**IMPORTANT MEDICINE SAFETY INFORMATION**

24 September 2020

**Dear Healthcare Professional**

**Re: FLUOROPYRIMIDINE CONTAINING MEDICINES AND RELATED SUBSTANCES: INCREASED DRUG EXPOSURE AND TOXICITY IN PATIENTS WITH DIHYDROPYRIMIDINE DEHYDROGENASE (DPD) DEFICIENCY**

In collaboration with the South African Health Products Regulatory Authority (SAHPRA), the companies listed below would like to inform you of the requirement of pre-testing to identify patients at increased risk of severe toxicity due to fluoropyrimidine containing medicines.

**Summary**

- **Patients with partial or complete dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe toxicity during treatment with fluoropyrimidines (5-FU, capecitabine, tegafur).**
- **Phenotype and/or genotype testing before initiation of treatment with fluoropyrimidines is recommended.**
- **Treatment with 5-FU, capecitabine or tegafur-containing medicinal products is contraindicated in patients with known complete DPD deficiency.**
- **Consider a reduced starting dose in patients with identified partial DPD deficiency.**
- **Therapeutic drug monitoring (TDM) of fluorouracil may improve clinical outcomes in patients receiving continuous 5-fluorouracil infusions.**
- **The Professional Information (PI) and Patient Information Leaflet (PIL) of fluoropyrimidine containing medicines will be updated accordingly.**

**Background on the safety concern**

Fluoropyrimidines consist of a group of cancer medicines including 5-fluorouracil (5-FU) and its prodrugs capecitabine and tegafur, with different presentations:

- Parenteral 5-FU: a component of the standard therapy for a variety of malignancies, including colorectal, pancreatic, gastric, breast and head and neck cancer, mostly used in combination with other anticancer agents;
- Capecitabine: an oral prodrug of 5-FU, indicated for the treatment of colorectal, gastric and breast cancer;
- Tegafur: an oral prodrug of 5-FU, available as mono therapy or in combination with two modulators of 5-FU metabolism, gimeracil, and oteracil for the treatment of gastric cancer.

Dihydropyrimidine dehydrogenase (DPD) is the rate limiting enzyme in the catabolism of 5-FU. DPD activity is subject to a wide variability. Complete DPD deficiency is rare (0,01 – 0,5 % of Caucasians). Partial DPD deficiency is estimated to affect 3 – 9 % of the Caucasian population.

Impaired DPD enzyme function leads to an increased risk for severe or life-threatening toxicity in patients treated with 5-FU or its prodrugs. Despite negative test results for DPD deficiency, severe toxicity may still occur.

- Patients with DPD deficiency are at high risk of life-threatening or fatal toxicity and must not be treated (contraindicated) with fluoropyrimidines.
- Patients receiving 5- fluorouracil and its prodrugs, capecitabine and tegafur, given by oral, injection or infusion, should be tested for DPD deficiency before starting treatment.
- A reduced starting dose should be considered to limit the risk of severe toxicity for patients with partial DPD deficiency (as they are at an increased risk of severe and potentially life-threatening toxicity). Subsequent doses may be increased in the absence of serious toxicity, as the efficacy of a reduced dose has not been established.

***Pre-treatment testing of DPD activity***

To identify patients at risk for severe toxicity, pre-treatment testing for DPD deficiency is recommended, despite uncertainties regarding optimal testing methodology. Both genotyping of the DPD coding gene (DPYD) and phenotyping by measurement of blood uracil levels are acceptable methods.

Clinical guidelines addressing DPD genotyping or phenotyping should be considered.

*Genotyping*

Four DPYD genotype variants (c.1905+1G>A, c.1679T>G, c.2846A>T and c.1236G>A/HapB3) are associated with an increased risk of severe toxicity. Other rare DPYD genotype variants may also be associated with increased risk of severe toxicity.

