

**DDAVP MELT 60 MICROGRAMS ORAL LYOPHILISATE (DESMOPRESSIN ACETATE)
PL 03194/0091**

**DDAVP MELT 120 MICROGRAMS ORAL LYOPHILISATE (DESMOPRESSIN ACETATE)
PL 03194/0092**

**DDAVP MELT 240 MICROGRAMS ORAL LYOPHILISATE (DESMOPRESSIN ACETATE)
PL 03194/0093**

**DESMOMELT 120 MICROGRAMS ORAL LYOPHILISATE (DESMOPRESSIN ACETATE)
PL 03194/0094**

**DESMOMELT 240 MICROGRAMS ORAL LYOPHILISATE (DESMOPRESSIN ACETATE)
PL 03194/0095**

UKPAR

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**DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0091, PL03194/0092, PL 03194/0093**

**DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0094, PL 03194/0095**

LAY SUMMARY

The MHRA granted Ferring Pharmaceuticals Limited Marketing Authorisations (licences) on the 19th January 2006, for the following medicinal products:

DDAVP Melt 60 micrograms oral lyophilisate (PL 03194/0091)
DDAVP Melt 120 micrograms oral lyophilisate (PL 03194/0092)
DDAVP Melt 240 micrograms oral lyophilisate (PL 03194/0093)
DesmoMelt 120micrograms oral lyophilisate (PL 03194/0094)
DesmoMelt 240 micrograms oral lyophilisate (PL 03194/0095)

These prescription only medicines (POM) are anti-diuretics, used to treat extreme thirst and continuous production of large volumes of dilute urine (diabetes insipidus), extreme thirst and continuous production of large volumes of dilute urine following surgical removal of the pituitary gland and also in the treatment of bed-wetting. Oral lyophilisates are placed under the tongue where they dissolve completely and are recommended in patients who do not like swallowing tablets and in situations where water consumption is to be avoided.

DDAVP Melt oral lyophilisates and DesmoMelt oral lyophilisates contains the active ingredient desmopressin (as the acetate), which works by acting on the kidneys to increase urine concentration and decrease urine production.

The clinical data presented to the MHRA, pre licensing, demonstrated that DDAVP Melt oral lyophilisates and DesmoMelt oral lyophilisates are equivalent to the approved products, DDAVP tablets (PL 03194/0040-41) and DESMOTABS tablets (PL 03194/0046) and, as such, can be used interchangeably.

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking DDAVP Melt 60, 120 & 240 micrograms oral lyophilisate and DesmoMelt 120 & 240 micrograms oral lyophilisate outweigh the risks, hence Marketing Authorisations have been granted.

**DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0091, PL03194/0092, PL 03194/0093**

**DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0094, PL 03194/0095**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy the UK granted marketing authorisations for the following medicinal products:

DDAVP Melt 60 micrograms oral lyophilisate (PL 03194/0091)
DDAVP Melt 120 micrograms oral lyophilisate (PL 03194/0092)
DDAVP Melt 240 micrograms oral lyophilisate (PL 03194/0093)
DesmoMelt 120micrograms oral lyophilisate (PL 03194/0094)
DesmoMelt 240 micrograms oral lyophilisate (PL 03194/0095)

to Ferring Pharmaceuticals Limited on 19th January 2006. The products are prescription only medicines.

The applications were submitted as abridged applications according to article 8.3(i) of Directive 2001/83/EC as amended, a complete application of a known active substance. These applications are considered line extensions on the basis of a new pharmaceutical form. The oral lyophilisates also differ from the existing products in having different pharmacokinetic characteristics. These applications have been demonstrated to be essentially similar or equivalent to the approved products, DDAVP tablets (PL 03194/0040-41) and DESMOTABS tablets (PL 03194/0046).

The products contain the active ingredient desmopressin (as the acetate) and are indicated in the treatment of vasopressin-sensitive cranial diabetes insipidus, in the treatment of post-hypophysectomy polyuria/polydipsia and in the treatment of primary nocturnal enuresis.

Desmopressin is an analogue of an antidiuretic hormone (vasopressin) and has a more potent and prolonged duration of action, and decreased pressor activity.

These applications for DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate and DesmoMelt 120 and 240 micrograms oral lyophilisate were submitted at the same time and were assessed simultaneously. Consequently, all sections of this Scientific Discussion refer to all products.

PHARMACEUTICAL ASSESSMENT

1. INTRODUCTION

These are abridged applications for Marketing Authorisation in the UK submitted under Article 8.3(i) of Directive 2001/83 (as amended), a complete application of a known active substance. These are considered line extensions on the basis of a new pharmaceutical form, and change of pharmacokinetics.

2. DRUG SUBSTANCE

General information

A Certificate of Suitability (R0-CEP 2000-142-Rev 01) granted 15th March 2002, has been supplied, with permission for use with desmopressin products.

The re-test date on the certificate of suitability is 24 months when stored between 2°C and 8°C in a HDPE container with a polypropylene screw cap placed in an aluminium foil bag. Certificates of analysis have been provided for three batches tested at the active substance manufacturer's laboratories.

Control of drug substance

Specification

The specifications provided by the active substance manufacturer for desmopressin acetate are satisfactory. These include the requirements of the European Pharmacopoeia. The specifications are taken from the manufacturers certificate of analysis.

The residual solvent limits are those stated on the certificate of suitability.

Upon receipt of new batches the finished product manufacturer determines appearance and identification by IR, in conjunction with the certificate of analysis from the supplier. This approach is acceptable.

Container closure system

There are no details of the container closure system used for desmopressin acetate. Reference is made to the certificate of suitability.

Stability

Stability has been performed on three batches at long term and accelerated conditions. The packaging used was small replicas of the commercial packaging materials.

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

After 18 months at both conditions the batches remain in specification.

A recommendation has been made for a re-test period of 24 months when the product is stored in a refrigerator with the container tightly closed and the foil bag being re-sealed after opening. The active substance manufacturer set a retest period of 12 months when stored in original packaging. This is in compliance with the certificate of suitability.

DRUG PRODUCT

Composition

The qualitative composition of the products is summarised in table 1. The products are oral lyophilisate. The products are packed in blisters consisting of a 5 layer aluminium bottom foil and a laminated aluminium lid foil.

Table 1

| Name of Ingredients | Reference |
|----------------------------|------------------|
| Desmopressin* | Ph Eur |
| Gelatin | Ph Eur |
| Mannitol | Ph Eur |
| Citric acid | Ph Eur |

Each unit contains desmopressin acetate equivalent to 60, 120 or 240 micrograms of desmopressin free base respectively.

Pharmaceutical Development

Formulation development

Compatibility of desmopressin acetate with the excipients is cross referred to the stability studies conducted during formulation development. The excipients used are gelatin, mannitol and citric acid which are widely used excipients in pharmaceutical products. The gelatin and mannitol form the matrix and structure of the product. Citric acid is used to modify pH as desmopressin is stable at low pH with an optimal at around pH 5.

Purified water is used to form a solution of the desmopressin and excipients, and is then removed from the product during the freeze drying process.

The dosage form is a technology already used in commercially available products.

The optimisation demonstrated that the amount of gelatin in the unit was fundamental in the production of a suitable appearance and disintegration time. The overall amount of excipients in the formulation was also deemed to be important for mouthfeel. Products were made using 30, 60, 120, 240, 360 and 480µg desmopressin. These were produced at bench scale. The physical properties of the units at the lowest and highest strengths were comparable and acceptable.

Water uptake of the product was investigated using dynamic vapour sorption (DVS) and Karl Fischer.

Manufacture

Batch formula

The batch formula has been supplied. The actual amount of desmopressin acetate used is dependent on the potency of the substance.

Manufacturing process and process controls

A flow diagram detailing the manufacturing process and in-process control testing has been provided for the different strengths. A written summary of the process has also been included.

Control of critical steps (in-process controls)

Acceptance criteria and methods have been supplied for the process parameters identified as critical steps.

Process validation or evaluation

Verification of the process parameters has been conducted during the development stage at pilot scale. Three batches were manufactured with the dose strengths 60, 240 and 360µg.

The data provided demonstrates a controlled process at the pilot scale with many of the elements of validation being investigated.

An acceptable process validation protocol has been provided. Full details are provided on the sampling plan. On completion of validation the batches are tested to the finished product specification.

The manufacturing process is considered to be a standard process. As the product has been demonstrated to be a homogeneous solution there are no issues with content uniformity.

Data has been presented for consecutive three batches of the 60µg and 120µg products. The quality of the product throughout batch manufacture has been demonstrated on appearance, weight uniformity, composite assay and dry dose weight. All batches also satisfied the release specification.

Control of excipients

Specification

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Gelatin, mannitol, citric acid and purified water have monographs in the European Pharmacopoeia. Certificates of analysis have been provided from the excipient manufacturers and the finished product manufacturer.

Appropriate documentation regarding sourcing has been supplied for the gelatin.

