LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

# Public Assessment Report
# Scientific discussion

# Altermol
# (paracetamol, codeine phosphate hemihydrate)

# SE/H/1401/01/DC

**This module reflects the scientific discussion for the approval of Altermol. The procedure was finalised on 2015-10-01. For information on changes after this date please refer to the module 'Update'.**

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# I. INTRODUCTION

The application for Altermol, 500 mg/30 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Alternova A/S, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FI, NO as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Citodon, 500 mg/30 mg, tablets, authorised in Sweden since 1982, with BioPhausia AB as marketing authorisation holder.

For approved indications, see the Summary of Product Characteristics.

For recommendations to the marketing authorisation not falling under Article 21a/22 of Directive 2001/83 and conditions to the marketing authorisation pursuant to Article 21a or 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

# II. QUALITY ASPECTS

## II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

## II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

# III. NON-CLINICAL ASPECTS

## III.1 Discussion on the non-clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to preclinical data, no further such data have been submitted or are considered necessary.

# IV. CLINICAL ASPECTS

## IV.1 Pharmacokinetics

No bioequivalence study has been submitted since the applicant applies for a BCS-based biowaiver. From a pharmacokinetic point of view, a BCS-class I based biowaiver is acceptable for an immediate release drug product if the drug substance has proven to exhibit complete absorption and the excipients that might affect bioavailability are quantitatively and qualitatively the same. It should also be confirmed that the substance is not a narrow therapeutic index drug.

Absorption

*Paracetamol*

In a study by Rawlins et al, absolute bioavailability was estimated to 0.63, 0.89 and 0.87 after a dose of 500 mg, 1000 mg and 2000 mg respectively. This is in line with other studies, where absolute bioavailability within the range of 60-80% has been reported (Eandi et al., 1984 and Clements et al., 1984).

Since no metabolism is considered to occur in the gastric or intestinal fluid, urinary excretion data could be used to assess fraction absorbed for paracetamol. In a study by Tukker et al. (1986), the fraction absorbed based on urinary excretion data was > 90% when urine was collected up to 24 hours after dosing. In another study, the fraction absorbed is estimated to 70-76% based on urine collection up to 12 hours after dose administration (Goicoechea et al. 1998). In these studies, paracetamol and some of the metabolites were measured (not exactly the same in the two studies), i.e. neither of the studies used radio-labelled drug substance, but this is considered acceptable.

No original publication by Prescott has been submitted by the applicant, only a review article (1980). Thus, it is hard to make an assessment of this data. However, according to table 1 in the review article, the urinary excretion of parent drug and sulphate, glucuronide and cysteine and mercapturic acid conjugates was 93% in healthy subjects given an oral dose of 20 mg/kg. Urinary concentrations were measured by HPLC, i e this study was not performed with radio-labelled drug substance. Urine was collected for 24 hours. Thus, these results are in line with the results by Tukker et al and suggest a fraction absorbed above 85%.

Depending on the data source paracetamol may be classified as a BCS I or BCS III drug substance, but taken together the data point toward that paracetamol has a fraction absorbed greater or equal to 85% of the dose, which is the cut-off value used in the European guidelines. Thus, it is agreed to classify paracetamol as a BCS class I substance from a pharmacokinetic point of view.

*Codeine*
Two studies by Yue et al (1991) have been submitted by the applicant. The study by Yue and Hasselström et al (1991) studies the pharmacokinetics of codeine in Caucasian extensive and poor metabolisers. The study by Yue and Svensson et al (1991) compares the pharmacokinetics of codeine in Caucasian and Chinese extensive metabolisers. In the first study the urinary recovery of codeine and its metabolites following 48 hours sampling was 84.4 ± 15.9% (mean ± SD) and 90.2 ± 15.3% of the administered dose in extensive and poor metabolisers respectively. In the second study, the urinary recovery of drug-related material in urine following 48 hours sampling was similar in Chinese (82.2 ± 15.6% of dose) and Caucasians (84.4 ± 15.9%). In both studies, codeine and its seven known metabolites (morphine, M3G, M6G, normorphine, codeine-6-glucuronide, norcodeine, NC-glucuronide) were determined in urine using HPLC.

