Australian Government
Department of Health
Therapeutic Goods Administration

Advisory Committee on Medicines

Meeting Statement

Meeting 30, Thursday 2 and Friday 3 December 2021

Section A: Pre-market registration applications referred for advice

At this meeting, the committee's advice was sought on 17 applications under evaluation by the TGA. The applications included:

- five for the registration of a new chemical entity including one COVID-19 treatment
- one for the registration of a new biological entity
- six seeking an extension of indications (some including major variations)
- one seeking a major variation (new strength)
- one seeking a minor variation in the manufacturing process
- one seeking to vary the approved Product Information
- one seeking conversion of provisional to full registration
- one seeking input on a long-term application for consent to import, supply or export goods that do not conform with standards.

Further details of the ACM discussion and advice associated with these items may be released within the Australian Public Assessment Reports (AusPARs). Please note that there is a delay from when an application was considered at ACM and the publication of the AusPAR. To browse all AusPARs see: <https://www.tga.gov.au/browse-auspars-active-ingredient>

Section B: Post-market item referred for advice

Fluorouracil toxicity and dihydropyrimidine dehydrogenase (DPD) deficiency

Fluorouracil (5-FU) and the related medicine capecitabine are approved for use the treatment of malignant tumours, alone or in combination with other medicines. The enzyme dihydropyrimidine dehydrogenase (DPD) plays a crucial role in metabolism of 5-FU.

People vary in the amount of DPD contained in their liver cells. This reflects population and individual variations in genetics (genotypes) and the expression of genes (phenotypes) that affect the level of DPD. Patients receiving 5-FU treatment who do not make enough DPD have higher blood levels of 5-FU and may develop early and more severe toxicity from their chemotherapy with 5-FU. Most patients (>97%) have sufficient DPD. Toxicity varies with dosing schedule, and leucopenia, diarrhoea, mucositis, and hand-foot syndrome are common.

- The ACM considered the adequacy of the communication in the current Product Information of the risk of 5-FU toxicity related to DPD deficiency.

The current Product Information for 5-FU includes a contraindication ('do not use') for patients with known complete DPD deficiency.

In Australia laboratory tests for DPD deficiency follow international methods. However, there are international differences in clinical practice regarding whether to test for DPD prior to the start of treatment or to monitor the patient's experience.

The ACM advised that DPD testing can be a reasonable clinical choice but need not be mandated. The treating team would consider availability of the test (cost; potential delay to decision on drug and dosing) for the individual patient.

There continues to be uncertainty on the thresholds defining complete and partial DPD deficiency. There are no large studies confirming the best threshold for this biomarker, although blood uracil level > 150 ng/mL is associated with severe enzyme deficiency.

The ACM advised that if a partial DPD deficiency is detected, a reduced starting dose is supported by multiple studies. The wording about dosage used in Europe is appropriate for 5-FU and capecitabine in Australia.

The ACM noted that factors other than DPD deficiency remain important to minimise toxicity e.g. dosing and monitoring.

The ACM did not support the inclusion of detailed information on genotypic and phenotypic characterisation in the Product Information.

Further information

For further information on the Advisory Committee on Medicines, please visit: https://www.tga.gov.au/committee/advisory-committee-medicines-acm or contact the ACM Secretary by email: ACM@health.gov.au.