CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Alprazolam Hexal 0.25 mg, tablets
Alprazolam Hexal 0.5 mg, tablets
Alprazolam Hexal 1 mg, tablets
Hexal AG, Germany

alprazolam

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/1136/001-003/DC
Registration number in the Netherlands: RVG 100525, 100526, 100531

3 September 2009

Pharmacotherapeutic group:	benzodiazepine derivatives
ATC code:	N05BA12
Route of administration:	oral
Therapeutic indication:	symptomatic treatment of anxiety
Prescription status:	prescription only
Date of authorisation in NL:	14 October 2008
Concerned Member States:	Decentralised procedure with DE, PT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1) / Directive 2001/83/EC, Article 10(3)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Alprazolam Hexal 0.25/0.5/1 mg, tablets, from Hexal AG. The date of authorisation was on 14 October 2008 in the Netherlands.

The product is indicated for symptomatic treatment of anxiety. Alprazolam should only be used if the disorder is severe or is causing invalidity, or if the patient is experiencing inordinate suffering as a result of the disorder. The total length of treatment should not exceed 8-12 weeks.

A comprehensive description of the indications and posology is given in the SPC.

Alprazolam, like other benzodiazepines, has a high affinity for the benzodiazepine binding site in the brain. It facilitates the inhibitory neurotransmitter action of gamma-aminobutyric acid which mediates both pre- and post-synaptic inhibition in the central nervous system (CNS).
Alprazolam is an anxiolytic medicinal product. Like other Benzodiazepines, in addition to its anxiolytic properties, Alprazolam has sedative, hypnotic, muscle-weakening and anticonvulsive properties.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Xanax (NL RVG 14409 (0.25 mg) and 14440 (0.5 mg)) which has been registered in the Netherlands by Pfizer B.V. since 1990. In addition, reference is made to Xanax and Tafil authorisations in the individual member states (reference product).

Legal basis
The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC (generic application) and article 10(3) (hybrid application).
In the RMS the marketing authorisation for the 1 mg strength was granted based on article 10(3) of Directive 2001/83/EC, as the 1 mg strength of the innovator product Xanax was never authorised. In the CMS Germany the marketing authorisation for the 0.25 mg strength was granted based on article 10(3), as the 0.25 mg strength of the innovator product Tafil is not registered there.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. For this kind of application, it has to be demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the reference product. To this end the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the product is compared with the pharmacokinetic profile of the reference product Xanax 0.5 mg tablet, registered in the Netherlands. A bioequivalence study is the widely accepted means of demonstrating that difference of use of different excipients and different methods of manufacture have no influence on efficacy and safety. This generic product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products.

No paediatric development programme has been submitted.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is alprazolam, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is practically insoluble in water. Alprazolam exhibits polymorphism. The polymorphic form used by the MAH differs from the European Pharmacopoeia Chemical Reference Standard. The manufacturing process constantly yields the same polymorphic form which was shown to be stable during storage.

Manufacture
The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMEA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

The synthesis consists of three steps. The active substance was adequately characterized. Acceptable specifications were adopted for the starting materials, solvents, and reagents.

Quality control of drug substance
The drug substance specification is in line with the European Pharmacopoeia with additional requirements for physical parameters and residual solvents. The specifications are acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification were provided for two production scale batches. This was considered acceptable as additional batch analysis data of production scale batches was provided in the stability section.

Stability
Stability data on the active substance were provided for six production scale batches stored at 25°C/60% RH (60 (4 batches), 36, and 12 months) and for two production scale batches stored at 40°C/75% RH (6 months). The active substance remained stable under both conditions tested. The proposed re-test period of 60 months is justified. The active substance does not need to be protected from light.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Alprazolam Hexal 0.25 mg contains as active substance 0.25 mg of alprazolam, and is a white, oblong tablet with a score line and debossed "APZM 0.25".

Alprazolam Hexal 0.5 mg contains as active substance 0.5 mg of alprazolam, and is a pink, oblong tablet with a score line and debossed "APZM 0.5".

Alprazolam Hexal 1 mg contains as active substance 1 mg of alprazolam, and is a light blue, oblong tablet with a score line and debossed "APZM 1".

The tablets are packed in PVC/Aluminium-blister packs containing 10, 20, 30, 40, 50, 60 or 100 tablets.
The excipients are: docusate sodium, sodium benzoate (E211), pregelatinised starch (potato starch), microcrystalline cellulose (E460), lactose monohydrate, magnesium stearate (E572), colloidal anhydrous silica (E551), erythrosine aluminium lake (E 127) (only for 0. 5 mg), indigotine (E 132) (only for 1 mg).
The excipients and the quantities used are common in immediate release tablets. Except for the amount of lactose which is adapted to the amount of active substance and colouring agents, the amounts of excipients are identical in all three strengths. Other manufacturers of Alprazolam tablets used the same colouring agents for the 0.5 and 1 mg strengths. Problems with mixing up tablets of different strengths from different manufacturers are therefore not expected.

