

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 brivudine, the scientific conclusions are as follows:

Important Identified Risk: Administration of 5-FPyr with brivudine at the same time or before than 4 weeks since the end of treatment with brivudine

Brivudine induces an irreversible inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme which regulates the catabolism of both natural nucleosides (e.g. thymidine) and of pyrimidine-based drugs such as 5-FU, via its main metabolite bromovinyl uracil (BVU). As a result of the enzyme inhibition, overexposure and enhanced toxicity to fluoropyrimidines occur. This interaction between brivudine and fluoropyrimidines is potentially fatal.

"Cumulatively (up to 05-Jul-2019), 243 ADRs (of which 242 serious) were identified from 52 ICSRs (of which 51 serious)... Causal relationship between brivudine and ADRs was assessed as possible for 173 ADRs, probable for 57 ADRs, unlikely for 3 ADRs, related for 1 ADR and unassessable for 8 ADRs...

Cumulatively, up to the DLP (05-Jul-2019), the reporting rate of such serious ICSRs was 0.88 ICSRs per million DDDs (51 ICSRs/58.1 million DDDs)...

The below table 16.4.2 displays the reporting rate trend of the above-mentioned cases by periods, analysed taking into consideration both the ICSR receipt date and the Adverse Reaction onset date, to better identify trends in frequency without biases due to delay in reporting to the MAH.

Table 16.4.2. Reporting rate by periods (number of cases per 1,000,000 patients)

	First launch - 30 Jun 2011	01 Jul 2011 - 30 Jun 2012	01 Jul 2012 - 30 Jun 2013	01 Jul 2013 - 30 Jun 2014	01 Jul 2014 - 30 Jun 2015	01 Jul 2015 - 30 Jun 2016	01 Jul 2016 - 30 Jun 2017	01 Jul 2017 - 30 Jun 2018	01 Jul 2018 - 05 Jul 2019
RR by received date	5,94	7,57	13,58	0,00	1,73	3,31	1,59	13,44	10,32
RR by onset date	6,51	9,46	9,70	0,00	5,18	4,97	6,36	8,96	4,42

In the period from first launch to 30 Jun 2011, about 6 cases per million patients have been collected. Analysing separately the eight years of this PSUR interval, it can be observed that in the first two years the observed RR has been higher than in the previous period. Between August and October 2012 a DHPC on this issue has been disseminated, and in the period immediately subsequent a drop of the RR was observed. **In the following years, a rise of the RR was observed, returning to about the same values of the baseline, if analysed by Onset Date...**"

Although the incidence remains low, the number of cases has again increased in 2017/2018. As these cases are potentially serious and often fatal, additional risk minimisation measures are considered necessary to improve prescriber information and patient awareness, especially regarding the use of brivudine in the intervals between 5-FU-treatments: an update of the Product Information as well as

the introduction of a Patient Alert Card and a checklist for prescribers as additional risk minimisation measure are proposed. In addition, a DHPC should be circulated to inform prescribers accordingly.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for brivudine the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing brivudine is unchanged subject to the proposed changes to the product information and the conditions to the Marketing Authorisation(s).

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing brivudine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that the concerned Member States and applicant/marketing authorisation holders take due consideration of this CMDh position.

Annex II

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

Amendments to be included in the relevant sections of the Product Information (new and currently underlined text underlined, bold text **bold**, boxed text boxed, to be underlined text described thereafter in [square brackets] which should be deleted after underlining, red font in **red font**, deleted text ~~strike-through~~):

Summary of Product Characteristics

4.3 Contraindications

Cancer chemotherapy with fluoropyrimidines[whole heading to be underlined]

~~Premovir~~Brivudine must not be administered is contraindicated in case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

~~Cancer chemotherapy patients~~

~~The use of is contraindicated in patients under~~ who recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy, especially if treated with medicines containing 5-fluorouracil (5-FU) including also its topical preparations, its prodrugs (e.g. capecitabine, floxuridine, tegafur) and combination products containing these active substances or other 5-fluoropyrimidines (see also sections 4.3 Immunocompromised patients, 4.4, 4.5 and 4.58).

~~Patients under anti~~Anti-fungal therapy with flucytosine[whole heading to be underlined]

~~The use of Premovir~~Brivudine is contraindicated in patients under who recently received or are currently receiving antifungal therapy with flucytosine because it is a prodrug of 5-fluorouracil (5-FU) (see also sections 4.4, 4.5 and 4.8).

The interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-FU, etc.) is potentially fatal (see sections 4.4, 4.5 and 4.8).

Immunocompromised patients

~~The use of Premovir~~Brivudine is contraindicated in immunocompromised patients such as those under who recently received or are currently receiving cancer chemotherapy or patients under immunosuppressive therapy.