The finished product manufacturer tests all new batches of gelatin to the full pharmacopoeia monograph. The citric acid and mannitol are assessed on appearance and identification by FT-IR.

The purified water is produced on site. On a weekly basis the water is assessed in-line with the pharmacopoeia monograph, on a daily basis the tests for appearance, oxidisable substances and conductivity are performed.

Control of drug product

Specification

The finished product specifications for the product have been provided and are satisfactory.

Analytical procedures

The methods for disintegration, uniformity of mass, water content and microbiological quality are those described in the European Pharmacopoeia. The chromatographic method used for identity, assay and determination of degradation products has been provided.

Validation

The HPLC method for identification, assay and related impurities has been validated. The method has precision and accuracy. Specificity and robustness have been shown pH was shown to affect resolution. As the resolution is checked under system suitability the pH is considered to be under control.

The microbiology methods used to assess the quality of the product have been validated.

Batch analyses

Batch analyses have been provided for four batches of the 60µg, one batch of the 120µg and three batches of the 240µg. These are all pilot scale. It is argued that the data supplied provides assurance on the quality of all strengths as the ratio between excipients and active substance do not influence stability. This is an acceptable approach. All batches remain within specification and show a reasonable degree of conformity across the batches and strengths. From the results presented the chemical and microbiological purity appears to be well controlled with values well below the limits.

Container closure system

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Blister pack with ten cavities. The cavities are debossed in order to identify different strengths.

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester terephthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 10, 30 and 100 oral lyophilisates.

To distinguish between strengths the 60µg has one drop, the 120µg has two drops and the 240µg has three drops.

The foils are tested for description, identification (IR) and dimensions.

Reasonable specifications have been provided and are tested in full by the finished product manufacturer on receipt of new batches.

Certificates of analysis have been supplied by the packaging manufacturer of the foils.

Relevant certification on compliance with regulations on contact food stuffs have been supplied.

Stability

Three stability studies are presently ongoing.

The stability data presented fundamentally stays within specification. There are a few values for assay which exceed the limit. In each case the initial value is within specification as is the value at the next time point. This would not be considered to be a point of issue as the process has not yet been fully validated at production scale. The values determined for the related impurities are well below the specifications in the finished product specification. Though it remains in specification there appears to be a rise in the disintegration time.

The increase in disintegration time seen during stability is a consequence of different analysts as the melt disintegrates instantly. The methodology of assessment is being harmonised.

The applicant is proposing a shelf life of 24 months without any special precautions for storage. Two environmental conditions have been determined to be points of issue these are light and humidity. It is considered that the foil blister package provides adequate protection. The data presented supports the proposed shelf-life.

An acceptable post approval stability commitment has been supplied for the first three production scale batches.

Other information

Bioanalytical methods

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Desmopressin plasma concentrations were determined by the finished product manufacturer by a validated method using solid phase extraction and Radio Immuno Assay. The method and validation report have been provided.

Bioavailability

The study was an open, randomised, balanced, four-way cross-over design in healthy non-smoking volunteers. The doses investigated were 200µg, 400µg and 800µg of the oral lyophilisate and 2µg as an IV bolus..

Sample were taken at specified timepoints. Twenty four subjects were enrolled in the study. Data were analysed for all 24 subjects.

The absolute bioavailability was estimated to 0.26%, 0.30% and 0.29% for the 200µg, 400µg and 800µg respectively. The overall pooled estimate of absolute bioavailability was 0.28% (0.23%-0.34%). Linearity was not properly demonstrated due to the high variability observed.

For assessment of this study see the medical assessment report.

Bioequivalence

The study was not a bioequivalence study as the molar dose of the two products was different. However the standard bioequivalence criteria was applied to demonstrate similarity.

The study was an open-labelled, randomised, 2 period crossover study in non-smoking healthy volunteers. The comparison was between 240µg desmopressin oral lyophilisate and 2x200µg of the marketed desmopressin tablet (Minrin). (Note: the oral lyophilisate is labelled as the free base and the marketed product is labelled as the amount of the salt, though both products contain desmopressin acetate).

Twenty eight subjects were enrolled in the study. Data was analysed for all 28 subjects.

Samples were taken predose and at specified timepoints during the study.

Similarity was determined using the 90% confidence interval of the relative mean AUC 0-t, AUC ∞ and Cmax of the test to reference formulation which should be 80% to 125%.

The batch of Desmopressin 240 microgram oral lyophilisate is at least 1/10 of the proposed maximum batch size.

The 90% confidence intervals for the ln-transformed pharmacokinetic parameters were

| | |
|--------------|----------------------|
| AUC 0-t | 102.04% (87% - 121%) |
| AUC ∞ | 102.36% (86% - 121%) |
| Cmax | 86.73% (73% - 103%) |

The mean t_{max} values for Desmopressin 240microgram oral lyophilisate and Minrin 0.2mg tablets (x2) were 1.0 and 1.5 hours respectively.

The confidence intervals derived for AUC_{0-t} and AUC_∞ are within the 80% to 125% acceptance range of the Notes for Guidance on Bioavailability and Bioequivalence.

The C_{max} is marginally outside the limits 80% to 125%. This is explained by the low oral bioavailability of demopressin which is quoted as being 0.16% from the tablets. As a consequence large variations can be seen in C_{max}.

For assessment of this study see the medical assessment report.

Essential similarity

The doses selected for the oral lyophilisates are based on the conclusion of similarity between 240µg sublingually and the 400µg orally. They have related the 240µg, 120µg and 60µg oral lyophilisate to 400µg, 200µg and 100µg tablets respectively.

Dissolution data have been presented for the 30µg and 480µg development products and show rapid dissolution of the product.

PRODUCT LITERATURE

SPC

The pharmaceutical parts of the SPC are in compliance with the quality part of the dossier and the SPC guideline.

PIL

The PIL is in compliance with the relevant guidelines and SPC.

LABEL

The label is in compliance with the relevant guidelines and the SPC.

ADMINISTRATIVE

MAA form

Acceptable.

Quality Overall Summary

The summary has been done by a suitably qualified person. The report is a summary of the module.

CONCLUSIONS AND ADVICE

A marketing authorisation can be granted.

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

PRECLINICAL ASSESSMENT

Although this pre-clinical report only specifically mentions PL 03194/0091 and PL 03194/0094, it also applies to PL 03194/0092, PL 03194/0093 and PL 03194/0095, which are additional strengths of the same product.

I INTRODUCTION

These are abridged complex national applications for DDAVP Melt 60 micrograms oral lyophilisate and DesmoMelt 120 micrograms oral lyophilisate, submitted by Ferring Pharmaceuticals Limited (UK) under Article 8.3(i), known active substance, of Council Directive 2001/83/EC. They are line extensions of DDAVP® Tablets 0.1 mg (PL 03194/0040) and DESMOTABS® 0.2 mg (PL 03194/0046) respectively and contain the same active ingredient, desmopressin (as the acetate). This report will cover both PLs.

The products are oral lyophilisates containing the well-established active ingredient desmopressin (as the acetate) that are designed to disperse rapidly in the mouth. Desmopressin acts as an antidiuretic and has been used in the proposed indications in other pharmaceutical forms. The oral lyophilisates also differ from the existing products in having different pharmacokinetic characteristics. DDAVP Melt is intended for the treatment of vasopressin-sensitive cranial diabetes insipidus or of post-hypophysectomy polyuria and polydipsia. It is recommended that the dosage should be individualised but the total daily sublingual dose usually ranges between 120 µg and 720 µg. For the majority of patients, the maintenance dose is 60 µg to 120 µg three times daily. DesmoMelt is indicated for the treatment of primary nocturnal enuresis. The standard dose is 120 µg at bed-time and should only be increased if needed to 240 µg. A dose of 60 µg is equivalent to 1 µg/kg in a 60 kg adult and 720 µg is equivalent to 12 µg/kg. A dose of 120 µg is equivalent to 6.7 µg/kg in a child weighing 18 kg.

Because the active ingredient is well known, the nonclinical programme consisted of only a local tolerance study in hamsters; the nonclinical overview concentrates on this. No discussion of the literature on desmopressin has been included.

Good Laboratory Practice (GLP) aspects

The local tolerance study in hamsters was GLP-compliant.

II PHARMACODYNAMICS / PHARMACOKINETICS / TOXICOLOGY

Desmopressin is 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate, trihydrate. It is an analogue of antidiuretic hormone (vasopressin) and has a more potent and prolonged duration of action, and decreased pressor activity. Desmopressin is a
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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

nonapeptide, and differs from the natural hormone in position 1 where it is deaminated, and in position 8 where L-arginine is replaced by D-arginine.

The actions of desmopressin have been characterised in previous submissions and will not be recapitulated here. The drug has been on the market for approximately forty years. The absence of new pharmacology and pharmacodynamic studies was justified on this basis.

