posaconazole, fluconazole, isavuconazole or voriconazole)**
- **ketoconazole (used to treat Cushing's syndrome, a disease characterised by an excess production of the hormone cortisol)**

Annex III

Timetable for the implementation of this position>

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Adoption of CMDh position:	April 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	09 June 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	08 August 2024