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:

Based on post-marketing reports as well as literature data, the PRAC considered that a causal relationship between the adverse reactions 'thrombotic microangiopathy', 'infection', 'sepsis' and 'pseudocellulitis' cannot be excluded. As a consequence, it is recommended to add these as adverse drug reactions to section 4.8 of the SmPCs of products containing gemcitabine. Consequential updates of the Package Leaflet are also recommended.

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 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 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 gemcitabine are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that 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 text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.8

The following adverse reaction should be added under the SOC: Blood and lymphatic system disorders:

Thrombotic microangiopathy with a frequency **very rare**

The following adverse reactions should be added under the SOC: Infections and infestations:

Infections with a frequency **common**

Sepsis with a frequency **not known**

The following adverse reaction should be added under the SOC: Skin and subcutaneous tissue disorders:

Pseudocellulitis with a frequency **not known**

Package Leaflet

The package leaflet should be updated with these adverse reactions:

Section 4

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

- Extreme tiredness and weakness, purpura or small areas of bleeding in the skin (bruises), acute renal failure (low urine output or no urine output), and signs of infection. These may be features of thrombotic microangiopathy (clots forming in small blood vessels) and haemolytic uraemic syndrome, which may be fatal.

The following adverse reaction should be added to the table of other adverse reactions:

Thrombotic microangiopathy: clots forming in small blood vessels with frequency **very rare**

Infections with a frequency **common**

Sepsis: when bacteria and their toxins circulate in the blood and starts to damage the organs with a frequency **not known**

Pseudocellulitis: Skin redness with swelling with a frequency **not known**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2018 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	3 November 2018
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	2 January 2019