II.1 Pharmacokinetics

No pharmacokinetic studies were conducted in animals but bioavailability data in humans are discussed in the Clinical Overview. The bioavailability with oral lyophilisates has been shown to be greater than that from standard tablets.

II.2 Toxicology

The local tolerance of the sublingual tablets was investigated in three groups of hamsters dosed daily for 28 consecutive days.

It was concluded that there were no signs of local irritation following treatment with the oral lyophilisate.

III EXCIPIENTS / IMPURITIES / RESIDUAL SOLVENTS

The excipients are all commonly used in oral formulations and comply with the European Pharmacopoeia.

Assessor's comment

The absence of standard preclinical studies is acceptable. The local tolerance study, although conducted in small numbers of animals and at low doses relative to the clinical dose, provides reassurance that it is unlikely that the oral lyophilisates will cause any irritation or local reaction, given the short the duration of exposure. There were no reports of local irritation in the clinical overview of safety.

IV NONCLINICAL OVERVIEW

The Nonclinical Overview was written by an appropriately qualified person. It contains a brief but adequate review of the data.

V SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Sections 4.6 and 5.3 of the SPC are identical to those for DDAVP Tablets 0.1 mg (PL 03194/0040) and DESMOTABS® 0.2 mg (PL 03194/0046).

VI CONCLUSION

This application has not revealed any evidence of untoward toxicity with DDAVP Melt 60 micrograms and DesmoMelt 120 micrograms, beyond the known effects of desmopressin and adequate warnings are proposed.

CLINICAL ASSESSMENT

INTRODUCTION

Type of Application and aspects on development

These are complex abridged complete applications, submitted under Article 8.3(i) of Directive 2001/83/EC. They are for DDAVP and DESMOMELTS which are line-extensions of the DDAVP 0.1 and 0.2 mg tablets, PL 03194/0040-41, and DESMOTABS 0.2mg tablets (PL 03194/0046) involving the known active substance, desmopressin (as the acetate).

DDAVP and DESMOMELTS contain an oral lyophilisate of desmopressin (60, 120 or 240µg desmopressin for the former and 120 or 240µg, for the latter). Each unit also contains gelatine, mannitol and citric acid buffer. The lyophilisate is designed to disperse rapidly in the mouth and is therefore suitable for sublingual administration.

Desmopressin is a synthetic analogue of the pituitary hormone, arginine vasopressin. The difference lies in the desamination of cysteine and substitution of L-arginine by D-arginine. This results in a considerably longer duration of action and a complete lack of pressor effect in the dosages used.

For simplicity, hereafter, the sublingual lyophilisate (DDAVP and DESMOMELT) is referred to simply as the "MELT".

NB: The oral tablet dose is defined according to the amount of desmopressin acetate, whereas for the proposed MELT the amount of desmopressin is specified according to the free base. The following formula is applied to the oral tablets:

$$\text{Dose of desmopressin free base} = \text{dose of desmopressin acetate} \times 0.89$$

Thus 400µg (2 x 200µg) of the oral tablet (reference product in the bioequivalence study CS020; see below) provides 356µg of the free base.

Modules 2 and 5 are identical for all 5 applications.

Rationale for development

Desmopressin is a chemically stable peptide with low oral bioavailability (around 0.16%) which leads to variability in absorption and a food-effect. The aim of these sublingual line-extensions is to produce an improved oral formulation of desmopressin which, in contrast to the currently marketed products, can be taken without water. The Applicant claims this would be desirable given:

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

- The mode of action of the drug (antidiuretic) - which is an advantage as it is preferable that water consumption is avoided in relation to the administration of an antidiuretic drug.
- The fact that many children and some adults prefer not to have to swallow tablets hence compliance may be improved

Proposed indications

These correspond with the respective tablet formulations:

- DDAVP MELT 60, 120 or 240µg - treatment of vasopressin-sensitive cranial diabetes insipidus or in the treatment of post-hypophysectomy polyuria/polydipsia
- DESMOMELT 120 and 240µg - treatment of primary nocturnal enuresis

Proposed Posologies (extracted from the proposed SPCs)

DDAVP MELTS 60, 120 and 240micrograms

Treatment of diabetes insipidus:

Dosage is individual in diabetes insipidus but the total daily sublingual dose normally lies in the range of 120 micrograms to 720 micrograms. A suitable starting dose in adults and children is 60 micrograms three times daily, administered sublingually. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 60 micrograms to 120 micrograms sublingually three times daily.

Post-hypophysectomy polyuria/polydipsia:

The dose of DDAVP Melt should be controlled by measurement of urine osmolality.

DESMOMELT 120 and 240 micrograms

Children (from 5 years of age) and adults (up to 65 years of age) with normal urine concentrating ability who have primary nocturnal enuresis should take 120 micrograms at bedtime administered sublingually and only if needed should the dose be increased to 240 micrograms sublingually.

The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without DesmoMelt.

Clinical Development

The Application is supported by PK data comparing the MELT with the licensed tablets.

Originally two studies were submitted (CS004 and CS020). The applicant supplied data from two further studies, CS019 and CS021 conducted after the dossier was originally submitted, to adequately address dose proportionality.

MAIN DOSSIER

The two pharmacokinetic studies submitted in the main dossier are summarised in Table 1.

Table 1:

| Study No | Title | Treatment/doses | No. of subjects |
|--|---|--|------------------------|
| CS004 [DOSE- PROPORTIONALITY AT HIGHER DOSES] | Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy, non-smoking, volunteers | 200, 400 and 800µg MELT IV bolus desmopressin 2µg | N=24 |
| CS020 [PILOT BIOEQUIVALENCE STUDY] | Open-label, randomised, two- period, cross-over study investigating the relative bioavailability of two single doses of the currently marketed MINIRIN tablet (2x200µg) and a single dose of desmopressin administered as a new sublingual tablet (240µg) | 400µg MINIRIN Tablets (2 x 200µg) 240µg MELT | N=28 |

In response to dose proportionality issues, data from the following two additional studies were subsequently submitted:

SUPPLEMENTAL DATA – New Studies Received after the Main Dossier was Filed

| Study No | Title | Treatment/doses | No. of subjects |
|--|--|--|-----------------------------|
| CS019 [DEFINITIVE BIOEQUIVALENCE STUDY] | An open-label, replicated, randomised, cross- over study, with four periods and two sequences investigating the bioequivalence of a single dose of MINIRIN Tablets | 400µg MINIRIN Tablets (2 x 200µg) 240µg MELT | N=65 (32male; 33 female) |

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

| | | | |
|---|--|----------------------------|-------------------------|
| CS021 [DOSE- PROPORTIONALITY AT LOWER DOSES] | (2 x 0.2mg) and a single MINIRIN Melt (240µg) dose of desmopressin administered sublingually A three-period crossover study comparing the exposure of oral lyophilisates containing 60, 120 and 240 µg desmopressin in 24 healthy non- smoking subjects | 60, 120 and 240 µg MELT | N=24 (male & female) |
|---|--|----------------------------|-------------------------|

GCP aspects

The clinical studies complied with GCP and the Declaration of Helsinki.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Introduction

The Clinical Expert has given a full overview of the PK of desmopressin.

The studies supporting this application are discussed below:

FROM THE ORIGINAL DOSSIER

Study CS004

TITLE: Absolute bioavailability of three different doses of desmopressin in an orodispersible tablet in healthy non-smoking volunteers

This was a single-centre, open-label, randomised, balanced (6:6:6:6), four-way crossover Phase I study conducted between 30th Jan and 8th March 2002.

The objectives were as follows:

- 1°:** to investigate the absolute bioavailability of desmopressin administered as a fast orodispersible tablet of 200, 400 and 800µg (hereafter described as the ‘MELT’).
- 2°:**
- to investigate the pharmacokinetics of desmopressin administered as a 200, 400 and 800µg MELT.
 - To investigate safety and tolerability of desmopressin administered as a fast, orodispersible, tablet.

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

The subjects were healthy, non-smoking subjects.

Each subject was randomised to receive 200, 400 and 800 µg of desmopressin base in an orodispersible tablet (MELT) and 2 µg as an IV bolus. An adequate 72 hour washout period separated doses.

Blood samples were collected at specified timepoints.

1° Endpoints

F, AUC, Cmax and tmax

2° Endpoints

AUCt, CL (IV dose), CL/F (MELT), Vz (IV), Vz/F (MELT).

Safety parameters – see Safety Section, IV.

- **Analytical methods**

Desmopressin plasma concentrations were determined by a validated method. Details of the methodology are given in the Summary of Biopharmaceutic studies.

- **Pharmacokinetic data analysis**

24 subjects were planned and analysed. All PK parameters were analysed for the ITT analysis set and per protocol (PP) analysis set to investigate the influence of the outliers observed and described in the Statistical Analysis Plan.