Children

Safety and efficacy of ~~Premovir~~brivudine in children have not been established and therefore its use is not indicated.

Hypersensitivity[to be underlined]

Brivudine must not be administered in case of hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Pregnancy and lactation

Brivudine is contraindicated during pregnancy or in nursing mothers (see also section 4.6).

4.4 Special warning and precautions for use

Brivudine must not be administered in patients who recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy and with medicines containing 5-fluorouracil (5-FU), including also its topical preparations or its prodrugs (e.g. capecitabine, floxuridine, tegafur-) or and combination products containing these active substances and or other 5-fluoropyrimidines (e.g. see also sections 4.3, 4.5 and 4.8).

Brivudine must not be administered in patients who recently received or are currently receiving antifungal therapy with flucytosine) must not be concomitantly administered, and a minimum 4 (a prodrug of 5-fluorouracil).

The interaction between brivudine and fluoropyrimidines (e.g. capecitabine, 5-FU, tegafur, flucytosine, etc.) is potentially fatal. Fatal cases have been reported following this drug interaction. There must be at least a 4-week interval must be observed before starting waiting period between end of treatment with 5-brivudine and start of fluoropyrimidines (e.g. capecitabine, 5-FU, tegafur, flucytosine, etc.) therapy (see sections 4.3, 4.5 and 4.8).

In the event of accidental administration of brivudine in patients who recently received or are currently receiving fluoropyrimidines, all drugs must be discontinued, and effective measures must be taken to reduce the toxicity of the fluoropyrimidine drugs: Immediate admission to hospital and all measures to prevent systemic infections and dehydration. Special centres for poisoning (if available) have to be contacted as soon as possible to find appropriate action against fluoropyrimidine toxicity (see sections 4.3, 4.5 and 4.8). As a further precaution, DPD enzyme activity should be monitored before starting any treatment with 5-fluoropyrimidine drugs in patients who recently received Premovir (see also section 4.5 and 4.8).

Brivudine is not to be used if cutaneous manifestations are already fully developed.

Brivudine should be used with caution in patients with chronic liver diseases such as hepatitis. Post-marketing data indicate that extending treatment over the recommended duration of 7 days increases the risk for development of hepatitis (see also section 4.8).

Since lactose is present among the excipients, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

~~Contraindication of concomitant use with 5-fluorouracil (including also its topical preparations~~

A clinically significant interaction (potentially fatal) between brivudine and prodrugs, fluoropyrimidines (e.g. capecitabine, 5-FU, floxuridine, tegafur) or other 5-fluoropyrimidines such as, flucytosine, etc.) has been described (see also sections 4.3, 4.4 and 4.8). This interaction, which leads to increased fluoropyrimidines toxicity, is potentially fatal.

Brivudine, through its main metabolite bromovinyl uracil (BVU), exerts an irreversible inhibition of dihydropyrimidine dehydrogenase (DPD), an enzyme which regulates the metabolism of both natural nucleosides (e.g. thymidine) and of pyrimidine-based drugs (fluoropyrimidines) such as capecitabine or

5-fluorouracil (5-FU). As a consequence of the enzyme inhibition, overexposure and enhanced toxicity to 5-FU fluoropyrimidines occur.

Clinical evidence has shown that, in healthy adults receiving a therapeutic course of Premovir brivudine (125 mg once a day for 7 days), complete functional recovery of DPD enzyme activity occurs after 18 days from last dosing.

Anyway, Premovir **brivudine must not be administered in patients** who recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy and with medicines containing 5-fluorouracil or other 5-fluoropyrimidines such as (5-FU) including also its topical preparations, its prodrugs (e.g. capecitabine, floxuridine and tegafur) (or and combination products containing these active substances or flucytosine other fluoropyrimidines (see also sections 4.3, 4.4 and 4.8).

Brivudine Premovir must not be concomitantly administered, and in patients who recently received or are currently receiving anti-fungal therapy with flucytosine (a prodrug of 5-fluorouracil).

A minimum 4-week interval must be observed before between end of treatment with brivudine and starting treatment with capecitabine or other 5-fluoropyrimidine drugs including flucytosine. As a further precaution, DPD enzyme activity should be monitored before starting any treatment with 5-fluoropyrimidine drugs in patients who recently received Premovir.