Other studies regarding urinary excretion of codeine are available in the public domain. A study by Moffat et al (1986) demonstrates a urinary excretion of 86% following 24 hours urinary recovery. A study by Chen (1991) demonstrates a urinary excretion of 86.1 ± 11.4% following 12 hours urinary recovery. There are also studies with only 8 hours of urinary sampling where lower recovery values have been reported (Two studies by Yue et al 1989: 74-75.5% in Caucasians and 59.7% in Chinese).

The data above refers to excretion in the urine. In most of the studies the excretion was very close to or higher than 85% in urine. In two studies the excretion was clearly lower than 85% but in these cases the sampling time was much shorter (8 hours versus 48 hours at the most). The excreted amount of codeine and its phase I and II metabolites ranges between 82.2 % and 90.2 % in the studies where the sampling was performed between 12 and 48 hours (Chinese and Caucasians). These metabolites are formed after absorption. These data can be considered sufficient evidence to consider codeine as belonging to BCS class I from a pharmacokinetic point of view.

Excipients
The excipients are not identical in the test and reference product, but none of the excipients are known to affect drug bioavailability.

Narrow therapeutic index
Paracetamol and codeine are not considered to have a narrow therapeutic index in the sense that the acceptance criteria would need to be tightened in a bioequivalence study.

Pharmacokinetic conclusion
It is concluded that paracetamol and codeine have a fraction absorbed greater than or equal to 85% and thus can be classified as BCS class I substances from a pharmacokinetic point of view.

The justification for BCS (Biopharmaceutics Classification System) based biowaiver CAN be accepted.

## IV.2 Discussion on the clinical aspects

Since this product has been shown to be essentially similar and refer to a product approved based on a full application with regard to clinical efficacy/safety data, no further such data have been submitted or are considered necessary.

### IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Altermol.

The safety concerns will be addressed with routine pharmacovigilance activities, and no additional pharmacovigilance activities are suggested.
Routine risk minimisation measures are suggested and no additional risk minimisation measures are suggested.

**Safety concerns**

| | |
|---|---|
| **Important identified risks** | Bile duct spasm<br>Hypersensitivity<br>Use in post-operative in paediatric patients<br>Use in children with compromised respiratory function<br>Use during breast feeding in mothers who are ultra-rapid or extensive metabolisers<br>In patients who are CYP2D6 ultra rapid metabolisers<br>Interaction with quinidine<br>Overdose<br>Liver failure |
| **Important potential risk** | None |
| **Important missing information** | None |

Summary of the RMP

The RMP is approved.

## V. USER CONSULTATION

A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to Codalvonil 500 mg/30 mg, effervescent tablets, SE/H/1121/01/DC (contents) and Amiodaron Alternova 50 mg/ml solution for injection, nationally approved by DKMA (2810-51884-2012) (layout). The bridging report submitted by the applicant has been found acceptable.

## VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The benefit/risk ratio is considered positive and Altermol, 500 mg/30 mg, tablet is recommended for approval.

**List of recommendations not falling under Article 21a/22 of Directive 2001/83 in case of a positive benefit risk assessment**

N/A

**List of conditions pursuant to Article 21a or 22 of Directive 2001/83/EC**

N/A

# VII. APPROVAL

The Decentralised procedure for Altermol, 500 mg/30 mg, tablet was positively finalised on 2015-10-01.

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# Public Assessment Report – Update

| Scope | Procedure number | Product Information affected | Date of start of the procedure | Date of end of procedure | Approval/ non approval | Assessment report attached |
|---|---|---|---|---|---|---|
| | | | | | | Y/N (version) |

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