The following pharmacokinetic parameters were derived and were assessed by non-compartmental methods:

F, AUC, Cmax, t max, AUCt, CL(IV), CL/F (orodispersible tablet), V2 (IV), V2/F (orodispersible tablet), λ_z , $t_{1/2}$

Where F=absolute bioavailability; λ_z = first-order rate constant associated with the terminal (log-linear) portion of the plasma concentration-time curve estimated via linear regression of the time vs. log concentration; AUCt = area under the plasma concentration-time curve from time zero up to time t, where t is the last time point at which the subject shows concentrations above the lower limit of quantitation [time of last measurable (non-zero) concentration (tlast)]; AUC=area under the plasma concentration-time curve to infinity.

- **Statistical analysis**

No formal sample size calculation was performed, but 24 subjects were considered sufficient to distinguish between doses of the MELT.

Analyses were conducted on the ITT (Intent-to-Treat) and PP (Per-Protocol) data sets to investigate the influence of outliers as described in the Statistical Analysis Plan. The PP analysis was considered as primary.

The average absolute bioavailability and 95% CI were estimated for each dose of MELT. Linearity between dose of MELT and AUC was investigated using ANOVA. Furthermore, log-transformed data of AUC and Cmax were compared between doses of the MELT by pairwise one-sample t-tests. All other PK parameters were presented using descriptive statistics and no formal statistical testing was performed.

Safety is discussed in section IV. Descriptive statistics were used.

- **Results and conclusions**

After I.V. administration the volume of distribution at steady-state (V_{ss}) was 29.7 l (geometric mean). Clearance was 8.5 l/h and t_{1/2} was 2.8 h (geometric mean).

From the primary PP analysis:

Absolute bioavailability was 0.26%, 0.3% and 0.29% after 200, 400 and 800 µg, respectively. The overall pooled estimate of absolute bioavailability was 0.28% (0.23%-0.34%) for the MELT. AUC and C_{max} increased significantly with dose of the MELT. High variability was observed for AUC and C_{max} and it increased with dose (AUC: %CV of 46.9, 48.3 and 85.5 for 200, 400 and 800 µg, respectively). Linearity between the MELT and AUC could not be formally demonstrated because of the variability, as no (equivalence) limit was pre-specified. As can be seen from Figure 1 the variability was relatively high but a clear trend was shown and a slope of 1.10 [0.94-1.26] indicates linearity.

C_{max} for the MELT was observed 0.5 – 2.0 h after dosing. T_{max} was 14.25, 30.21 and 65.25 pg/ml after sublingual doses of 200, 400 and 800µg, respectively. t_{1/2} was 2.8-3.0 h.

The ITT analysis showed similar results for AUC and C_{max}. However, variability was less for 200 and 400µMELT due to the exclusion of two outliers.

The PP analysis, based on PK parameters, showed that the overall pooled estimate of absolute bioavailability was 0.28% [0.23% - 0.34%] for desmopressin administered as the MELT. AUC and C_{max} increased proportionally with dose over the range tested i.e. 200 to 800µg.

The most important PK parameters are tabulated below (Table 2):

Table 2. Summary of PK parameters – desmopressin MELT

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

| Parameter | Unit | 200µg MELT | | 400µg MELT | |
|-----------|---------|----------------|----------|----------------|------------|
| | | Geometric mean | 95% CI | Geometric mean | 95% CI |
| AUC | h*pg/ml | 64 | 52-78 | 150 | 122-184 |
| AUCt | h*pg/ml | 47 | 36-60 | 119 | 86-164 |
| Cmax | pg/ml | 14 | 11-18 | 30 | 23-41 |
| Tmax | h | 1.5† | 0.5-2.0† | 1.0† | 0.75-2.0†† |

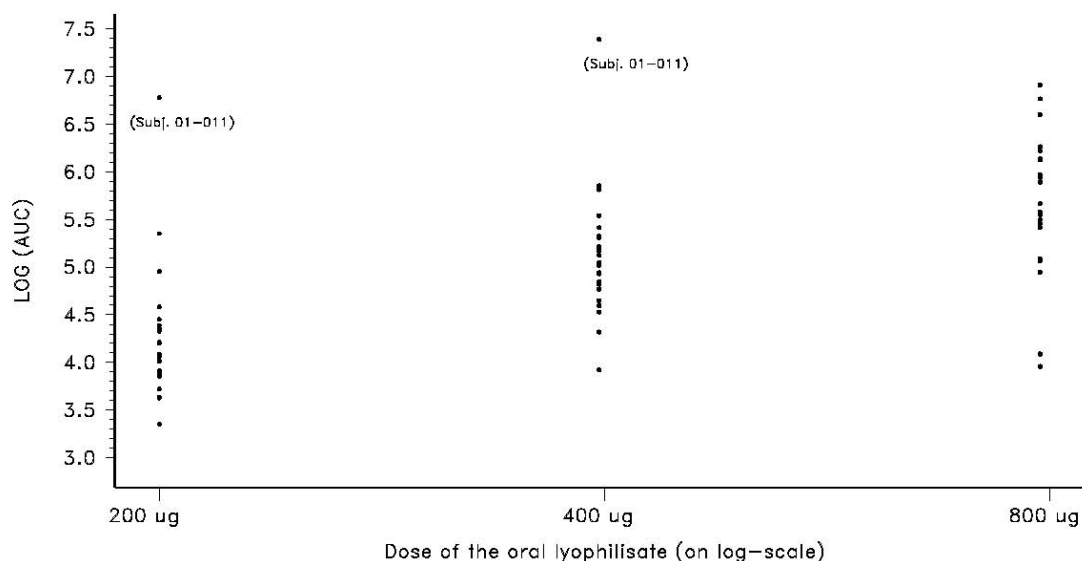
| Parameter | Unit | 800µg MELT | |
|-----------|---------|----------------|------------|
| | | Geometric mean | 95% CI |
| AUC | h*pg/ml | 283 | 205-389 |
| AUCt | h*pg/ml | 259 | 186-362 |
| Cmax | pg/ml | 65 | 46-92 |
| Tmax | h | 1.5† | 0.75-2.0†† |

† median

†† range

Figure 1.

Dose of desmopressin as an oral lyophilisate against log (AUC) – ITT analysis set



FE992026/DI_NOCT/CS004/26JAN2004-PES/MISC/PLOT_AUC.SAS

The applicant claims “the PK of the 400µg dose and of a lower and higher dose [200 and 800µg] were estimated in order to demonstrate linearity in absorption (and elimination) kinetics, allowing extrapolation to further studies using the MELT”. This study was, therefore, primarily intended to establish dose-proportionality over the 200-800µg range, in order to be able to extrapolated dose bioequivalence to doses below the 240µg MELT investigated in the bioequivalence study (CS020). However, given that the proposed dose-range (60-240µg) lies outside the range studied, these study findings do not allow extrapolation to the 60 and 120µg MELT. This aspect has been addressed by the new study; CS021 (supplemental data).

Study CS020

TITLE: An open-labelled, randomised, two-period cross-over study investigating the relative bioavailability of two single doses of the current marketed MINIRIN tablet (2 x 200µg) and a single dose of desmopressin administered as a new sublingual tablet (240µg)

Dosage justification

The dosage chosen for this study was primarily based on the data from the previous study, CS004, showing an increased bioavailability of the desmopressin MELT relative to historical data on the tablet.

This was a single-centre, open-label, randomised, two-period, crossover Phase I study involving non-smoking healthy volunteers and was designed to investigate the relative bioavailability of the newly developed sublingual desmopressin tablet 240µg (hereafter MHRA PAR

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

referred to as the ‘MELT’) compared to 2 x 200 µg (i.e. 400µg) of the currently marketed MINIRIN tablets (≡ 360µg of desmopressin free-base, based on the formula given in Section I. Introduction).

The objectives were as follows:

- 1°:** to investigate the relative bioavailability of one single sublingual 240µg dose of desmopressin administered as a new sublingual tablet (hereafter referred to as the MELT) vs. two x 200µg MINIRIN tablets.
- 2°:** to investigate the pharmacokinetics of one single 240µg MELT and of 2 x 200µg MINIRIN tablet. To investigate the safety and tolerability of a single dose of desmopressin administered to healthy volunteers as either of the two formulations.

Each subject was randomised to receive a 240µg desmopressin MELT and 2x200µg MINIRIN tablets.

Blood samples were collected according to a pre-determined schedule.

1° Endpoints

AUC, AUCt and Cmax

2° Endpoints

tmax, λz, t½

Safety parameters – see Safety Section, IV.

- **Analytical methods**

Desmopressin plasma concentrations were determined by a validated method.

