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 gemcitabine, the scientific conclusions are as follows:
In view of available data on acute generalised exanthematous pustulosis (AGEP) from two post-marketing case reports with confirmed diagnosis and causality considered likely related to gemcitabine including close temporal relationship, positive de-challenge and no alternative causes, the PRAC considers a causal relationship between gemcitabine products and AGEP is at least a reasonable possibility. The PRAC concluded that the product information of products containing gemcitabine should be amended accordingly. Furthermore, other types of severe cutaneous adverse reactions (SCARs) namely Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN), are already listed as undesirable effects of gemcitabine in section 4.8 of the SmPC. Given the seriousness of AGEP, SJS/TEN, a general warning regarding SCARs should be added.
Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Grounds for the variation to the terms of the marketing authorisation(s)
On the basis of the scientific conclusions for *gemcitabine* the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing *gemcitabine* is unchanged subject to the proposed changes to the product information
The CMDh recommends that the terms of the marketing authorisation(s) should be varied.

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 text **underlined and in bold**, deleted text ~~strike through~~)>

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

Severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), which can be life-threatening or fatal, have been reported in association with gemcitabine treatment. Patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gemcitabine should be withdrawn immediately.

- Section 4.8

The following adverse reaction(s) should be added under the SOC Skin and subcutaneous tissue disorders with a frequency **not known**: **acute generalised exanthematous pustulosis**.

Package Leaflet

2. What you need to know before you use gemcitabine

Talk to your doctor before using gemcitabine if:

- **you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after using gemcitabine.**

<...>

Serious skin reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalized exanthematous pustulosis (AGEP) have been reported in association with gemcitabine treatment. Seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4.

4. Possible side effects

You must contact your doctor immediately if you notice any of the following:

- **A red, scaly widespread rash with bumps under the swollen skin (including your skin folds, trunk, and upper extremities) and blisters accompanied by fever (Acute Generalized Exanthematous Pustulosis (AGEP)) (frequency not known).**

Annex III
Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2023 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 October 2023
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2023