Annex II

Scientific conclusions

Scientific conclusions

The German National Competent Authority (NCA) (BfArM) is of the view that recent publications cast doubt on the efficacy of medicinal products containing methocarbamol/paracetamol 380 mg/300 mg in the "*short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders*" (Cochrane Database of Systematic Reviews, 2016; Emrich, 2015; Luis-Miguel Gonzalez-Perez, 2015; Oliveras-Moreno, 2008). In addition, it is unclear whether any interaction may be expected when both substances are administered in combination (Bruce, 1971; Micromedex, 2014).

On 27 May 2019 the BfArM therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of medicinal products containing methocarbamol/paracetamol 380 mg/300 mg. The CHMP should give its opinion whether the relevant marketing authorisations should be granted, maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

Methocarbamol is a centrally acting muscle relaxant. It produces its muscle-relaxant effect by inhibiting polysynaptic reflexes in the spinal cord and subcortical centres. Paracetamol is an analgesic with antipyretic properties. It is thought to increase the pain threshold by inhibiting prostaglandin synthesis, by means of blocking cyclooxygenase enzymes (specifically COX-3) in the central nervous system and, to a lesser extent, in peripheral tissues. Its antipyretic action is related to the inhibition of Prostaglandin E1 (PGE1), synthesis in the hypothalamus.

In the EU/EEA a fixed dose combination (FDC) medicinal products containing methocarbamol/paracetamol 380 mg/300 mg was first authorised in Spain in 1985 under the name Robaxisal, for use in the "short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders". In adults the posology is 2 tablets every 4-6 hours (four to six times daily), depending on the severity of the symptoms. Hence the maximum daily dose is methocarbamol/paracetamol 4560 mg / 3600 mg (12 tablets).

The CHMP considered all available data on the efficacy and safety of methocarbamol/paracetamol from clinical trials, the literature and from post-marketing reports.

No clinical trial testing the superiority in efficacy of a methocarbamol/paracetamol combination over the single compounds alone was identified. However, there is data on these active substances in the treatment of painful muscle spasms in acute musculoskeletal disorders, particularly for low back pain. Indeed, the literature provides some evidence of efficacy of the mono-components and some evidence of their additive effect when given in FDC with respectively a muscle relaxant or an analgesic. Of note, these studies do not provide information as to whether the product may be used as "first-line", "add-on", or "switch" as is currently required in the guideline for FDC.

The more recent studies of fixed dose combinations of methocarbamol/paracetamol do not bring new relevant information on the efficacy of the FDC containing methocarbamol/paracetamol 380 mg/300 mg as their designs were inadequate.

Older studies were supportive of the efficacy of the paracetamol component in lower back pain, while conflicting results were obtained in more recent studies. A number of limitations were identified in those recent studies and CHMP concluded that these, or the reviews relying on these results, did not bring significant new elements raising serious doubt on the efficacy of paracetamol in lower back pain.

Considering the posology of other methocarbamol-containing medicinal products and the doses used in clinical trials, the CHMP concluded that there is no indication that the doses in the FDC with methocarbamol/paracetamol 380 mg/300 mg might be too low.

In conclusion, whilst limitations were identified to the data available in support of the efficacy of methocarbamol/paracetamol 380 mg/300 mg in the short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders, no data constituting sufficient evidence to question the efficacy was identified.

No pharmacokinetic interaction was observed for paracetamol and/or methocarbamol and the data from post-marketing sources do not suggest a higher risk of hepatotoxicity with the use of both active substances in combination. Therefore, and as sufficient data on the possible interactions for the mono-component is available, there is no need for additional pharmacovigilance or pharmacodynamic studies of the combination.

The CHMP concluded that no new significant information was identified with regards to the overall safety profile of the fixed dose combination methocarbamol/paracetamol. However, the adverse reactions 'dry mouth' and 'diarrhoea' were considered as at least possibly related to the methocarbamol component and as such are added to the product information with a frequency unknown. Furthermore, section 4.8 of the SmPC and section 4 of the package leaflet are being reformatted in line with the SmPC guideline and QRD template.

In conclusion, the CHMP considers the above issues do not impact the benefit-risk balance. Therefore, the benefit-risk balance of methocarbamol/paracetamol 380 mg/300 mg containing products for use in short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders remains favourable subject to changes to the product information as described above.

Grounds for CHMP opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 31 of Directive 2001/83/EC for methocarbamol/paracetamol 380 mg/300 mg containing products.
- The CHMP considered the totality of the data available for methocarbamol/paracetamol 380 mg/300 mg containing products for use in short-term, symptomatic treatment of painful muscle spasms associated with acute musculoskeletal disorders.
- The CHMP considered that, despite limitations, available data provided evidence of efficacy in the authorised indication and that no evidence raising serious doubts on the efficacy was identified.
- The CHMP further considered that the safety profile of both mono-components is well characterised, and no new significant evidence was identified for the fixed dose combination.

CHMP opinion

The CHMP, as a consequence, considers that:

a. the benefit-risk balance of methocarbamol/paracetamol 380 mg/300 mg containing products remains favourable subject to the agreed amendments to the product information. The Committee, consequently, recommends the variation to the terms of the marketing authorisations for methocarbamol/paracetamol 380 mg/300 mg containing products.

b. the issues raised in the notification triggering the present procedure dated 27 May 2019 do not impact the benefit-risk balance, and hence, do not preclude the granting of a marketing authorisation for the methocarbamol/paracetamol 380 mg/300 mg application, subject to the agreed amendments to the product information.