*Phenotyping*

DPD deficiency is associated with elevated pre-treatment plasma uracil levels. A blood uracil level ≥ 16 ng/mL and < 150 ng/mL is indicative of partial DPD deficiency, while a blood uracil level ≥ 150 ng/mL is indicative of complete DPD deficiency.

***Therapeutic drug monitoring (TDM) in patients treated with 5-FU (i.v.)***

Complementary to upfront DPD testing, TDM of fluorouracil may improve clinical outcomes in patients treated with intravenous 5-FU. The target AUC is supposed to be between 20 and 30mg x h/L.

***Call for reporting***

Healthcare professionals are urged to report any adverse drug reactions (ADRs) or product quality issues associated with the use of fluoropyrimidine containing medicines to SAHPRA via the eReporting link available on the SAHPRA website (www.sahpra.org.za). Alternatively, please complete the ADR reporting form accessible via the SAHPRA website at https://www.sahpra.org.za/documents/12e54dcaADRForms.pdf and email it to adr@sahpra.org.za or fax to (021) 448 6181. For more information on ADR reporting of below listed fluoropyrimidine containing medicines, please call the National Adverse Events Monitoring Centre (NADEMC) on (021) 447 1618.

For further information, kindly use the contact details indicated below:

| Company | Product Name | Active Ingredient(s) | Registration Number | Contact Details |
|---|---|---|---|---|
| **Roche Products (Pty) Ltd.** | Xeloda 150 | Capecitabine 150 mg | 33/26/0198 | **Tel:** +27 11 502 5000 **Fax:** +27 11 268 5748 **Email:** global.irt_sahubtcs@roche.com |
| | Xeloda 500 | Capecitabine 500 mg | 36/26/0199 | |
| **Cipla Medpro (Pty) Ltd** | Capeloda 150 | Capecitabine 150 mg | 47/26/0363 | **Tel:** 021 943 4200 **Fax:** 021 914 1587 **Email:** drugsafetysa@cipla.com |
| | Capeloda 500 | Capecitabine 500 mg | 47/26/0364 | |
| **Accord Healthcare** | Floracor | Fluorouracil 50 mg / ml | 41/26/0246 | **Tel:** 011 234 5701 **Fax:** 011 234 5700 Email: medinfo@accordhealth.co.za |
| | Accord Fluorouracil | Fluorouracil 50 mg / ml | 41/26/0247 | |
| | Pecaset 150 mg | Capecitabine 150 mg | 49/26/0681 | |
| | Pecaset 500 mg | Capecitabine 500 mg | 49/26/0682 | |
| | Capexa 150 mg | Capecitabine 150 mg | 49/26/0683 | |
| | Capexa 500 mg | Capecitabine 500 mg | 49/26/0684 | |
| **Teva** | Fluracedyl 250 mg | 5-fluorouracyl 250 mg | 35/26/0144 | **Tel:** 011 055 0200 **Fax**: 011 388 2688 **Email:** safety.south-africa@teva.co.il |
| | Fluracedyl 500 mg | 5-fluorouracyl 500 mg | 35/26/0349 | |
| | Fluracedyl 1000 mg | 5-fluorouracyl 1000 mg | 35/26/0350 | |
| | Fluracedyl 5000 mg | 5-fluorouracyl 5000 mg | 35/26/0351 | |

Yours sincerely,

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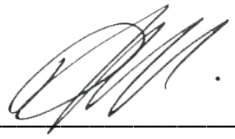
***(Roche) Dr Nick Mangeya***
***Head: Medical Affairs***



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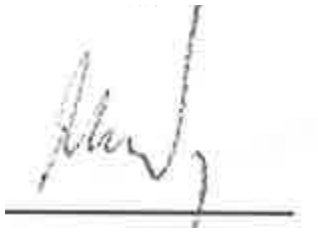
***(Cipla) Dr Dhiveja Smith***
***Head of Medical Affairs***



**(*Accord) Reshlan Nagoor***
***Responsible Pharmacist***

***(Teva) Salomie Keyser***
***Responsible Pharmacist***