

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 opium the scientific conclusions are as follows:

Based on evidence from the scientific literature and considering the plausible mechanism by which morphine (one of the active substances of opium) delays gastric emptying and thus reduces absorption of P2Y12 inhibitors (e.g. prasugrel, clopidogrel, ticagrelor), the PRAC considers that an interaction between P2Y12 inhibitors and morphine in opium-treated patients cannot be excluded. Furthermore, this interaction has been added to the respective product information of P2Y12 inhibitors (e.g. clopidogrel, prasugrel and ticagrelor) within recent years.

Therefore, an update of the product information is warranted in order to minimise the risk of delayed and reduced effect of and/or decreased exposure of P2Y12 inhibitors when co-administered with opium.

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 opium the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing opium 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 opium 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 text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

The warning should be added as follows:

- Section 4.4

[...]

Administer at reduced doses and with the utmost caution to patients who are also being treated with other narcotic agents, sedatives, and tricyclic antidepressants and MAO-inhibitors (see also section 4.2)

Oral P2Y12 inhibitor antiplatelet therapy

Within the first day of concomitant P2Y12 inhibitor and morphine treatment, reduced efficacy of P2Y12 inhibitor treatment has been observed (see section 4.5).

Should only be used with caution in patients in high-risk groups, such as patients with epilepsy and hepatic disease.

[...]

The interactions should be added as follows:

- Section 4.5

Interaction with other medicinal products and other forms of interaction

[...]

Rifampicin induces CYP3A4 in the liver thus increasing the metabolism of morphine, codeine and methadone. The effect of these opioids is thereby decreased or counteracted.

A delayed and decreased exposure to oral P2Y12 inhibitor antiplatelet therapy has been observed in patients with acute coronary syndrome treated with morphine. This interaction may be related to reduced gastrointestinal motility and apply to other opioids. The clinical relevance is unknown, but data indicate the potential for reduced P2Y12 inhibitor efficacy in patients co-administered morphine and a P2Y12 inhibitor (see section 4.4). In patients with acute coronary syndrome, in whom morphine cannot be withheld and fast P2Y12 inhibition is deemed crucial, the use of a parenteral P2Y12 inhibitor may be considered.

Concurrent administration of morphine and antihypertensive drugs may increase the hypotensive effects of antihypertensive agents or other drugs with hypotensive effects.

[...]

Package Leaflet

- Section 2

Other medicines and [tradenam]

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

It is especially important that you tell your doctor or pharmacist if you are taking:

[...]

- Medicines to treat tuberculosis (rifampicin) decreases the effect of morphine
- **Some medicines used to treat blood clots (e.g. clopidogrel, prasugrel, ticagrelor) may have delayed and decreased effect when taken together with opium**
- Cimetidine may increase the effect of morphine

[...]

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	May 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	12 July 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	10 September 2020