Pharmaceutical development
The development of the product was described, the choice of excipients was justified and their functions explained. The development focussed on obtaining a product which is essentially similar to the reference product. The conditions as described in the USP monograph on Alprazolam tablets were used. Comparative dissolution profiles at different pH values showed that more than 85% of both the test and the reference product were dissolved within 15 minutes and that the products can therefore be regarded as similar without further mathematical evaluation. The batch used in the bioequivalence study corresponded to a pilot scale batch. Dissolution of this batch was compared to production scale batches and again found to be similar due to rapid dissolution. Impurity profiles of the test and the reference product were comparable with slightly lower levels of the test product. The pharmaceutical development of the product was adequately performed.

Manufacturing process
The manufacturing process consists of wet granulation followed by compression. The product is manufactured using conventional manufacturing techniques. Due to the low amount of active substance (< 2%), the manufacturing process is regarded as non-standard. The manufacturing process was adequately validated according to relevant European guidelines. Process validation data on the product was presented for three production scaled 0.25 mg batches and four production scaled 0.5 mg batches. These batches were seen as representative for the 1 mg strength, as the composition of the excipients is identical except for a slightly lower amount of lactose monohydrate to compensate for the higher amount of active substance and the colouring agent.

Excipients
Except for the colouring agents, all excipients comply with the respective specifications of the European Pharmacopoeia. The colouring agents comply with the specifications for E127 and E132 as laid down in Directive 95/45/EC. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for appearance, mean weight, uniformity of mass of tablets divided into halves, disintegration time, friability, hardness, identification, assay, uniformity of dosage units, related substances, dissolution, microbial purity, and identification of colouring agents. The release and shelf-life limits differ with regard to assay and related substances. Due to an increase of related substances observed during stability studies, the lower limit of the assay was widened. The drug product specifications are acceptable. The analytical methods were adequately described. Validation data was provided for the HPLC methods for the assay and related substances. Batch analytical data from the proposed production site were provided on three production scale batches of each strength, demonstrating compliance with the release specification.
The tablets possess a score line which may be used to achieve the individual optimal dose. The uniformity of mass of the halves is tested according to section *Subdivision of tablets* of the Ph.Eur. monograph on tablets.

Stability tests on the finished product

Stability data on the product was provided for two pilot and two production scale batches of each strength stored at 25°C/60% RH (36 months) and stored at 30°C/65% RH (pilot scale batches: 18 months, production scale batches: 12 months). All batches including an additional three pilot scale batches were stored at 40°C/75% RH (6 months) as well. The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Aluminium/PVC blisters. At both intermediate and long term storage conditions, significant changes were observed. The active substance is not susceptible to light, but the colouring agents used are. This is the reason why the tablets should be stored protected from light. The proposed shelf-life of 36 months and storage condition "Do not store above 25°C, Keep the blister in the outer carton in order to protect from light" are justified.
The MAH committed to submit the results of the long term stability studies of a 1 mg batch after termination of the study or sooner if a significant change occurs.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

Lactose monohydrate is the only material of animal origin. A statement confirming compliance of lactose monohydrate with the criteria of the Note for Guidance on TSE/BSE (milk sourced from healthy animals under the same conditions as milk collected for human consumption) was provided. Magnesium stearate is of vegetable origin.

II.2 Non clinical aspects

No formal pre-clinical assessment was performed since alprazolam containing medicinal products have been marketed in many countries for many years and no new data was submitted. This is acceptable for this type of application.

Environmental risk assessment

The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of alprazolam released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal. Therefore, an environmental risk assessment is not deemed necessary.

II.3 Clinical aspects

Alprazolam is a well-known active substance with established efficacy and tolerability.

For this generic application, the MAH has submitted a bioequivalence study in which the pharmacokinetic profile of the test product Alprazolam Hexal 0.5 mg is compared with the pharmacokinetic profile of the reference product Xanax 0.5 mg, registered in the Netherlands.

The choice of the reference product

The choice of the reference product in the bioequivalence study has been justified by comparison of dissolution results and compositions of reference products in different member states (see also section "Pharmaceutical Development" on page 4).

