LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Azalonum
(cinnarizine/dimenhydrinate)

SE/H/1798/01/DC

This module reflects the scientific discussion for the approval of Azalonum. The procedure was finalised on 2019-03-13. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

The application for Azalonum, 20 mg/40 mg, tablet, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, Medochemie Limited, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and BG, HR, CY, CZ, EE, EL, LV, LT, MT, RO, SK as concerned member states (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Arlevert, 20 mg/40 mg, tablet authorised in United Kingdom since 2005-05-20, with HENNIG ARZNEIMITTEL GmbH & Co. KG, as marketing authorisation holder.

The reference product used in the bioequivalence study is Arlevert, 20 mg/40 mg, tablet from Germany with HENNIG ARZNEIMITTEL GmbH & Co. KG 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

To support the marketing authorisation application the applicant has conducted one pivotal bioequivalence study (study code: CNMD-BEFI-03-MDM/15) comparing Azalonum with the reference product Arlevert.

A pilot study (study code: CNMD-BEFI-01-MDM/13) was performed. The same batch of the test product was used in the pilot study as used in the pivotal study. It is noted that bioequivalence was shown for all parameters except for 8-chlorotheophylline (i.e. the confidence interval was outside the acceptance range for AUC_{0-t}) in the pilot study. However, no issue is raised since this is a pilot study which was intended to preliminary assess the potential for bioequivalence. Bioequivalence has also been shown for all parameters in the much larger pivotal bioequivalence study where 56 subjects were included compared to only 16 subjects that were included in the pilot study.

Pharmacokinetic properties of the active substances

Absorption and distribution:
Dimenhydrinate rapidly releases its diphenhydramine moiety after oral administration. Diphenhydramine and cinnarizine are rapidly absorbed from the gastro-intestinal tract. Maximum plasma concentrations (C_{max}) of cinnarizine and diphenhydramine are reached in humans within 2-4 hours. The plasma elimination half-lives of both substances range from 4-5 hours, when given either alone or as the combination product.

Biotransformation:
Cinnarizine and diphenhydramine are extensively metabolised in the liver. The metabolism of cinnarizine involves ring hydroxylation reactions that are in part catalysed by CYP2D6 and N-desalkylation reactions of low CYP-enzyme specificity. The main pathway in the diphenhydramine metabolism is the sequential N-demethylation of the tertiary amine. Studies in human liver microsomes *in vitro* indicate the involvement of various CYP-enzymes, including CYP2D6.

Elimination:
Cinnarizine is mainly eliminated via the faeces (40-60%) and to a lower extent also in urine, mainly in the form of metabolites conjugated with glucuronic acid. The major route of elimination of diphenhydramine is in the urine, mainly in the form of metabolites, with the

deaminated compound, diphenylmethoxy acetic acid, being the predominant metabolite (40-60%).

Linearity:
Not applicable since there is only one strength available for the reference product, i.e. 20mg/40mg.

Method of administration:
The SmPC of the originator product Arlevert recommends administration with some liquid after a meal.

Study (CNMD-BEFI-03-MDM/15)
Methods
Bioequivalence was evaluated in one single dose, two-way crossover study conducted in 56 healthy volunteers, comparing cinnarizine 20 mg and dimenhydrinate 40 mg, tablet with Arlevert 20 mg/40 mg, tablet under fed conditions. Blood samples were collected pre-dose and up to 72 hours post-dose. Plasma concentrations of cinnarizine, diphenhydramine and 8-chlorotheophylline were determined with adequately validated LC-MS/MS methods. Analysis of variance (ANOVA) was performed on the log-transformed data for AUC_{0-t} and C_{max}.

The study was conducted between 2015-06-09 and 2015-07-17.

Results
For AUC_{0-t} and C_{max} the 90% confidence interval for the ratio of the test and reference products fell within the conventional acceptance range of 80.00-125.00% for cinnarizine, diphenhydramine and 8-chlorotheophylline, see results tables below:

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for cinnarizine, n=56.

