

**PUBLIC ASSESSMENT REPORT  
of the Medicines Evaluation Board  
in the Netherlands**

**Desmopressine-acetaat 0,1 TEVA, 0.1 mg tablets  
Desmopressine-acetaat 0,2 TEVA, 0.2 mg tablets  
Teva Pharma B.V., the Netherlands**

**desmopressin acetate**

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/1454/001-002/MR  
Registration number in the Netherlands: RVG 32002-32003**

**3 May 2010**

Pharmacotherapeutic group:	vasopressin and analogues
ATC code:	H01BA02
Route of administration:	oral
Therapeutic indication:	vasopressin-sensitive central diabetes insipidus; primary nocturnal enuresis (from 5 years of age), only after organic causes have been excluded.
Prescription status:	prescription only
Date of first authorisation in NL:	11 September 2006
Concerned Member States:	Mutual recognition procedure with AT, BE, BG, DE, DK, ES, IT, LU, PL, PT, RO, SI, SK, UK.
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

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 Desmopressine-acetaat 0,1 TEVA and Desmopressine-acetaat 0,2 TEVA, 0.1 mg and 0.2 mg tablets from Teva Pharma B.V. The date of authorisation was on 11 September 2006 in the Netherlands.

The product is indicated for:

- the treatment of vasopressin-sensitive central diabetes insipidus
- the treatment of primary nocturnal enuresis (from 5 years of age). The treatment of nocturnal enuresis should take place after organic causes have been excluded. Non-medicinal therapies are preferred.

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

Desmopressin acetate tablet contains desmopressin, a synthetic structural analogue of the natural human posterior pituitary gland hormone arginine-vasopressin.

Structural differences from vasopressin result in a significant elevation of the antidiuretic effect while the vasopressor effect is simultaneously and considerably reduced. In addition, the duration of action of the antidiuretic effect is considerably lengthened. Desmopressin is a powerfully active material with an EC50 of 1.6 pg/ml for the antidiuretic effect. A duration of action of 6 to 14 hours is to be expected after oral administration.

This mutual recognition procedure concerns a generic application claiming essential similarity with the innovator product Minrin 0.1 and 0.2 mg tableter which have been registered in Denmark by Ferring AB since 1972. In addition, reference is made to Minrin authorisations in the individual member states (reference product). In the Netherlands, Minrin 0.1 and 0.2 mg tablets have been registered since 7 February 1989 (NL License RVG 12624 and 12625).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

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 DDAVP 0.2 mg tablets, registered in the United Kingdom. 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, and no paediatric development programme has been submitted, as this is not required for a generic medicinal product.

## 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 desmopressin acetate, an established active substance described in the European Pharmacopoeia (Ph.Eur.\*). The drug substance is a white fluffy powder, which is soluble in water, in ethanol and in glacial acetic acid.

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/EMA 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.

#### Manufacturing process

Desmopressin is produced using a sequentially build-up program. A cyclization process leads to the crude desmopressin. After purification and desalting a lyophilisate is formed.

#### Quality control of drug product

The MAH has adopted the specification from the Ph.Eur. monograph and included some additional requirements for the residual solvents. The other specifications are acceptable in view of the various ICH guidelines. Batch analytical data demonstrating compliance with this specification have been provided for 4 batches.

#### Stability

Stability data on the active substance have been provided for up to 16 batches in accordance with applicable European guidelines. Based on these data, a re-test period of 24 months could be granted, with a storage condition of 2-8°C, when packed in the proposed packaging.

\* *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

Desmopressine-acetaat 0,1 TEVA contains as active substance 0.1 mg of desmopressin acetate, corresponding to 0.089 mg of desmopressin, and is a white, biconvex, oval tablet, debossed "D", scoreline and "0.1" on one side and plain on the other.

Desmopressine-acetaat 0,2 TEVA contains as active substance 0.2 mg of desmopressin acetate, corresponding to 0.178 mg of desmopressin, and is a white, biconvex, round tablet, debossed "D", scoreline and "0.2" on one side and plain on the other.

The tablets are packed in OPA/Alu/PVC-Aluminium blister packs and 30 ml white opaque PE bottles with a white opaque PP cap with desiccant and child-resistant closure.

