

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 pemetrexed, the scientific conclusions of the PRAC are as follows:

In view of available data on the pharmacokinetics of pemetrexed and considering *in vitro* studies indicated that pemetrexed is actively secreted by organic anion transporter 3 (OAT3) and IC50 values for proton pump inhibitors, the PRAC considers a drug-drug interaction between proton pump inhibitors and pemetrexed is at least a reasonable possibility. The PRAC concluded that the product information of products containing pemetrexed should be amended accordingly.

Having reviewed the PRAC recommendation, the CHMP 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 pemetrexed the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing pemetrexed is unchanged subject to the proposed changes to the product information

The CHMP 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 Summary of Product Characteristics (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.5

The interactions/s should be amended as follows:

Pemetrexed is mainly eliminated unchanged renally by tubular secretion and to a lesser extent by glomerular filtration. Concomitant administration of nephrotoxic drugs (e.g. aminoglycoside, loop diuretics, platinum compounds, cyclosporin) could potentially result in delayed clearance of pemetrexed. This combination should be used with caution. If necessary, creatinine clearance should be closely monitored.

Concomitant administration of **pemetrexed with OAT3 (organic anion transporter 3) inhibitors** ~~substances that are also tubularly secreted~~ (e.g. probenecid, penicillin, **proton pump inhibitors (PPIs)**) ~~could potentially result~~**s** in delayed clearance of pemetrexed. Caution should be made when these drugs are combined with pemetrexed. ~~If necessary, creatinine clearance should be closely monitored.~~

~~**Pemetrexed is eliminated by tubular secretion via human organic anion transporter 3 (hOAT3). Caution should be exercised when pemetrexed is coadministered with proton pump inhibitors or other hOAT3 inhibitors.**~~

[...]

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Amendments to be included in the relevant sections of the Package Leaflet (new text **underlined and in bold**, deleted text ~~strike through~~)

Package Leaflet

- Section 2

Other medicines and [product name]

Please tell your doctor if you are taking any medicine for pain or inflammation (swelling), such as medicines called “nonsteroidal anti-inflammatory drugs” (NSAIDs), including medicines purchased without a doctor’s prescription (such as ibuprofen). There are many sorts of NSAIDs with different durations of activity. Based on the planned date of your infusion of pemetrexed and/or on the status of your kidney function, your doctor needs to advise you on which medicines you can take and when you can take them. If you are unsure, ask your doctor or pharmacist if any of your medicines are NSAIDs.

Please inform your doctor if you are taking medicines called proton pump inhibitors (omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole) used to treat heartburn and acid regurgitation.