- **Pharmacokinetic data analysis**

The following PK parameters were derived from the individual plasma concentration versus time curves in the non-compartmental analysis:

| | |
|---------|---|
| AUC | Area under the plasma concentration-time curve to infinity according to the formula: $AUC = AUCt + \frac{C_{last}}{\lambda z}$ Where C _{last} is the last measurable plasma concentration |
| AUCt | Area under the plasma concentration-time curve from time zero up to time t, where t is the last time point at which the subject shows concentrations above the LLOQ. |
| %Extrap | %age of AUC that is due to extrapolation from the last time point at which the subject shows a concentration above the LLOQ to infinity. |
| Cmax | Maximum observed plasma concentration |
| Tmax | Time to Cmax |

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

| | |
|-------------|--|
| λ_z | First-order rate constant associated with the terminal (log-linear) portion of the plasma concentration-time curve estimated via linear regression of log concentration vs time. |
| $t_{1/2}$ | Terminal half-life |

Since 2 x 200µg MINIRIN tablets equals 356µg of free base, the bioavailability of desmopressin free base in the MELT (240µg) relative to desmopressin free base in MINIRIN tablets was calculated using the following formula:

$$F_{\text{relative}} = \frac{AUC_{A \text{ Dose B}}}{AUC_{B \text{ Dose A}}} = \frac{AUC_{\text{MELT}}}{AUC_{\text{MINIRIN}}} \times \frac{\text{Dose}_{\text{MINIRIN}} (365\mu\text{g})}{\text{Dose}_{\text{MELT}} (240 \mu\text{g})}$$

where A=MINIRIN tablets; B = MELT

The following PK parameters were derived from the individual concentration vs. time curves for desmopressin: AUC, AUCt, Cmax, Tmax and $t_{1/2}$.

AUC was calculated using the linear trapezoid method.

All 28 subjects received treatment as described in the protocol and comprised the ITT set and none of the data points were excluded from the analysis. Therefore the ITT and PP sets were the same.

The average relative bioavailability of the two tested products was investigated in line with methodology described in the current CPMP guidelines.

The following supplementary analyses were also conducted:

- An analysis of the relative bioavailability of the MELT vs the MINIRIN tablet, adjusting for different dosages
- A supportive analysis of the bioequivalence assessment for the whole population excluding one subject due to very high absorption compared to the remaining subjects.

- **Statistical analysis**

No formal sample size calculation was performed. The statistical analysis was descriptive. All 28 randomised subjects were included with all their data in each of the three analysis sets: intention-to-treat (ITT), per-protocol (PP) and safety. Descriptive statistics were used to summarise each PK parameter by formulation. tmax, λ_z , $t_{1/2}$ were also described by harmonic mean. The average relative bioavailability of the two formulations was assessed in accordance with the relevant CPMP Guideline. The non-parametric wilcoxon test was used to compare tmax between formulations. No statistical tests were conducted on the other secondary endpoints.

1° PK Endpoints

The average absolute bioavailability and 95% CI were estimated for each dose of the MELT (in the full model) to discuss the robustness of the results.

2° PK Endpoints

All were presented using descriptive statistics only.
Safety is discussed in the Safety Section, IV.

• Results

A total of 28 subjects were included and there were no drop-outs, withdrawals or major protocol deviations.

Measurable levels of desmopressin were obtained in all healthy volunteers after administration of MINIRIN tablets and the MELT.

The sampling schedule provided a reliable estimate of the extent of absorption as the AUCt derived from measurements were, for all subjects on both treatments, > 80% of the AUC.

The PK parameters are summarised in Table 3:

Table 3: Summary of the PK Parameters for both treatments

| Parameter | Units | A: MINIRIN tablets (2 x 200µg) ≡ 360µg free base | | B: MELT (240µg) | |
|-----------|---------|--|------------|-----------------|-----------|
| | | Geometric mean | 95% CI | Geometric mean | 95% CI |
| AUC | h.pg/mL | 77.2 | 63 – 94 | 79.0 | 64-98 |
| AUCt | h.pg/mL | 71.8 | 58 – 88 | 73.2 | 59 – 91 |
| Cmax | pg/mL | 20.8 | 17 – 26 | 18.0 | 15 – 22 |
| Tmax | h | 1.0* | 0.5 – 3.0† | 1.5 | 0.5 – 4.0 |

*median
† range

The ratios for the PK parameters were also calculated as shown in Table 4:

Table 4: Ratios/differences for the PK parameters between the two treatments

| Parameter | Estimate B/A Ratio | 90% CI |
|-----------|--------------------|---------------|
| AUC | 102% | 87 -121% |
| AUCt | 102% | 86 – 121% |
| Cmax | 87% | 73 - 103% |
| Tmax | +0.25 h* | ± 0.0h, +0.5h |

* $p=0.0144$

The 90% CI for AUC [87%-121%] and AUCt [86%-121%] were fully contained within the prespecified bioequivalence range of 80-125%, but not for Cmax [73% -103%].

A supplementary bioequivalence analysis, excluding one subject who had a high absorption, again resulted in bioequivalence results within the standard criteria for AUC [90% CI 89% - 124%] and AUC_t [90% CI 88-124%] and, again, was just outside for C_{max} 76-106%.

However, the two treatments, 240µg MELT and 2 x 200µg MINIRIN tablets were not statistically significantly different comparing C_{max}. T_{max} was obtained slightly, but statistically significantly later with the MELT. Neither the slight difference in C_{max} nor T_{max} is considered to be of clinical relevance.

The applicant considers that a reliable estimate of the extent of absorption was achieved as reflected by the relative bioavailability of 240µg MELT and 2 x 200µg MINIRIN tablets. The relative bioavailability was 1.52 [95% CI 1.25, 1.85] thus an increased oral bioavailability from the MELT was seen.

Safety findings are discussed in Section IV.

Bioequivalence between the 240µg MELT and 2 x 200µg i.e. 400µg MINIRIN tablets (≡ 356 µg of free base) for AUC has been demonstrated. C_{max} is below the acceptance range but the Applicant has discussed why this finding is not clinically relevant.

SUPPLEMENTAL DATA FROM NEW STUDIES RECEIVED AFTER THE MAIN DOSSIER WAS FILED

Study CS019

TITLE: An open-labelled, replicated, randomised, cross-over study with four periods and two sequences investigating the bioequivalence of a single dose of MINIRIN tablets (2 x 0.2mg) and a single MINIRIN Melt (240 µg) dose of desmopressin administered sublingually.

This study was conducted after the pilot Study CS020 (discussed above). Although the objectives were as for the pilot study 020, it was an adequately powered formal bioequivalence study.

Design: single-centre, open-label, randomised, four-period, two-sequence cross-over study with replicate design in healthy non-smoking males and females.

Treatments: Subjects were randomised to one of two sequences: TRTR and RTRT [where T=test (oral lyophilisate) and R=reference products (marketed desmopressin)]. Each subject therefore received 240 µg of desmopressin in a sublingually administered oral lyophilisate and 2 x 200 µg on a predetermined number of treatment days.

Number of patients: 65 subjects were enrolled.

Results: the bioavailability of the MINIRIN Melt was approximately 57% higher than for DDAVP tablets and the C_{max} the lower limit of the 90% CI was below the lower limit of the bioequivalence interval and was significantly lower for the MINIRIN Melt (240µg)

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

with an estimate of 83% of C_{max} for the tablet. In addition, t_{max} was statistically significantly later by about 17 minutes for MINIRIN Melt (240 µg). For AUC and AUC_t, the 90% CIs for the ratio test/reference were included within the bioequivalence limits of 80-125% (AUC: [0.92,1.22], AUC_t [0.91, 1.22]).

These findings are consistent with those of Study CS019.

As the MELT is absorbed from the orobuccal mucosa, and thereby avoids first pass metabolism, it is not surprising that the extent of absorption is greater, dose for dose, than for the MINIRIN tablet. The applicant's justification for claiming that a difference in C_{max} test vs. reference product is clinically not relevant is accepted by the Assessor and is outlined below.

Applicant's justification for acceptance of a lower C_{max} for the MELT cf. MINIRIN tablets

Bioequivalence between the two formulations was established for both AUC and AUC_t in two separate studies (CS019 and CS020). However, for C_{max}, the lower limit of the 90% CI for the test/reference point estimate was below the acceptance range for bioequivalence according to the CHMP Guideline. The Applicant considers it is highly unlikely that a lower C_{max} will have any influence on safety and efficacy.

If anything, a lower C_{max}, will mean a better safety profile. And in terms of efficacy, the high potency of desmopressin will mean that efficacy is not adversely affected as efficacy is not influenced by C_{max} but by total exposure over time i.e. AUC.

The Applicant cites a paper by Hammer H and Vilhardt H (Peroral treatment of diabetes insipidus with polypeptide hormone analog, desmopressin. Journal of Pharmacology and Experimental Therapeutics; 234:1985) in which the maximal effect of desmopressin on water permeability of the collecting ducts was reached at plasma levels of 4-5 pg/ml. the geometric mean value of C_{max} obtained in the CS020 study was 18pg/ml – thus a maximal effect was obtained. Even at the lower dose levels, the maximal effect of desmopressin should be expected and therefore total exposure AUC will determine the duration of action.