Treatment	**AUC_{0-t}** ng*h/ml	**C_{max}** ng/ml	**t_{max}** h
Test	**581.272 ± 266.504**	**74.794 ± 26.375**	**3.5 (1.5-8.0)**
Reference	**595.146 ± 262.044**	**73.792 ± 25.627**	**3.5 (1.5-8.0)**
***Ratio (90% CI)**	**97.044 (93.250-100.993)**	**101.052 (95.037-107.448)**	**-**

AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours
C_{max} maximum plasma concentration
t_{max} time for maximum plasma concentration

**calculated based on ln-transformed data*

Table 2. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for diphenhydramine, n=56.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**233.008 ± 129.192**	**25.736 ± 14.583**	**2.5 (0.75-5.5)**
Reference	**242.598 ± 121.320**	**25.972 ± 13.718**	**2.5 (0.75-6.0)**
***Ratio (90% CI)**	**94.79 (89.563-100.323)**	**99.303 (91.531-107.734)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Table 3. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} median, range) for 8-chlorotheophylline, n=56.

Treatment	AUC_{0-t} ng*h/ml	C_{max} ng/ml	t_{max} h
Test	**24761.1 ± 17951.9**	**1521.18 ± 603.577**	**1.75 (0.33-8.0)**
Reference	**21599.6 ± 13745.5**	**1502.96 ± 543.255**	**1.5 (0.5-8.0)**
***Ratio (90% CI)**	**109.217 (95.928-124.35)**	**99.802 (92.294-107.92)**	**-**
AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours C_{max} maximum plasma concentration t_{max} time for maximum plasma concentration			

**calculated based on ln-transformed data*

Discussion and overall conclusion

Dimenhydrinate dissociates to diphenhydramine and 8-chlorotheophylline. In this study the plasma concentration of diphenhydramine was determined and used for bioequivalence assessment as an indicator of dimenhydrinate, which is acceptable. 8-chlorotheophylline was also determined but was only presented as supportive data and was not considered for bioequivalence assessment. It is not clear if 8-chloroteophylline should also be considered to be an active substance, since it cannot be excluded to have a slight stimulant effect, but bioequivalence was demonstrated also for this substance and thus no concern is raised.

The bioequivalence study and its statistical evaluation were in accordance with accepted standards for bioequivalence testing, as stated in the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr). The bioanalytical methods were adequately validated.

Based on the submitted bioequivalence study, Azalonum is considered bioequivalent with Arlevert.

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 Azalonum.

Safety specification
The MAH has submitted the version 1.1 RMP dated 10.04.2017 and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	Risk in patients with angle-closure glaucoma Risk in patients with convulsions Risk in patients with suspicion of raised intracranial pressure Risk in patients with alcohol abuse Risk in patients with urine retention due to urethroprostatic disorders
Important potential risks	Risk in patients with conditions that might be aggravated by anticholinergic therapy: raised intra-ocular pressure, pyloro-duodenal obstruction, prostatic hypertrophy, hypertension, hyperthyroidism, severe coronary heart disease. Risk in patients with Parkinson's disease
Missing information	Patients with severe hepatic impairment Patients with severe renal impairment Use in children Use in pregnancy and lactation

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures
Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP
The submitted Risk Management Plan, version 1.1, signed 10.04.2017, is considered *acceptable*.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk

profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

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 Arlevert 20 mg/40 mg tablets (UK/H/0984/001/MR) and Encapia 200 mg film-coated tablets (NL/H/2497/001/DC). The bridging report submitted by the applicant has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Azalonum, is found adequate. There are no objections to approval of Azalonum, from a non-clinical and clinical point of view. Bioequivalence between the test and reference product has been adequately demonstrated. The product information is acceptable.
The application is therefore recommended for approval.

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

Post approval commitments

Quality

Description	Due date
Introduction of the updated CEP (R0-CEP 2015-019) of the cinnarizine drug substance manufacturer, Fleming Laboratories, via the variation procedure.	Within 3 months from the end of this procedure.

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

N/A

VII. APPROVAL

The Decentralised procedure for Azalonum, 20 mg/40 mg, tablet was positively finalised on 2019-03-13.

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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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