Public Assessment Report
Scientific discussion during the initial procedure

Pinohexal
Amlodipine besilate

DK/H/964/1-3/MR

MT-holder: Hexal A/S, Hvidovre, Denmark

This module reflects the scientific discussion for the approval of Pinohexal, 5 mg, 7.5 mg and 10 mg tablets. The procedures were finalised at 11-10-06. For information on changes after this date please refer to the module 'Update'.

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the RMS considered that the applications for the Pinohexal, Hexal A/S, 5 mg, 7.5 mg and 10 mg tablets in the treatment of Essential hypertension and Chronic stable and vasospastic angina pectoris, could be approved.

A national marketing authorisation was granted on 20 February 2006. Pinohexal has afterwards been approved though Mutual Recognition Procedure on 11 October 2006

The application was applied through MRP by Stichting Registratiebeheer. In February 2007 the MT-holder for the product was changed to Hexal A/S, Hvidovre, Danmark

The applications for Pinohexal, 5 mg, and 10 mg tablets are applied are in accordance with article 10.1, Directive 2001/83/EC as amended, where as the application for amlodipine besilate 7.5 mg tablet is applied in accordance with article 10.3, Directive 2001/83/EC as amended
Essential similarity to the original product in Denmark, Norvasc 5 mg and 10 mg tablets, marketed by Pfizer A/S, registered in Denmark since 1990 is claimed. The reference product used in the Bioequivalence study is Norvasc 10 mg tablets, Pfizer.

No clinical studies, besides the bioequivalence studies were conducted. This is acceptable for this abridged application.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all of the sites responsible for the manufacture and assembly of this product prior to granting its National authorisation.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For the manufacturing sites outside the Community, the RMS has accepted copy of current GMP Certificates or satisfactory inspection summary reports, ”close-out letters” or ”exchange of information” issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

Consultation with target patient groups (user-test):
The applicant has submitted a test report. The test was carried out with 20 participants in two rounds of 10 race-to face questionnaire-based interviews each. The results are accepted.

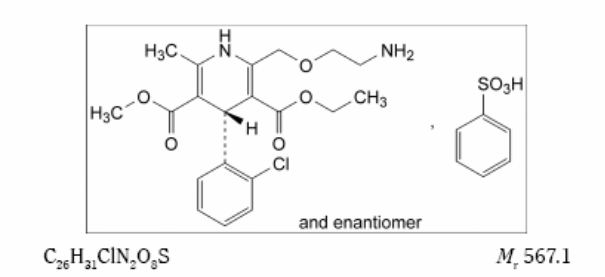
II Quality aspects

II.1 INTRODUCTION

Application type: Generic application, national procedure, MRP is considered after national approval.
Dosage form: Tablet.
Active substance: Amlodipine besilate.
Strength: 5 mg, 7.5 mg and 10 mg.
The finished product, are to be marketed in either 2 different qualities of blister packs (PVC/Al or OPA/AL/PVC/AL) or in a PE container.

II.2 DRUG SUBSTANCE

General Information



$C_{26}H_{31}ClN_2O_8S$ M_r 567.1

Active Substance: Amlodipine besilate.

The active substance is described in the European Pharmacopoeia. It is a white or almost white powder. It is freely soluble in methanol, slightly soluble in water and 2-propanol and sparingly soluble in ethanol and in 2-propanol. It is optically active as it possesses one chiral center. The monograph is for the racemic mixture.

The manufacturer of the active substance has obtained a Certificate of Suitability, a copy of which is presented in the documentation.

The active substance is controlled according to the requirements of the Ph. Eur. Monograph. Additional requirements for related substances and residual solvents are included in the specification from the drug product manufacturer and are as reported in the CEP.

Batch analyses: Certificates of analysis issued by the finished product manufacturer. The results comply with the proposed specifications.

Re-test period: A retest period on 36 months is acceptable according to the CEP and supported by submitted stability data.

II.3 MEDINCAL PRODUCT

Excipients:
Excipients: Sodium starch glycolate, anhydrous calcium hydrogen phosphate, microcrystalline cellulose, magnesium stearate,

All excipients comply with Ph.Eur.

Analytical Procedures: All procedures are Ph. Eur. methods.

Validation of Analytical Procedures: All procedures are Ph. Eur. methods. Therefore no further validation is required.
Justification of Specifications: As the specifications comply with the monographs, no further justification is necessary.
Excipients of Human or Animal Origin: As none of the excipients are of animal or human origin, there is no TSE risk. The quality of magnesium stearate is of none-animal origin. A statement has been enclosed.

Drug product:
Analytical Procedures: All analytical procedures used for testing the drug product have been properly described.

Batch Analyses: Certificates of analysis of 5 mg, 7.5 mg and 10 mg batches are enclosed. The results comply with the specification and confirm consistency of the product.

Justification of Specification(s): The specification has been justified according to the tablet monograph of EP and relevant EU/ICH Q6A Guideline *Specifications: Test procedures and acceptance criteria for new drug substances and new drug products*.

The following shelf-life/storage condition is accepted: A shelf-life of 3 years with no special storage precautions and additional labelling statement “Store in the original package” can be established for all strengths and packaging materials.

ASSESSOR’S OVERALL CONCLUSIONS ON QUALITY
The pharmaceutical issues that were raised during the evaluation of application have been resolved and all data provided gave assurance of the quality of the finished product.