The excipients are: lactose monohydrate, maize starch, povidone, pregelatinised starch, colloidal anhydrous silica, magnesium stearate.

Both tablets have the same quantitative composition, except a small difference in lactose to compensate for the small difference in active substance.

#### Pharmaceutical development

The qualitative composition of the reference product used in the biostudies and the reference products from 7 other EU countries was provided. The reference products and the product for registration have a comparable qualitative composition (in the products for registration starch and silica colloidal are added). The packaging materials used are common for tablets. Dissolution studies were performed, demonstrating equivalence between the reference product and the current products.

The pharmaceutical development of the product has been described in sufficient detail.

#### Manufacturing process of drug product

A description of the manufacturing process is given. The manufacturing process is a granulation process and consists of six steps. The process steps have been adequately presented. The equipment used is described sufficiently. A non-standard manufacturing process is used. Process validation data on the product have been presented for full-scale batches in accordance with the relevant European guidelines.

#### Control of excipients

All excipients comply with their Ph. Eur monographs. These specifications are acceptable.

#### Quality control of drug product

The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification, assay, uniformity of dosage units, dissolution, disintegration, related peptides and degradation products, microbial limit, thickness, resistance to crushing, friability, average tablet weight and residual ethanol. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from 3 batches of each strength have been provided, demonstrating compliance with the specification.

#### Stability tests on the finished product

The tablets were stored at 25°C/60% RH (24 months), 30°C/60% RH (12 months) and 40°C/75% RH (6 months). No out of specification results were observed during the stability studies; only at accelerated conditions assay is slightly decreasing. The claimed shelf life of 2 years could therefore be granted, with the labelled storage conditions *Do not store above 30°C, store in the original package*.

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

The only product of animal origin is lactose monohydrate, which is derived from milk and calf rennet. The milk is sourced from healthy animals in the same conditions as milk for human consumption. According to the EMEA public statement (EMEA/CPMP/571/02) on lactose prepared using calf rennet, a TSE Certificate of Suitability is not required. Therefore, it is acceptable that no such document was provided.

## **II.2 Non clinical aspects**

These products are generic formulations of Minrin tablets, which are available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. 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 desmopressin acetate 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.

### II.3 Clinical aspects

Desmopressin acetate 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 Desmopressine-acetaat 0,2 TEVA (Teva Pharma B.V., the Netherlands) is compared with the pharmacokinetic profile of the reference product DDAVP 0.2 mg tablets (Ferring Pharmaceuticals Ltd, UK).

#### *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.

The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing.

#### *Design*

An open-label, single-dose, randomised, two-period, two-treatment, two-sequence, two-way crossover bioequivalence study was carried out under fasted conditions in 40 healthy subjects (25 male/ 15 female), aged 18-49 years. Each subject received four 0.2 mg tablets (0.8 mg) of one of the 2 desmopressin formulations. The tablets were orally administered with 240 ml water after an overnight fast. There were 2 dosing periods, separated by a washout period of 7 days.

Blood samples were collected pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 3, 4, 6, 7.5, 9, 10.5, and 12 hours after administration of the products.

#### *Analytical/statistical methods*

The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

#### *Results*

Two subjects were removed from the study due to an elevated pulse rate prior to dosing in period 2 and due to difficult venipunctures in period 2. Data from 38 subjects were evaluated for pharmacokinetic analysis.

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

<b>Treatment N=38</b>	<b>AUC<sub>0-t</sub> pg.h/ml</b>	<b>AUC<sub>0-∞</sub> pg.h/ml</b>	<b>C<sub>max</sub> pg/ml</b>	<b>t<sub>max</sub> h</b>	<b>t<sub>1/2</sub> h</b>
<b>Test</b>	293 $\pm$ 198	293 $\pm$ 179 <sup>1</sup>	102 $\pm$ 96	1 (0.5-12.0)	2.7 $\pm$ 0.5
<b>Reference</b>	282 $\pm$ 143	307 $\pm$ 149 <sup>2</sup>	88 $\pm$ 50	1.0 (0.5-2.0)	2.9 $\pm$ 0.6
<b>*Ratio (90% CI)</b>	0.98 (0.85-1.13)	0.93 (0.83-1.05) (n=34)	1.04 (0.87-1.25)	-	-
<b>CV (%)</b>	37	29	50	-	-