Bioequivalence study

A open, single-dose, randomized, two-way crossover bioequivalence study was carried out under fasted conditions in 24 healthy male subjects, aged 18-35 years. Each subject received a single dose (= 2 tablets of 0.5 mg) of one of the 2 alprazolam formulations. The tablet was orally administered with 200 ml water after a 10 hour fasting period. There were 2 dosing periods, separated by a washout period of 17 days.
Blood samples were collected pre-dose and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 15, 24, 28 and 36 after administration of the products. All 24 subjects were eligible for pharmacokinetic analysis. Plasma samples were analysed for alprazolam content with an HPLC method in combination with UV-detection. The method was well validated and a validation report was provided, the bioanalytical method is adequate The statistical analysis is assessed and judged as being acceptable.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of alprazolam under fasted conditions.

Treatment N=24	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Test	202 ± 55	246 ± 89	16.3 ± 4.4	0.67 (0.33 - 3.0)	12.9 ± 3.9
Reference	210 ± 53	256 ± 90	15.5 ± 3.1	1.25 (0.33 - 4.0)	13.2 ± 4.3
***Ratio (90% CI)**	0.96 (0.92-0.996)	0.96 (0.92-1.00)	1.03 (0.95-1.12)	-	-
CV (%)	9.2	10	16	-	-

$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity
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 concentration
$t_{1/2}$ half-life

**ln-transformed values*

The 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are in agreement with those calculated by the MAH and are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the pharmacokinetic parameters of alprazolam under fasted conditions, it can be concluded that Alprazolam Hexal 0.5 mg and Xanax 0.5 mg are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

A biowaiver for the 0.25 mg and 1 mg strengths is allowed according to EMEA guideline if:

- pharmaceutical products are manufactured by the same manufacturer and process.
- drug input has shown to be linear over the therapeutic dose range.
- qualitative composition of the different strengths is the same.
- ratio between the amounts of excipients is similar for preparations containing a low concentration of active substance (less than 5%).
- dissolution profile should be similar under identical conditions for the additional strengths and the strength of the batch used in the bioequivalence study.

All these criteria are fulfilled. All batches meet the requirement of at least 85% release within 15 minutes. The total weight of the 0.25 and 1 mg tablets was equal compared with the 0.5 mg tablet. The different amount of active compound was compensated with lactose monohydrate Ph.Eur. Because the amounts of active compound are relatively small compared to the total weights of the tablets (less than 5%) and the ratios between the excipients are equal (except for lactose monohydrate Ph.Eur.), the lack of bioequivalence studies with the two other strengths is acceptable.
In conclusion, the results of the bioequivalence study with the 0.5 mg formulation can be extrapolated to the 0.25 and 1 mg strengths.

The MEB has been assured that the bioequivalence study has been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

Risk management plan

Alprazolam was first approved in 1980, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of alprazolam can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or postauthorisation, which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. Routine pharmacovigilance activities are

sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The content of the SPC approved during the decentralised procedure is in accordance (except for some administrative data) with the final product information for NL/H/355/01-03/R01, for which a renewal procedure was finalised.

Readability test
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. Two rounds of tests were performed with 11 randomly selected people in the first test and a further 12 new participants in the second part of the testing. Participants aged 19-70 years of age were recruited as either group can be affected by severe anxiety symptoms. The education of the participants was divided over several levels of education. Additionally, 13 participants did not use medicinal products at all, 4 one medicinal product, 4 two medicinal products, 2 three to four medicinal products.

A diagnostic and scoring readability testing was performed to test traceability and comprehensibility.
Fifteen questions were asked relating to the content of the PIL and 17 questions to the structure of the PIL. Questions were asked about several important parts (Indication/Contra-indication, some side effects/dosage/stopping treatment/use during lactation) of the leaflet.
Additionally the participants were asked to give their personal opinion of the final PIL.

Before testing the PIL was reviewed and amended in accordance with most recommendations made (mostly related to lay-out). Scoring concerning location of information was more than 90%. Scoring concerning comprehensibility was less but above 80%, except for one question in round 1. The information regarding one absolute contra-indication (severe liver insufficiency) was difficult to understand (score below 80%) in round 1. However, after the amendment of the PIL this was enhanced in round 2. It can be concluded that the PIL has been improved following testing. The problems found were reduced by amending the PIL. The readability test has been sufficiently performed.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Alprazolam Hexal 0.25/0.5/1 mg, tablets have a proven chemical-pharmaceutical quality and are generic forms of Xanax. Xanax is a well-known medicinal product with an established favourable efficacy and safety profile.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other alprazolam containing products.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Alprazolam Hexal 0.25/0.5/1 mg, tablets with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 12 August 2008. Alprazolam Hexal 0.25/0.5/1 mg were authorised in the Netherlands on 14 October 2008.

A European harmonised birth date has been allocated (12-3-1980) and subsequently the first data lock point for alprazolam is March 2010. The first PSUR will cover the period from August 2008 to March 2010, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 23 December 2010.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to submit the results of the long term stability studies of a 1 mg batch after termination of the study or sooner if a significant change occurs.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached