**Brivudine: potentially fatal toxicity of fluoropyrimidines if administered shortly before or at the same time with brivudine or used within 4 weeks after the end of treatment with brivudine**

Dear Healthcare Professional,

<Marketing Authorisation Holder> in agreement with the European Medicines Agency and the <National Competent Authority> would like to inform you of the following:

## *Summary*


- **Fatalities can occur as a result of an interaction between brivudine and fluoropyrimidines (e.g. fluorouracil, capecitabine, tegafur, flucytosine).**
- **At least 4 weeks must be awaited after the end of brivudine treatment before starting treatment with a fluoropyrimidine. In many cases, fatalities have occurred when this 4-week waiting period was not respected (for example, brivudine was taken between cycles of fluorouracil).**
- **Therefore, the following measures have been taken:**
    - **The summary of product characteristics, the package leaflet and outer carton labelling will be amended, to strengthen the emphasis on observing the 4-week interval between brivudine and fluoropyrimidine treatment;**
    - **A patient alert card, highlighting the essential information for patients and healthcare professionals, will be included in the package;**
    - **In addition, a prescriber checklist will be provided, to help the prescribers to check the suitability of the patient to receive brivudine treatment.**


## *Background on the safety concern*

Brivudine, through its main metabolite bromovinyl uracil (BVU), inhibits dihydropyrimidine dehydrogenase (DPD), an enzyme which metabolises pyrimidine-based drugs such as fluorouracil, capecitabine, tegafur and flucytosine. As a consequence of the enzyme inhibition levels of fluoropyrimidines are increased. This interaction, which increases fluoropyrimidine toxicity, is potentially fatal.

Therefore, brivudine is contraindicated in:

- patients who recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy with medicines containing fluorouracil including its topical preparations, its prodrugs (e.g. capecitabine, tegafur) and combination products containing these active substances or other fluoropyrimidines.
- patients who recently received or are currently receiving antifungal therapy with flucytosine because a small amount of it is metabolised to fluorouracil.

- immunocompromised patients such as those who recently received or are currently receiving cancer chemotherapy or patients under immunosuppressive therapy.

In addition, a patient alert card (PAC), containing important information for the patient and the healthcare professional on this potentially fatal interaction will be inserted into the package. Please advise your patient that he/she shall carry the PAC to any visit with any physician (including dermatologists) and he/she shall show the PAC to the pharmacist before being dispensed with any other medicinal products, for at least 4 weeks after the end of treatment with brivudine.

Furthermore, a prescriber checklist will be provided, to help prescribers to check the suitability of the patient to receive brivudine treatment (see Annex).

## *Call for reporting*

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:

<details on the national reporting system>

## *Company contact points*

<A table of Companies, their concerned products and contact points.>

| DHPC COMMUNICATION PLAN | |
|---|---|
| **Medicinal product(s)/active substance(s)** | Brivudine-containing products.<br>ATC code: J05AB15<br>Direct acting antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors |
| **Marketing authorisation holder(s)** | Berlin-Chemie AG<br>Berlin-Chemie Menarini Hrvatska d.o.o.<br>Laboratori Guidotti S.p.A. |
| **Safety concern and purpose of the communication** | Potentially fatal toxicity of fluoropyrimidines if administered shortly before or at the same time with brivudine or used within 4 weeks after the end of treatment with brivudine |
| **DHPC recipients** | -general practitioners<br>-dermatologists<br>-geriatrists<br>-internists<br>-oncologist in practice and clinics (e.g. stationary cancer centres)<br>-pharmacists<br>-Patients associations (if any) to be agreed with National Competent Authorities<br>and potential recipients depending on local requirements. |
| **Member States where the DHPC will be distributed** | AT, BE, DE, EE, ES, GR, HR, IT, LT, LU, PT, RO, SI, SK |

| Timetable | Date |
|---|---|
| **DHPC and communication plan (in English) agreed by PRAC** | 18 March 2020 |
| **DHPC and communication plan (in English) agreed by CMDh** | 26 March 2020 |
| **Submission of translated DHPCs to the national competent authorities for review** | 10 April 2020 |
| **Agreement of translations by national competent authorities** | 24 April 2020 |
| **Dissemination of DHPC** | 12 May 2020 |