Another paper is cited by Callreus T et al (Indirect-response modelling of desmopressin at different levels of hydration. J of Pharmacokinetics and Biopharmaceutics; 27: 1999). Using this modelling method, an IC₅₀ value of 3.7 pg/ml was obtained. As the indirect response model of the PK/PD relation was found to be very steep (Hill factor of 13) the maximal effect would be in a similar range (approx. 5 pg/ml), to that found by Hammer and Vilhardt. It can be concluded, therefore, that the maximum effect on urine concentrating capacity of the kidney is reached with a plasma concentration of 4-5pg/ml. Plasma concentrations above this level will only increase the duration of action, thus AUC is the more important measure for establishing efficacy of a desmopressin dosage form.

Study CS021

TITLE: Design: single-centre, open-label, randomised, three-period, cross-over study in 24 healthy subjects. The main objective of the study was to demonstrate dose proportionality i.e. that linear PK applies for the MINIRIN melt and the following dose levels were tested: 60, 120 and 240µg.

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

This was a single-centre, open-label, randomised, three-period, phase I cross-over study in 24 healthy subjects. The main objective of the study was to demonstrate dose proportionality i.e. that linear PK applies for the MINIRIN melt and the following dose levels were tested: 60, 120 and 240µg.

Treatments were as follows:

Desmopressin 60, 120 and 240 µg as the oral lyophilisate (MELT).

The 24 subjects who completed the study as scheduled were dosed on three different occasions.

1° Endpoints: AUC, AUCt and Cmax

2° Endpoints:

PK: % extrap. AUC, tmax, t½ and λz

Safety – standard parameters (discussed in Section IV).

Dose proportionality was demonstrated for AUC, AUCt and Cmax using a log (dose) – log (AUC) test.

In conclusion, the MELT showed a dose-proportional increase in AUC, AUCt and Cmax with increasing dose over the range 60, 120 and 240µg. Dose-linearity was confirmed for the PK parameters Cmax, AUC and AUCt in an ANOVA power model as the 90% CI included unity. All three doses were well tolerated and no safety concerns arose (see Section IV).

These studies/arguments provide the required reassurance that a 240µg MELT is therapeutically equivalent to 2 x 200µg tablets, that a somewhat reduced Cmax for the MELT is of no clinical consequence and that there is dose proportionality across the 60-240µg range.

Absorption

Although desmopressin is a peptide it may be administered via the oral route and this has been shown to induce maximal antidiuresis for up to 6 hours following a single 200µg MINIRIN tablet. This is observed even though the absolute oral bioavailability is only around 0.08 -0.16 %. For drugs having such a low bioavailability, the variability in bioavailability (F) is inherently high. Plasma desmopressin concentrations appear after 15-30 minutes following either intranasal or peroral administration, maximum concentrations being achieved within 2 hours. Cmax is dose-dependent.

In study CS004 described above, the new MELT (at 200, 400 and 800µg doses) was compared to IV desmopressin in 24 healthy subjects and absolute bioavailability was found to be approximately 0.25%. Therefore, not surprisingly perhaps, given the different route of administration, bioavailability of the MELT is greater than for the tablet.

- **Bioavailability**

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

This has been discussed in study CS004.

- **Bioequivalence**

This has been addressed in the originally submitted study CS020 and subsequent study CS019.

Comparing Studies CS020 and CS019

As these showed similar results regarding the dose-adjusted AUC, AUCt and Cmax the dose is considered to have been well predicted. The exposure after both administrations produced similar exposure, as doses chosen for CS020 were adjusted in relation to the estimated relative bioavailability found in CS004.

The results from the subsequently submitted CS019 are therefore consistent with those of CS020.

Influence of food

N/A

Distribution

Desmopressin does not cross the blood-brain barrier in humans.

Elimination

- **Excretion**

Previous work on desmopressin has shown that the plasma profile indicates exponential elimination and reported values for the half-life of desmopressin after intravenous administration vary between 55 minutes to 3.6 hours in different studies.

A substantial fraction of intact desmopressin is excreted in the urine.

- **Metabolism**

Desmopressin is not metabolised by the cytochrome P450 enzyme system in the liver, intestine or kidney but is subject to common peptidic catabolism in man especially the hepatobiliary system. It is therefore unlikely that the altered route of absorption of the MINIRIN MELT compared to the tablets would affect the metabolic pathways of desmopressin.

- **Inter-conversion**

N/A

- **Pharmacokinetics of metabolites**

N/A

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

- **Consequences of possible genetic polymorphism**

N/A

Dose proportionality and time dependency

- **Dose proportionality**

See the originally submitted Study CS004, and subsequently submitted Study, CS021, above.

- **Time dependency**

N/A

Intra- and inter-individual variability

N/A

Pharmacokinetics in target population

N/A

Special populations

- **Impaired renal function**

No new work has been done. The SPC wording, requiring caution in patients with reduced renal function, is consistent with that of the tablets.

- **Impaired hepatic function**

N/A

- **Gender**

Both sexes were included in the pivotal bioequivalence study, CS020.

- **Race**

N/A

- **Weight**

N/A

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

- **Elderly**

N/A

- **Children**

No PK studies have been conducted in children but the Applicant has justified this in the dossier. From the widespread experience with desmopressin, data in adults can be extrapolated to children.

Assessor's overall comments on pharmacokinetics in special populations

Interactions

- ***In vitro***

N/A

- ***In vivo***

N/A

Assessor's overall comments on Interactions

Desmopressin had no effect on any of the nine cytochrome P450 subtypes tested. It is therefore unlikely that desmopressin would have any effect on co-administered drugs *in vivo* by this mechanism.

The proposed SPCs will contain the same wording as for the tablets i.e.

Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatraemia.

NSAIDs may induce water retention and/or hyponatraemia.

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

Assessor's overall conclusions on pharmacokinetics

The data provided originally showed that the choice of a 240µg dose of desmopressin MELT as being equivalent to 2x200µg of desmopressin tablets (MINIRIN) was justified. The data also provided good evidence of dose-linearity in the 200-800µg range for the MELT. The Applicant was able to provide additional data, from studies which have adequately addressed dose proportionality.

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

The MHRA Statistical Assessor consulted is also satisfied with these data and concurs with these conclusions.

In summary, 240µg of MELT is bioequivalent in terms of AUC to 2 x 200µg of tablets and there is dose proportionality across the proposed dose range. C_{max} is lower for the MELT but this poses no safety or efficacy concern as C_{max} is above the threshold for maximal renal effect while the AUC ensures an adequate duration of action.

Pharmacodynamics

Introduction

ATC Code : HO1B A02 – vasopressin and analogues

The indications being sought are:

Diabetes insipidus (DI) and post-hypophysectomy polyuria/polydipsia

This is characterised by excessive urine production resulting from a partial or complete defect in vasopressin function. Before the availability of desmopressin, it was treated with posterior pituitary extracts, lysine-vasopressin and certain non-hormonal drugs with antidiuretic effect. However, these treatments were limited by short duration of action, serious adverse reactions and failure of, or incomplete, antidiuretic action. Desmopressin was introduced to overcome some of these problems – it has a specific antidiuretic effect and adequate duration of action.

Primary nocturnal enuresis (PNE)

This is voiding during sleep after the age when bladder control would normally be expected. In many children it is a deficiency in the night-time secretion of vasopressin which can explain the commonly seen polyuric component which signifies a night-time urine production that exceeds bladder capacity. The first studies of desmopressin in the treatment of PNE were reported in 1977-1978. Both investigators reported treatment outcome to be excellent in 50% of cases and satisfactory in the remaining 50%. The subsequent finding that the normal nocturnal increase in endogenous vasopressin secretion is absent in many enuretics provided a rationale for replacement therapy. Desmopressin now has an established therapy in the management of this disorder.

No clinical studies of PK/PD comparisons between the MINIRIN MELT and tablets were performed as these are considered unnecessary if bioequivalence and dose-proportionality from the two new studies are accepted. The applicant cites various studies which were conducted in support of a previous MINIRIN tablet application and these are detailed in the dossier.

Mechanism of action

Primary pharmacology

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

From previous work supporting the licensed tablet formulation, the maximal effect on urine osmolality is reached at low doses of IV desmopressin (which would be equivalent to 60-120 µg of the MELT). Higher concentrations do not influence osmolality, but increase duration of action. The maximal osmolality achieved was found to be about 1000 mosm/L, which is similar to the maximal concentrating capacity for healthy subjects according to the literature (referenced). The anticipated mean C_{max} of the lowest strength (60µg) of the MELT would be about 5pg/mL which is in the range of plasma concentration necessary to obtain maximal effect (4-5pg/mL).

Secondary pharmacology

N/A

Relationship between plasma concentration and effect

This has been discussed in Section II in relation to C_{max}.

Pharmacodynamic interactions with other medicinal products or substances

N/A

Genetic differences in PD response

N/A

Assessor's overall conclusions on pharmacodynamics

The PD effects of desmopressin are well established and are adequately referenced in the dossier. No further work has been required for the MELT.

