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 metamizole, the scientific conclusions are as follows:

In view of available data on drug-induced liver injury from published cases, case series and spontaneous reports including some cases with probable causality and a positive re-challenge, and in view of a plausible biological mechanism, the PRAC considers a causal relationship between metamizole and drug-induced liver injury is at least a reasonable possibility. The PRAC concluded that the product information of products containing metamizole should be amended accordingly.

Based on review of *in vitro/ex vivo* pharmacokinetic data, individual case safety reports, and the worldwide scientific literature, the PRAC also concluded that the weighted cumulative evidence is sufficient to support that there is a risk of pharmacokinetic interaction of metamizole with CYP2B6 and CYP3A4 substrates *via* enzyme induction. Therefore, the interaction with bupropion and cyclosporin currently addressed in the product information of metamizole-containing medicinal products should be extended to other CYP2B6 and CYP3A4 substrates with sufficiently documented cases of significantly decreased therapeutic levels and/or lack of efficacy.

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 metamizole the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing metamizole 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 metamizole 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~~)

SmPC Section 4.4

A warning should be added as follows:

Drug-induced liver injury

Cases of acute hepatitis of predominantly hepatocellular pattern have been reported in patients treated with metamizole with an onset of few days to few months following treatment initiation. Signs and symptoms include elevated serum hepatic enzymes with or without jaundice, frequently in context of other drug hypersensitivity reactions (e.g. skin rash, blood dyscrasias, fever and eosinophilia) or accompanied by features of autoimmune hepatitis. Most patients recovered on discontinuation of metamizole treatment; nevertheless, in isolated cases, progression to acute liver failure requiring liver transplantation was reported.

The mechanism of metamizole-induced liver injury is not clearly elucidated, but data indicate an immuno-allergic mechanism.

Patients should be instructed to contact their physician in case symptoms suggestive of liver injury occur. In such patients metamizole should be discontinued and liver function should be assessed.

Metamizole should not be re-introduced in patients with an episode of hepatic injury during treatment with metamizole for which no other cause of liver injury has been determined.

SmPC Section 4.8

The following adverse reaction(s) should be added under the SOC Hepatobiliary disorders with a frequency unknown:

Drug-induced liver injury including acute hepatitis, jaundice, increased liver enzymes (see Section 4.4)

Package Leaflet

Section 2. What you need to know before you take <invented name>

Warnings and precautions

Liver problems

Inflammation of the liver has been reported in patients taking metamizole with symptoms developing within a few days to a few months following the start of treatment.

Stop using <invented name> and contact a doctor if you have symptoms of liver problems such as feeling sick (nausea or vomiting), fever, feeling tired, loss of appetite, dark-coloured urine, light-coloured bowel movements, yellowing of the skin or white part of the eyes, itching, rash or upper stomach pain. Your doctor will check the functioning of your liver.

You should not take <invented name> if you have previously taken any metamizole-containing medicinal product and had liver problems.

Section 4. Possible side effects

Stop using <invented name> and immediately contact a doctor if you experience any of the following symptoms:

Feeling sick (nausea or vomiting), fever, feeling tired, loss of appetite, dark-coloured urine, light-coloured bowel movements, yellowing of the skin or white part of the eyes, itching, rash or upper stomach pain. These symptoms may be signs of liver injury. See also section 2 Warnings and precautions.

[List of side effects]

Frequency not known (cannot be estimated from the available data):

Inflammation of the liver, yellowing of the skin and white part of eyes, increase in the blood level of liver enzymes

Section 4.5

The interactions should be amended as follows:

Pharmacokinetic induction of metabolising enzymes:

Metamizole **may induce metabolising enzymes including CYP2B6 and CYP3A4.**

Co-administration of metamizole with bupropion, efavirenz, methadone, valproate, cyclosporine, tacrolimus or sertraline, may cause a reduction in plasma concentrations **of these drugs with a potential decrease in clinical efficacy**. Therefore, caution is advised when metamizole is administered concurrently; **clinical response and/or drug levels should be monitored as appropriate**.

~~Metamizole may cause a reduction in serum cyclosporin levels; cyclosporin concentrations must, therefore, be monitored when metamizole is administered concomitantly.~~

Package Leaflet

Section 2. What you need to know before you take <invented name>

Other medicines and <invented name>

- bupropion, a medicine used to treat depression **or used as an aid to smoking cessation**
- **efavirenz, a medicine used to treat HIV/AIDS**
- **methadone, a medicine used to treat dependence to illicit drugs (so called opioids)**
- **valproate, a medicine used to treat epilepsy or bipolar disorder**
- **tacrolimus, a medicine used to prevent organ rejection in transplanted patients**
- **sertraline, a medicine used to treat depression.**

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	November 2020 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	27 December 2020
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	25 February 2021