COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Paracetamol/Codeine Accord 500 mg/8 mg, 500 mg/15 mg and 500 mg/30 mg, effervescent tablets (paracetamol and codeine)

NL/H/4537/001-003/DC

Date: 21 March 2022

This module reflects the scientific discussion for the non-approval of Paracetamol/Codeine Accord 500 mg/8 mg, 500 mg/15 mg and 500 mg/30 mg, effervescent tablets. The procedure was finalised at 7 December 2021.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have refused granted a marketing authorisation for the fixed dose combination Paracetamol/Codeine Accord 500 mg/8 mg, 500 mg/15 mg and 500 mg/30 mg, effervescent tablets, from Accord Healthcare B.V.

The indication applied for was for the relief of moderate pain.
Paracetamol/Codeine Accord is indicated in adults and children older than 12 years of age for the treatment of acute moderate pain which is not considered to be relieved by other analgesics such as paracetamol or ibuprofen (alone).

The marketing authorisation was applied pursuant to Article 10(1) of Directive 2001/83/EC for the 500 mg/30 mg strength, and pursuant to Article 10(3) for the 500 mg/8 mg and 500 mg/15 mg strengths.

The concerned member states (CMS) involved in this procedure were Czech Republic, Finland, France, Italy, Norway, Poland, Romania, Spain and Sweden for the 500 mg/30 mg strength. For the 500 mg/8 mg and 500 mg/15 mg strengths, the CMS were Poland and Romania.

II. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The marketing authorisation could not be granted as the requested biowaiver was not considered approvable. Therefore, bioequivalence between Paracetamol/Codeine Accord 500 mg/30 mg and the reference product Solpadol 30mg/500mg Effervescent Tablets/Ireland, has not been shown.

<u>Clinical</u>
For a waiver of solutions, the criteria as mentioned in the EMA Guideline on the Investigation of Bioequivalence as well as the ICH M09 guideline should be followed. In the EMA guideline it is mentioned that oral solutions should comply to Biopharmaceutical Classification System (BCS) waiver criteria, as set Annex II stating that, in case an oral solution contains excipients that might affect bioavailability, a bioequivalence study should be conducted, unless the differences in the amounts of these excipients can be adequately justified by reference to other data. In addition, in the ICH M09 guideline it is mentioned that for a waiver for BCS Class I drugs containing critical excipients an absolute difference of max 10% between formulations is allowed. If this difference is more than 10 %, in principle a bioequivalence study should be performed, unless appropriate justification can be given.

For justification of the biowaiver, reference is made by the applicant to European Public Assessments Reports (EPARs)/ FDA applications of codeine containing products, in which products containing different amounts of some specific excipients were compared. The

applicant concluded that a difference in the amount of these excipients does not affect the absorption of codeine. Also dissolution data were provided to study the effect of the excipients concentration on dissolution of codeine phosphate.

However, those data are not considered valid since the EPARs/FDA applications concerns either products with a different legal base, products with a different formulations or older products which have not been assessed according to the current guidelines, or the documents contain too limited information to draw conclusions. The dissolution data cannot be used for justification, since they are not considered representative for giving information on permeation.

In conclusion, insufficient data is provided to support that some specific excipients do not influence the absorption of codeine. A bioequivalence study should be submitted to support that the difference in excipients does not influence the absorption of codeine differently between the Test and Reference, unless appropriately justified. At present, no reference can be made to the preclinical and clinical data in the dossier of the reference product.

Therefore, the Board concluded that the marketing authorisation for Paracetamol/Codeine Accord 500 mg/8 mg, 500 mg/15 mg and 500 mg/30 mg, effervescent tablets cannot be granted. Agreement on this conclusion was reached with the concerned member states. The decentralised procedure was finalised with a negative outcome on 7 December 2021.