III Clinical aspects

It is acceptable that specific studies have not been performed, as the application is submitted in accordance with article 10.1 of Directive 2001/83/EC-

Amlodipine was introduced into clinical medicine during the 1980s and is therefore a well-established medicinal product.

Pharmacotherapeutic group: Dihydropyridine derivatives. ATC code: C08CA01

III.1 Pharmacodynamic properties

Amlodipine is a calcium antagonist and inhibits the influx of calcium ions into cardiac and vascular smooth muscle. The mechanism of the antihypertensive is due to a direct relaxant effect on vascular smooth muscle. The precise mechanism by which amlodipine relieves angina has not been fully determined but the following two actions play a role:

Amlodipine dilates peripheral arterioles and thus, reduces the total peripheral resistance (afterload) against which the heart works. This unloading of the heart reduces myocardial energy consumption and oxygen requirements.

The mechanism of action also probably involves dilatation of the main coronary arteries and coronary arterioles. This dilation increases the supply in oxygen to myocardiac muscle in patients with Prinzmetal anginal attack.

III.2 Pharmacokinetic properties

Absorption/Distribution
After oral administration of therapeutic doses, amlodipine is slowly absorbed. Absorption of amlodipine is not influenced by concomitant food intake. Absolute bioavailability of the unchanged active substance is estimated to be 64-80%. Peak plasma levels are reached 6-12 hours after administration. The volume of distribution is approximately 20 l/kg. The pK_a of amlodipine is 8.6. *In vitro* studies have shown that amlodipine is bound to plasmatic proteins up to 98%.

Metabolism/Elimination
The plasma elimination half-life is about 35-50 hours. Steady-state plasma levels are reached after 7-8 consecutive days. Amlodipine is extensively metabolised to inactive metabolites. About 60% of the administered dose is excreted in the urine, of which 10% as unchanged amlodipine

III.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In animal studies with respect to the reproduction in rats at high doses delayed parturition, difficult labour and impaired foetal and pup survival were seen.

III.4 Bioequivalence

CLINICAL STUDIES TO ENSURE BIOEQUIVALENCE WITH BRAND LEADER

Assessment of bioavailability data
Brand leader: In Denmark the Brand Leader is Norvasc, Pfizer 5 mg and 10 mg tablets.
The reference product used in the study is the Brand Leader, Norvasc, Pfizer 10 mg tablets.

The test product used in the study is the 10 mg formulation. Differences in composition: The qualitative composition of the test product and the reference product is identical.

A dissolution study has been performed according to Ph. Eur. Comparative dissolution profiles for the 2.5 mg, 5 mg, 7.5 mg and 10 mg strengths and Pfizer tablets have been presented. All tested batches show a fast dissolution and a complete release within 30 minutes.

Pharmacokinetics:
The drug substance is administered as its active moiety, amlodipine. According to the brand leader SPC it is absorbed between 60% and 84%. In the Clinical Overall Summary reference is given to a review on amlodipine stating that amlodipine exhibits dose independent kinetics up to 10 mg. According to the SPC of the brand leader formulation the elimination t½ is between 35 hours and 50 hours. Amlodipine is extensively metabolised in the liver. 60% is excreted as metabolites and 10% as amlodipine through urinary excretion.

Number of studies: 1 study was performed.

Design:
The study was a single-dose, randomized, open-labelled, laboratory blinded, two-way crossover bioequivalence study conducted under fasting conditions with a wash out period of 21 days between the two administrations.

Data analysis:
Parameters reported or calculated:
Cmax,
Tmax,
AUC0-t,
AUC0-inf,
ke,
Residual area = AUC0-t * 100%/ AUC0-inf,
T½ = ln2/ke,
Frel % = AUC(test)* 100% /AUC(reference)

The parameters analysed were AUC0-t, AUC0-inf, Cmax, tmax.

Statistical analysis:
ANOVA were performed on the ln-transformed Cmax, AUC0-t and AUC0-inf.
Nonparametric test was carried out on tmax.

Results/ Discussion:
The study design is considered acceptable for this kind of formulation and for this kind of active substance. The residual area under the curve is below 20% cf. table above. It is considered justified only to perform a single dose study of the highest strength according to section 5.4 in the EU Guideline Note for Guidance on the Investigation of Bioavailability and Bioequivalence. A literature reference has been enclosed stating dose-independent pharmacokinetics up to 10 mg. The 90% log transformed confidence intervals are within the interval on 80-125% for Cmax, AUC0-t and AUC0-inf. The AUC0-inf is considered to be a secondary pharmacokinetic parameter.

Conclusion:
Pinohexal, Hexal A/S, 5 mg, 7.5 mg and 10 mg, are considered bioequivalent with Norvasc, Pfizer.

III.5 Discussion on the clinical aspects.

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

IV Overall conclusion, benefit/risk assessment and recommandation

The risk/benefit ratio is considered postive and Pinohexal tablets are recommended for approval

IV.1 Outstanding issues.

During the procedure, the applicant has made the following commitments:

- To provide process validation data on full scale batches.
- To provide the results of the microbial testing of the first 10 batches
- To provide certificate of analysis for full scale batches
- To provide results for microbiological quality at the end of shelf-life.
- To perform stability studies on the first three industrial scale batches of each strength and to provide results to authorities if requested.
- To re-evaluate the impurity limits when more stability data will be available.
- To include and provide a test for identification of amlodipine besilate in the finished product.