In case the event of accidental administration of 5-FU and related drugs to patients treated with Premovir, both drugs **brivudine in patients** that recently received or are currently receiving fluoropyrimidines, all drugs must be discontinued and aggressive effective measures must be taken to reduce the 5-FU toxicity have of the fluoropyrimidine drugs: Immediate admission to be taken. Prompt hospitalisation is recommended hospital and all measures to prevent systemic infections and dehydration should be taken. Special centres for poisoning have to be contacted (if available) as soon as possible to find appropriate action against fluoropyrimidine toxicity (see sections 4.3, 4.4 and 4.8). Signs of 5-FU fluoropyrimidine drugs toxicity include nausea, vomiting, diarrhoea, and in severe cases stomatitis, mucositis, toxic epidermal necrolysis, neutropenia and bone marrow depression.

...

4.8 Undesirable effects

...

Description of selected adverse reactions

Brivudine can interact with chemotherapeutic agents of the 5-fluoropyrimidine class. This interaction, which leads to increased fluoropyrimidines toxicity, is potentially fatal (see also sections 4.3, 4.4 and 4.5).

Signs of 5-FU **fluoropyrimidine drugs toxicity** include nausea, vomiting, diarrhoea, and in severe cases stomatitis, mucositis, toxic epidermal necrolysis, neutropenia and bone marrow depression (see also section sections 4.3, 4.4 and 4.5).

Package leaflet

<Brand name>

Brivudine

DO NOT TAKE <Brand name> (BRIVUDINE) IF YOU recently received or are currently receiving or are planned to receive (within 4 weeks) certain cancer chemotherapy. DO NOT TAKE <Brand name> IF YOU HAVE A FUNGAL INFECTION and you recently received or are currently receiving certain anti-fungal therapy with flucytosine (see section 2, including red box). The INTERACTION between <Brand name> (brivudine) and certain cancer medicines or flucytosine is POTENTIALLY FATAL.

...

2. What you need to know before you take Premovir<Brand name>

Do ~~not~~NOT take Premovir<Brand name>:

- ▶ if you recently received or are currently receiving or are planned to receive (within 4 weeks) certain cancer chemotherapy (e.g. capecitabine, 5-fluorouracil (5-FU), tegafur, etc.) (see red box and section "Other medicines and <Brand name>")
- ▶ if you have a fungal infection and you recently received or are currently receiving anti-fungal therapy with flucytosine (see red box and section "Other medicines and <Brand name>")
- ▶ if you are allergic (hypersensitive) to the active substance brivudine
- ▶ if you are allergic (hypersensitive) to any of the other ingredients of <Brand name>Premovir (see Section 6)
- ▶ if you are pregnant or breast-feeding
- ▶ if you are less than 18 years old.

In particular, ~~do~~You MUST NOT["NOT" is to be underlined] take Premovir<Brand name>:

▶ if you recently received or are currently receiving medicines to treat or are planned to receive (within 4 weeks) certain cancer (chemotherapy), (especially if you are being treated with: 5-fluorouracil (also called 5-FU, an active substance belonging to a group called 5-capecitabine, 5-fluorouracil (5-FU) or other fluoropyrimidines) by mouth or by injection or locally as creams, ointments, eye drops or any other form of externally applied medicine) that contains 5-fluorouracil

~~—active substances which~~

▶ if you have a fungal infection and you recently received or are currently receiving anti-fungal therapy with flucytosine

▶ if you recently used or are currently converted by the body into 5-fluorouracil such as:

~~—capecitabine~~

~~—floxuridine~~

~~—tegafur~~

~~any other active substance of the 5-using or are planned to use (within 4 weeks) a wart medicine containing a fluoropyrimidine group (5-fluorouracil or others)~~

~~◆ combinations of any of the above mentioned active substances~~

▶ if your immune system (i.e. your body's defence against infections) is severely impaired; for example, if you ~~are being treated with;~~ recently received or are currently

receiving:

- **cancer medicines (chemotherapy), or**
- **immunosuppressant-immuno-suppressant medicines (i.e. medicines that suppress or diminish the function of your immune system)**

~~▶ if you are being treated for a fungal infection with a medicine containing flucytosine~~

~~▶ if you are using a wart medicine containing an active substance of the 5-fluoropyrimidine group~~



▶ In particular:

• You must NOT take <Brand name> at the same time as fluoropyrimidines (e.g. capecitabine, 5-FU, tegafur, flucytosine) treatment (including during any rest periods between treatment when you are not taking any capecitabine tablets or receiving 5-FU infusions or other fluoropyrimidine formulation or you have recently received such medicines)

• If you have taken <Brand name> you must wait for at least 4 weeks after stopping <Brand name> before starting to take capecitabine or 5-FU or other fluoropyrimidines. See also section "Do not take <Brand name> (brivudine)".

Warnings and precautions

Do not take <Brand name> and talk to your doctor or pharmacist: ~~before taking Premovir~~

~~Do not take Premovir together with medicines containing 5-FU~~ • if you recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy (by mouth or by injection or locally as creams, ointments, eye drops or any other 5-fluoropyrimidines form of externally applied medicine)

• if you have a fungal infection and you recently received or are currently receiving anti-fungal therapy with flucytosine (see sections "Do NOT["NOT" to be underlined]ot take <Brand name>-Premovir", red box, and "Other medicines and <Brand name>-Premovir").

Do not take <Brand name>Premovir if your **skin rash** is already fully developed (beginning of crusting). If you are unsure, ask your doctor.

Ask your doctor for advice before taking <Brand name>Premovir if you are suffering from **chronic diseases of the liver** (e.g. chronic hepatitis).

You should not take <Brand name>Premovir for more than 7 days, because extending treatment over the recommended duration of 7 days increases the risk of developing hepatitis (see also section 4).

Children and adolescents

Do not give <Brand name>Premovir to children and adolescents between 0 to 18 years, since the safety and efficacy in this age group have not been studied.

Other medicines and <Brand name> Premovir

Before starting treatment with <Brand name>, tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription. This is extremely important, as <Brand name> can strengthen the toxic effect of other medicines.

PLEASE NOTE:

Special warning for patients receiving therapy with products containing 5-fluorouracil or other 5-fluoropyrimidines cancer chemotherapy or fungal infections (see also the red box above):

<Brand name> Premovir **must not be used** together **in patients** with any cancer who recently received or are currently receiving or are planned to receive (within 4 weeks) certain cancer chemotherapy, medicine which contains one of the following active substances, as The harmful effects of these medicines (fluoropyrimidines) could be strongly increased and **may be fatal**.

- ▶ 5-fluorouracil (5-FU), including forms to be used locally
- ▶ capecitabine
- ▶ ~~flouxuridine~~
- ▶ tegafur
- ▶ other 5-fluoropyrimidines
- ▶ combinations of any of the above-mentioned substances with other active substances.

~~Do not take <Brand name> Premovir~~ must not be used together with medicines containing the active substance flucytosine used to treat fungal infections.

Do not take <Brand name> Premovir and contact your doctor immediately if you:

- ▶ recently received or are currently receiving or will receive (within 4 weeks) therapy with any of the above medicines
- ▶ recently received or are currently receiving therapy with anti-fungal medicine with flucytosine
- ▶ will be receiving therapy with any of the above medicines within 4 weeks of the end of treatment with Premovir.

If you have accidentally used <Brand name> Premovir and one of the medicines listed above:

- ▶ stop taking both medicines
- ▶ consult a doctor immediately-

You may need to **▶ go to the hospital for immediate treatment:** (Protect yourself from systemic infections and dehydration).

Symptoms and signs of 5-fluorouracil (and other fluoropyrimidines) toxicity due to the above interactions include:

- ▶ feeling sick; diarrhoea; inflammation of the mouth and/or inner lining of the mouth; fatigue, increased sensitivity to infections, tiredness (decreased white blood cell count and depressed bone marrow function); flat red rash all over the body, with skin becoming painful to touch, followed by large blisters leading to extensive areas of peeling skin (toxic epidermal necrolysis) (see also sect. 4).

Post-marketing experience indicates a possible interaction of brivudine with anti-Parkinson dopaminergic drugs, that may facilitate the onset of chorea (abnormal, involuntary, dance-like movements, especially of arms, legs and face).

...

Outer package labelling

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Front:

 **WARNING: PLEASE NOTE: MustThe INTERACTION between <Brand name> and certain cancer medicines or medicines against fungal infections is POTENTIALLY FATAL. <Brand name> MUST NOT BE USED["NOT BE USED" to be underlined] in patients** ~~under~~if they recently received or are currently receiving or are planned to receive (within 4 weeks) certain cancer chemotherapy. **<Brand name> MUST NOT BE USED["NOT BE USED" to be underlined] in patients** if they recently received or are currently receiving anti-fungal therapy with flucytosine.

Please read the back.

Back:

 **WARNING: PLEASE NOTE:The INTERACTION between <Brand name> and certain anti-cancer medicines or medicines against fungal-infections is POTENTIALLY FATAL. You MUST NOT TAKE["You MUST NOT TAKE" to be underlined] Premovir<Brand name>** if you recently received or are a patient currently receiving ~~or~~ are planned to receive (within 4 weeks) certain cancer chemotherapy. **You MUST NOT TAKE["You MUST NOT TAKE" to be underlined] <Brand name>** if you recently received or are currently receiving anti-fungal therapy with flucytosine.