CLINICAL EFFICACY

Introduction

Efficacy data is not required given the bioequivalence and dose proportionality data (see Section II) as efficacy can be extrapolated from the corresponding licensed desmopressin tablet formulation.

Dose-response studies and main clinical studies

N/A

Dose response study(ies)

N/A

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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Main study(ies)

N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive study(ies)

N/A

Assessor's overall conclusions on clinical efficacy

N/A

CLINICAL SAFETY**Introduction**

The clinical experience and knowledge of the safety of desmopressin, however, is extensive as the drug has been marketed worldwide for >10 years.

Patient exposure

In the bioequivalence study CS020, 28 subjects were exposed twice during the study. Each was dosed, in random order, with 400 µg MINIRIN tablet i.e. 2 x 200 µg tablets (desmopressin acetate, ≡ 356 µg desmopressin free base) and 240 µg MELT (as desmopressin free base), i.e. a total of 596 µg.

In the dose-proportionality study CS004, 24 subjects received a 200, 400 and 800 µg MINIRIN MELT and a 2 µg intravenous bolus injection of desmopressin free base, giving a total of 1402 µg desmopressin administered to each subject.

Additional exposure has been provided from the Supplemental Data from Studies CS019/021.

Adverse events**ORIGINALLY FILED STUDIES****Study CS020 Bioequivalence**

A total of 10 subjects experienced a total of 21 AEs during the study. Four experienced AEs after both treatment. All 21 were judged to be possibly related to study medication. All resolved. Eight subjects (29%) experienced a total of 12 post-dose AEs after the tablet and six subjects (21%) experienced a total of nine post-dose AEs after the MELT. The most

frequent AE was headache, which accounted for around 50% of the AEs. Only one AE required treatment.

Study CS004 bioavailability/dose-proportionality

Thirteen subjects (54%) reported a total of 24 Adverse drug reactions (ADR) whereas five subjects (21%) reported a total of eleven ADR events judged as related to the study medication. The two most frequently reported AEs were headache and clinically significant abnormal laboratory tests. No tendency towards any relationship between dose of desmopressin administered and incidence of AE or ADR was seen. With respect to the number of events, headache was the most frequent AE reported by 25% of the subjects.

In most of the subjects who had an AE a clinically significant finding for a laboratory parameter at the post-study examination constituted this AE. Other AEs were back pain and phlebitis, which occurred once in one subject, each. Laboratory events were bacteriuria, increases in bilirubin, creatine phosphokinase, urea, uric acid, abnormal liver function tests and skeletal muscle enzymes. All AE were reported as mild or moderate in intensity.

No trends in any organ system were observed in these two studies. No clinically relevant changes in heart rate, BP (systolic or diastolic) were observed. Vital signs did not differ to any clinically relevant extent after treatment with desmopressin (MELT or tablet).

SUPPLEMENTAL DATA

Study CS019 Bioequivalence study

This study is described in Section II.

All doses were well tolerated and there were no withdrawals due to an AE. In total, 65 treatment emergent adverse events (TEAEs) were reported for 31 subjects (47.7%) with slightly more TEAEs reported after the reference MINIRIN tablets. After MINIRIN 37 TEAEs for 24 subjects (37.5%) were recorded whereas after the MELT 28 TEAEs in 17 subjects (26.2%) were documented.

Study CS021 Dose-proportionality – 60-240µg

This study is described in Section II.

All doses were well tolerated and there were no withdrawals due to an AE. None of the treatment emergent adverse events (TEAEs) required treatment and all had resolved by the end of the study. There were a total of 11 TEAEs, all of mild to moderate intensity in 10 of the 25 subjects. Three TEAEs occurred in 3 subjects following 60µg desmopressin, 2 TEAEs in 2 subjects after 120 µg desmopressin and 6 TEAEs in 6 subjects following 240µg desmopressin. The most frequent TEAEs with altogether 5 events were renal and urinary disorders such as pollakiuria and polyuria. Seven TEAEs were considered to be possibly related to the MELT among which were three events of pollakiuria (including two of moderate intensity) and one event of polyuria.

Serious adverse events and deaths

No deaths or serious adverse events occurred in either the originally filed studies CS004 and CS020 or the subsequently filed studies CS019 and CS021.

Laboratory findings/other safety parameters

ORIGINALLY FILED STUDIES

Study CS004

There was no relationship between desmopressin dose and incidence of laboratory AEs or ADRs. Mean serum Na⁺ did not change to any clinically relevant degree. Nor were there any other safety concerns.

Study CS020

No laboratory events or abnormal Na⁺ values were recorded as AEs. Nor were there any other safety concerns.

SUPPLEMENTAL DATA

Studies CS019 and CS021

No apparent effect was observed on other safety parameters (laboratory tests, vital signs, 12-lead ECG, exam) following the MELT. In particular, no subject developed hyponatraemia after taking the MELT.

Safety in special populations

N/A

Immunological events

N/A

Safety related to drug-drug interactions and other interactions

N/A

Discontinuation due to AES

N/A

Post marketing experience

SPC contains adequate information relating to post-marketing experience.

Assessor's overall conclusions on clinical safety

The limited data from the Phase I studies indicate no new safety signal arising with the MELT cf. the tablet.

CLINICAL EXPERT REPORT

This was written by a medically qualified person.

MHRA PAR

- 36 -

DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

SPC

These are consistent with the SPCs for the corresponding tablets and no amendments are required.

PIL

Satisfactory

LABEL

Satisfactory

Overall Conclusions and Risk-Benefit Assessment

The main rationale of the present line extension development programme is to provide a new formulation of desmopressin which is more bioavailable and does not require water for administration cf. the licensed oral tablets (Minirin, DDAVP and Desmotab tablets). Furthermore many children, and some adults, do not like swallowing tablets. The applicant has provided adequate data to support the application - in the form of the originally filed dossier together with the supplemental data from two new studies (CS019 and CS021) [which were submitted after the original filing (in response to correspondence with the Applicant regarding issues with C_{max} differences and queries regarding dose proportionality at the lower end of the dose range)]. MA may, therefore, be granted. There are no new safety or efficacy issues in association with the MELT.

The SPC and PIL are consistent with MINIRIN tablet product literature and appropriate dosage of the MELT is provided to correspond with the tablet dosages – based on the bioequivalence and dose-proportionality data submitted.

There are therefore no outstanding issues.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate and DesmoMelt 120 and 240 micrograms oral lyophilisate are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

The absence of new pharmacology and pharmacodynamic studies was justified on the basis that desmopressin has been on the market for many years. As such, the pre-clinical programme consisted of only a local tolerance study in hamsters. It was concluded that there were no signs of local irritation following treatment with the oral lyophilisate.

EFFICACY

Desmopressin is a well known drug and has been used as an anti-diuretic for many years. The applicant has demonstrated bioequivalence of the proposed doses of the melt compared to the currently marketed reference product, Desmopressin tablets and efficacy may, therefore, be extrapolated.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the desmopressin oral lyophilisates and the currently marketed desmopressin tablets are interchangeable. Extensive clinical experience with desmopressin is considered to have demonstrated the therapeutic value of the compound. The risk benefit is therefore considered to be positive.

**DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0091, PL03194/0092, PL 03194/0093**

**DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0094, PL 03194/0095**

STEPS TAKEN FOR ASSESSMENT

| | |
|---|---|
| 1 | The MHRA received the marketing authorisation application on 30/03/2004. |
| 2 | Following standard checks and communication with the applicant the MHRA considered the application valid on 10/05/2004. |
| 3 | Following assessment of the application the MHRA requested further information relating to the quality dossier on 10/11/2004, 17/06/2005 and again on 24/08/2005. |
| 4 | The applicant responded to the MHRA's requests, providing further information on 07/03/2005, 25/07/2005 and 08/12/2005. |
| 5 | The applicant submitted supplemental clinical studies on 14 th March 2005. |
| 6 | Following assessment of the application the MHRA requested additional information relating to the clinical dossier on 03/06/2005 and 17/06/2005. |
| 7 | The applicant responded and all medical issues were resolved by 20 th June 2005. |
| 8 | The application was determined on 19/01/2006. |

**DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0091, PL03194/0092, PL 03194/0093**

**DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0094, PL 03194/0095**

STEPS TAKEN AFTER ASSESSMENT

| Date submitted | Application type | Scope | Outcome |
|-----------------------|-------------------------|--------------|----------------|
| | | | |
| | | | |
| | | | |
| | | | |
| | | | |

**DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0091, PL03194/0092, PL 03194/0093**

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DDAVP[®] Melt xx micrograms oral lyophilisate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit contains xx micrograms desmopressin (as acetate).

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Oral lyophilisate

60 micrograms: White, round, oral lyophilisate marked with a drop shaped figure on one side.

120 micrograms: White, round, oral lyophilisate marked with two drop shaped figures on one side.