**AUC<sub>0-∞</sub>** area under the plasma concentration-time curve from time zero to infinity  
**AUC<sub>0-t</sub>** area under the plasma concentration-time curve from time zero to t hours  
**C<sub>max</sub>** maximum plasma concentration  
**t<sub>max</sub>** time for maximum concentration  
**t<sub>1/2</sub>** half-life

<sup>1</sup> Extrapolation from AUC<sub>0-t</sub> to AUC<sub>0-∞</sub> was not possible for three subjects.

<sup>2</sup> Extrapolation from AUC<sub>0-t</sub> to AUC<sub>0-∞</sub> was not possible for two subjects.

*\*In-transformed values*

The 90% confidence intervals calculated for AUC<sub>0-t</sub>, AUC<sub>0-∞</sub> and C<sub>max</sub> 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 desmopressin under fasted conditions, it can be concluded that Desmopressine-acetaat 0,2 TEVA and DDAVP 0.2 mg tablets are bioequivalent with respect to rate and extent of absorption, and fulfil the bioequivalence requirements outlined in the relevant CHMP Note for Guidance.

#### *Food interaction*

Desmopressin should be taken without reference to food intake. From the literature it is known that food interacts with the absorption of desmopressin. The SPC clearly states that simultaneous use of food delays the speed and degree of desmopressin absorption by approximately 40%. No food interaction study is not deemed necessary. The bioequivalence study under fasting conditions is in accordance with CPMP/EWP/QWP/1401/98 Note for Guidance on the investigation of bioavailability and bioequivalence.

#### *Extrapolation of results*

The two dosage strengths are manufactured with the same process and the same ingredients, the amounts of active substance of 0.1 mg versus 0.2 mg desmopressin being the only difference. The amount of desmopressin constitutes less than 5% of the table weight. Desmopressin pharmacokinetics is linear. Therefore, the conclusion of bioequivalence also applies to 0.1 mg tablet.

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

Desmopressin was first approved in 1972, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of desmopressin 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**

##### 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. The test consisted of a pilot test, followed by two rounds with 10 participants each. The questions covered the key safety issues sufficiently.

The leaflet passed the user test criteria. However, an open question about difficult parts of the text revealed in both rounds that amendments could be made in order to clarify the part in the PIL about the use in children. Formatting changes were made and one more round with 10 participants was conducted to check for effectiveness of the amendments made. The criterion of 81% was met and overall, the user test was conducted in an acceptable manner.

During the mutual recognition procedure, the PIL underwent some significant revisions. The use of headings and sub-headings was amended and standard terminologies as per QRD template were included. Also, consistency with the SPC was established. In view of these changes, the MAH made the commitment to re-conduct the user testing.

### III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Desmopressine-acetaat 0,1 TEVA and Desmopressine-acetaat 0,2 TEVA, 0.1 mg and 0.2 mg tablets have a proven chemical-pharmaceutical quality and are generic forms of Minrin 0.1 and 0.2 mg tablets. Minrin 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 desmopressin containing products.

The Board followed the advice of the assessors. Desmopressine-acetaat 0,1 TEVA and Desmopressine-acetaat 0,2 TEVA were authorised in the Netherlands on 11 September 2006.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The concerned member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Desmopressine-acetaat 0,1 TEVA and Desmopressine-acetaat 0,2 TEVA with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finished on 7 November 2008.

The PSUR submission cycle is 3 years. The first PSUR will cover the period from November 2008 to November 2011.

The date for the first renewal will be: 6 September 2011.

The following post-approval commitment has been made during the procedure:

Readability test

- The MAH committed to submit a new user test on the revised PIL.



## 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 <sub>max</sub>	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 <sub>1/2</sub>	Half-life
t <sub>max</sub>	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
Addition of pack size of 10 tablets.	NL/H/1454/001/IA/001	IA	27-1-2009	10-2-2009	Approval	N
Addition of pack size of 10 tablets.	NL/H/1454/002/IB/002	IB	27-1-2009	26-2-2009	Approval	N