Please read carefully the special warnings in section "What you need to know before you take Premovir<Brand name>" ~~carefully~~ and inform your doctor.

...

15. INSTRUCTIONS ON USE

To be completed nationally

Open here

...

Patient Alert Card

PULL OUT

<Brand name> (brivudine) Patient Alert Card

Carry this card with you at all times until 4 weeks after the end of treatment

This card contains important safety information you should know before you take <Brand name> and/or during treatment with <Brand name>.

Show this card to any doctor you visit and to the pharmacist before being dispensed with any other medicinal products.



PLEASE NOTE: The INTERACTION between <Brand name> (brivudine) and certain chemotherapeutic medicines (e.g. capecitabine, 5-fluorouracil, tegafur, etc.) or anti-fungal medicines containing flucytosine is POTENTIALLY FATAL.

<Brand name> MUST NOT BE USED in patients if they recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy (e.g. capecitabine, 5- fluorouracil, tegafur, etc.) or in patients with fungal infections if they recently received or are currently receiving anti-fungal therapy with flucytosine.

Prior to <Brand name> treatment

Before taking <Brand name> speak to your doctor if you:

- recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy (especially capecitabine, fluorouracil (5-FU) or other fluoropyrimidines)
- have a fungal infection and recently received or are currently receiving anti-fungal therapy containing flucytosine
- if you recently used or are currently using or are planned to receive a wart medicine containing a fluoropyrimidine group (5- fluorouracil or other)
- if your immune system (i.e. your body's defence against infections) is severely impaired; for example, if you recently received or are currently receiving:
 - o cancer medicines (chemotherapy), or

During and after <Brand name> (brivudine) treatment

• Let your doctor know that you use or used brivudine in the last four weeks in case you need to undergo chemotherapy (by mouth, or by injection or locally as creams, ointments, eye drops or any other form of externally applied medicine) or anti-fungal therapy with flucytosine.

• Call your doctor if you feel dizzy or sick, become sick or experience any unexpected symptoms after starting <Brand name>.

Go to the hospital for immediate treatment if you feel sick; diarrhoea; inflammation of the mouth and/or inner lining of the mouth; fatigue, increased sensitivity to infections, tiredness; flat red rash all over the body, with skin becoming painful to touch, followed by large blisters leading to extensive areas of peeling skin.

Protect yourself from systemic infections and dehydration.

Brivudine treatment:

Start.....

End.....

Waiting period after <Brand Name> intake:

<Brand Name>	Week 1	Week 2	Week 3	Week 4
Potentially fatal toxicity of fluoropyrimidines				

See the <Brand name> package leaflet for more information.

Please make sure you have a list of all your other medicines with you at any visit to the health care professional.

Patient's name.....

Doctor's name.....

Doctor's phone.....

o immuno-suppressant medicines (i.e. medicines that suppress or diminish the function of your immune system)

Conditions to the Marketing Authorisation(s) for nationally authorised products:

The following conditions pursuant to Article 21a of Directive 2001/83/EC shall be implemented:

Additional risk minimisation measures

Patient alert card (part of labelling)

The patient alert card (PAC) shall include key information on the potentially life threatening interaction with 5 FU and advice to carry the card to any visit with any physician (including dermatologists) and to 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.

DHPC (see attached agreed English version and communication plan)

Prescriber checklist

The prescriber checklist shall include the following key elements:

Important Risk: Potentially fatal toxicity of fluoropyrimidines (e.g. 5-fluorouracil, capecitabine, tegafur, flucytosine) if administered recently or with brivudine at the same time or used within 4 weeks after the end of treatment with brivudine.

Waiting period after brivudine administration:

I--Brivudine administration--I I--Week 1 --I I --Week 2 --I I --Week 3 --I I --Week 4 --I

I -----Potentially fatal toxicity of fluoropyrimidines -----I

For the above-mentioned reason please fill out the following checklist to be sure that your patient is suitable to receive brivudine:

Prescribe brivudine only if all the following questions are answered with “No”:

	Yes	No
Is the patient in treatment with or has recently received cancer chemotherapy?		
Is the patient in the rest period between cycles of chemotherapy?		
Is a treatment planned with fluoropyrimidines?		
Has the patient recently been in treatment with anti-fungal therapy with flucytosine?		
Is the patient recently being diagnosed with a systemic fungal infection and treatment is initiated with flucytosine?		
Is the patient immunocompromised?		

A dedicated patient alert card (PAC), containing important information for the patient and the healthcare professional on this potentially fatal interaction, is inserted in the package. Please advise your patient that he/she shall carry the PAC to any visit with any physician (including dermatologists) and that the patient 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.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	March 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	10/05/2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09/07/2020