BOPA Position Statement

DPYD guided dosing for Tegafur containing products

The BOPA Genomics Cancer Advisory Group has been made aware that some centres in the UK are considering using Teysuno products in patients who may otherwise have been started on Raltitrexed, in light of ongoing shortages. We are aware of the uncertainty and limited experience about how *DPYD* genetic testing applies to Teysuno and this statement sets out key considerations.

Background

Teysuno is a fluoropyrimidine; raltitrexed is not.

Teysuno contains tegafur, an oral pro-drug of 5-fluorouracil (5-FU), in combination with gimeracil and oteracil. Tegafur is metabolised into 5-FU to exert its cytotoxic effects.

- Gimeracil is a reversible inhibitor of dihydropyrimidine dehydrogenase (DPD). It is included to slow the breakdown of 5-FU so that adequate concentrations are achieved from a lower dose of oral tegafur. Gimeracil has a shorter elimination half-life and therefore a shorter duration of action than tegafur. For this reason, genetic variants in *DPYD* that influence DPD enzyme activity are clinically relevant for tegafur in combination with a DPD inhibitor.
- Oteracil is an orotate phosphoribosyltransferase inhibitor which decreases the activity of 5-FU in normal gastrointestinal mucosa, reducing gastrointestinal toxicity.
- Teysuno use is expected to primarily be in individuals who are considered otherwise unsuitable for other fluoropyrimidines; capecitabine and 5-fluorouracil (5-FU).

Key considerations

- Pre-emptive testing for DPD deficiency is recommended for all patients prior to starting on fluoropyrimidine treatments, to identify those at increased risk of severe and fatal toxicity 5-fluorouracil (intravenous), capecitabine, tegafur: DPD testing recommended before initiation to identify patients at increased risk of severe and fatal toxicity - GOV.UK.
- Teysuno is **contraindicated** in patients with complete dihydropyrimidine dehydrogenase (DPD) deficiency.
- There is limited clinical evidence on the safety of tegafur containing products in individuals with complete or partial DPD deficiency.
- Teysuno should therefore be avoided in patients who are identified as *DPYD* poor (complete deficiency) or intermediate (partial deficiency) metabolisers.
- Where no suitable alternative treatment is available, the manufacturer (Nordic Pharma) recommends that Teysuno is used with caution in patients with partial DPD deficiency.

- In patients who are identified as *DPYD* intermediate metabolisers, where there is no suitable alternative treatment, it is recommended to start with a low dose of tegafur and titrate dose based upon toxicity within the licensed indication. It is recommended to discuss individual patient cases with someone with expertise in pharmacogenetics where possible.
- Decisions on starting dose should be made as part of a holistic clinical decision considering individual patient co-morbidities, clinical status and treatment plan and with regard to available formulations.
- Further information on *DPYD* guided prescribing of fluoropyrimidines can be found in the UK SACT Board guidance, Personalised Medicine Approach for Fluoropyrimidine-based Therapies 638ee8_4d24d37a598c485d9ef4d1ba90abccd5.pdf.

UK Pharmacogenetic Study

- Patients receiving Teysuno who experience significant toxicity despite prior *DPYD* genotyping can be considered for referral to the Molecular Genetics of Adverse Drug Reactions (MOLGEN) study. This is a national research study investigating the genetic basis of severe adverse drug reactions, including the identification of rare *DPYD* variants in patients who develop grade 3 or higher fluoropyrimidine-related toxicity despite standard *DPYD* testing.

- For further information on the MOLGEN study please contact: Eunice Zhang (eunzhang@liverpool.ac.uk) or Clare Roberts (clarerob@liverpool.ac.uk).