PART VI. : SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR BRIDIC, BRIVAL, BRIVEX, BRIVIR, BRIVIRAC, BRIVOX, BRIVUMEN, MEVIR, NERVINEX, PREMOVIR, VIRUDIN, ZECOVIR, ZERPEX, ZONAVIR, ZONUDIN, ZOSTEVIR, ZOSTEX, ZOVUDEX (BRIVUDINE)

This is a summary of the risk management plan (RMP) for Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex. The RMP details important risks of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex, how these risks can be minimised, and how more information will be obtained about the risks of these products and uncertainties (missing information).
The summary of product characteristics (SmPC) of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex and their package leaflets give essential information to healthcare professionals and patients on how they should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex.

I. THE MEDICINE AND WHAT IT IS USED FOR

Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex are authorised for the early treatment of acute herpes zoster in immunocompetent adults (see SmPC for the full indication). It contains brivudine as the active substance and it is given by oral formulation (125 mg tablets).

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex together with measures to minimise such risks and the proposed studies for learning more about risks of these products, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of important risks and missing information

Important risks of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

Summary of safety concerns	
Important identified risks	Administration of 5-FPyr with brivudine at the same time or before than 4 weeks since the end of treatment with brivudine
Important potential risks	None
Missing information	None

II.B. Summary of important risks

Important Identified Risk: Administration of anticancer drug (containing fluoropyrimidines) with brivudine at the same time or before than 4 weeks since the end of treatment with brivudine	
Evidence for linking the risk to the medicine	Clinical evidence has shown that, in healthy adults receiving a therapeutic course of brivudine (125 mg once a day for 7 days), complete functional recovery of the activity of an enzyme named Dihydropyrimidine Dehydrogenase (DPD) occurs after 18 days from last dosing. The inhibition of DPD has been investigated in healthy subjects receiving 125 mg once daily for 7 days, in order to investigate the potential of over-exposure and enhanced toxicity to the anticancer drugs containing fluoropyrimidines) in the case brivudine and these anticancer drugs are concomitantly administered. The inhibition of DPD is complete and starts immediately after the administration of brivudine. A prolonged DPD recovery time cannot be excluded in patients with severe liver impairment.
Risk factors and risk groups	In patients who recently received or are currently receiving or are planned to receive (within 4 weeks) cancer chemotherapy with medicines containing 5 fluorouracil (5 FU) including also its topical

	preparations, its prodrugs (e.g. capecitabine, tegafur) and combination products containing these active substances or other fluoropyrimidines, the use of brivudine is contraindicated because the interaction is potentially fatal. The use of brivudie is also contraindicated in patients who recently received or are currently receiving antifungal therapy with flucytosine because it is a prodrug of 5-Fluorouracil (5-FU).
Risk minimisation measures	Routine risk minimisation measures: - SmPC section 4.3 Contraindications - SmPC section 4.4 Special warnings and precautions for use - SmPC section 4.5 Interaction with other medicinal products and other forms of interaction - SmPC section 4.8 Undesirable effects The PL of the concerned products is in line with the information contained in the SmPC previously described. Such information is given in the following sections of the PL: - PL Section 2 What you need to know before you take – Do not take – Warnings and precautions – Other medicines - PL Section 4 Possible side effects - Outer Packaging - Legal status: prescription only medicine Additional risk minimisation measures: - Direct Healthcare Professional Communication (DHPC) - Patient Alert Card (PAC) - Prescriber's checklist

II.C. Post-authorisation development plan

II.C.1. Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex.

II.C.2. Other studies in post-authorisation development plan

There are no studies required for Bridic, Brival, Brivex, Brivir, Brivirac, Brivox, Brivumen, Mevir, Nervinex, Premovir, Virudin, Zecovir, Zerpex, Zonavir, Zonudin, Zostevir, Zostex, Zovudex.