240 micrograms: White, round, oral lyophilisate marked with three drop shaped figures on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DDAVP Melt is indicated for the treatment of vasopressin-sensitive cranial diabetes insipidus or in the treatment of post-hypophysectomy polyuria/polydipsia.

4.2. Posology and method of administration

DDAVP Melt is for sublingual use.

Treatment of diabetes insipidus:

Dosage is individual in diabetes insipidus but the total daily sublingual dose normally lies in the range of 120 micrograms to 720 micrograms. A suitable starting dose in adults and children is 60 micrograms three times daily, administered sublingually. This dosage regimen should then be adjusted in accordance with the patient's response. For the majority of patients, the maintenance dose is 60 micrograms to 120 micrograms sublingually three times daily.

Post-hypophysectomy polyuria/polydipsia:

The dose of DDAVP Melt should be controlled by measurement of urine osmolality.

4.3. Contraindications

DDAVP Melt is contraindicated in cases of cardiac insufficiency and other conditions requiring treatment with diuretic agents.

Before prescribing DDAVP Melt, the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.

4.4. Special warnings and precautions for use

Care should be taken with patients who have reduced renal function and/or cardiovascular disease. In chronic renal disease the antidiuretic effect of DDAVP Melt would be less than normal.

Precautions to prevent fluid overload must be taken in:

- conditions characterised by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure.

4.5. Interactions with other medicinal products and other forms of interaction

Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatraemia.

NSAIDs may induce water retention and/or hyponatraemia.

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water

retention and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased the absorption (rate and extent) of a 0.4mg dose of oral desmopressin tablets. Although it did not significantly affect the pharmacodynamic effect (urine production and osmolality), there is the potential for this to occur at lower doses. If a diminution of effect is noted, then the effect of food should be considered before increasing the dose.

4.6. Pregnancy and lactation

Pregnancy:

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Lactation:

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 micrograms intranasally) indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

4.7. Effects on ability to drive and use machines

None

4.8. Undesirable effects

Side-effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disturbances in children have been reported. Treatment with desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

4.9. Overdose

An overdose of DDAVP Melt leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:

Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the desmopressin treatment, fluid restriction and symptomatic treatment if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues

ATC code: H01B A02

In its main biological effects, DDAVP does not differ qualitatively from vasopressin. However, DDAVP is characterised by a high antidiuretic activity whereas the uterotonic and vasopressor actions are extremely low.

5.2. Pharmacokinetic properties

The overall mean systemic bioavailability of desmopressin administered sublingually as Melts at doses of 200, 400 and 800 micrograms is 0.25% with a 95% confidence interval of 0.21% - 0.31%. The C_{max} was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms respectively. t_{max} was observed at 0.5 – 2.0 hours after dosing. The geometric mean terminal half-life is 2.8 (CV= 24%) hours.

Correlation table between Desmopressin in Tablet and Melt forms:

| Tablet | Tablet | Melt | Melt |
|----------------------|------------------------|------------------------|-------------------------|
| Desmopressin acetate | Desmopressin free base | Desmopressin free base | Desmopressin acetate |
| 0.1mg | 89 micrograms | 60 micrograms | Approx. 67 micrograms* |
| 0.2mg | 178 micrograms | 120 micrograms | Approx. 135 micrograms* |
| 0.4mg | 356 micrograms | 240 micrograms | Approx. 270 micrograms* |

*calculated for comparative purposes

The distribution volume of desmopressin after intravenous administration is 33 L (0.41 L/kg). Desmopressin does not cross the blood-brain barrier. Desmopressin

exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant use of food decreases the rate and extent of absorption by 40%.

In vitro, in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolised in the liver and thus human liver metabolism *in vivo* is not likely to occur.

It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in *in vitro* studies with human microsomes. However, formal *in vivo* interaction studies have not been performed.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Gelatin
Mannitol
Citric acid, anhydrous

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

Store in the original package.

MHRA PAR

DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

6.5. Nature and contents of container

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester terephthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 10, 30 and 100 oral lyophilisates.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

None.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Ltd.
The Courtyard
Waterside Drive
Langley
Berkshire SL3 6EZ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/01/2006

10. DATE OF REVISION OF THE TEXT

DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE
PL 03194/0094, PL 03194/0095

1. NAME OF THE MEDICINAL PRODUCT

DesmoMelt xx micrograms oral lyophilisate

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each unit contains xx micrograms desmopressin (as acetate).

For excipients, see 6.1

3. PHARMACEUTICAL FORM

Oral lyophilisate

120 micrograms: White, round, oral lyophilisate marked with two drop shaped figures on one side.

240 micrograms: White, round, oral lyophilisate marked with three drop shaped figures on one side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DesmoMelt is indicated for the treatment of primary nocturnal enuresis.

4.2. Posology and method of administration

DesmoMelt is for sublingual use.

Children (from 5 years of age) and adults (up to 65 years of age) with normal urine concentrating ability who have primary nocturnal enuresis should take 120 micrograms at bedtime administered sublingually and only if needed should the dose be increased to 240 micrograms sublingually.

The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without DesmoMelt.

4.3. Contraindications

DesmoMelt is contraindicated in cases of cardiac insufficiency and other conditions requiring treatment with diuretic agents. DesmoMelt should only be used in patients with normal blood pressure.

Before prescribing DesmoMelt, the diagnoses of psychogenic polydipsia and alcohol abuse should be excluded.

Desmopressin should not be prescribed to patients over the age of 65 for the treatment of primary nocturnal enuresis.

4.4. Special warnings and precautions for use

Care should be taken with patients who have reduced renal function and/or cardiovascular disease or cystic fibrosis. In chronic renal disease the antidiuretic effect of DesmoMelt would be less than normal.

When DesmoMelt is used for the treatment of enuresis, fluid intake must be limited from 1 hour before until 8 hours after administration.

Patients being treated for primary nocturnal enuresis should be warned to avoid ingesting water while swimming and to discontinue DesmoMelt during an episode of vomiting and/or diarrhoea until their fluid balance is once again normal.

Precautions to prevent fluid overload must be taken in:

- conditions characterised by fluid and/or electrolyte imbalance
- patients at risk for increased intracranial pressure

4.5. Interactions with other medicinal products and other forms of interaction

Substances which are known to induce SIADH e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine and carbamazepine, may cause an additive antidiuretic effect leading to an increased risk of water retention and/or hyponatraemia.

NSAIDs may induce water retention and/or hyponatraemia.

Concomitant treatment with loperamide may result in a 3-fold increase of desmopressin plasma concentrations, which may lead to an increased risk of water retention and/or hyponatraemia. Although not investigated, other drugs slowing intestinal transport might have the same effect.

A standardised 27% fat meal significantly decreased the absorption (rate and extent) of a 0.4mg dose of oral desmopressin tablets. Although it did not significantly affect the pharmacodynamic effect (urine production and osmolality) there is the potential for this to occur at lower doses. If a diminution of effect is noted, then the effect of food should be considered before increasing the dose.

4.6. Pregnancy and lactation

Pregnancy:

Data on a limited number (n=53) of exposed pregnancies in women with diabetes insipidus indicate rare cases of malformations in children treated during pregnancy. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development.

Caution should be exercised when prescribing to pregnant women. Blood pressure monitoring is recommended due to the increased risk of pre-eclampsia.

Lactation:

Results from analyses of milk from nursing mothers receiving high dose desmopressin (300 micrograms intranasally) indicate that the amounts of desmopressin that may be transferred to the child are considerably less than the amounts required to influence diuresis.

4.7. Effects on ability to drive and use machines

None

4.8. Undesirable effects

Side-effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disturbances in children have been reported. Treatment with desmopressin without concomitant reduction of fluid intake may lead to water retention/hyponatraemia with accompanying symptoms of headache, nausea, vomiting, weight gain, decreased serum sodium and in serious cases, convulsions.

4.9. Overdose

An overdose of DesmoMelt leads to a prolonged duration of action with an increased risk of water retention and/or hyponatraemia.

Treatment:

Although the treatment of hyponatraemia should be individualised, the following general recommendations can be given. Hyponatraemia is treated by discontinuing the desmopressin treatment, fluid restriction and symptomatic treatment if needed.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: vasopressin and analogues
ATC code: H01B A02

In its main biological effects, desmopressin does not differ qualitatively from vasopressin. However, desmopressin is characterised by a high antidiuretic activity whereas the uterotonic and vasopressor actions are extremely low.

5.2. Pharmacokinetic properties

The overall mean systemic bioavailability of desmopressin administered sublingually as Melts at doses of 200, 400 and 800 micrograms is 0.25% with a 95% confidence interval of 0.21% - 0.31%. The C_{max} was 14, 30 and 65pg/ml after administration of 200, 400 and 800 micrograms respectively. t_{max} was observed at 0.5 – 2.0 hours after dosing. The geometric mean terminal half-life is 2.8 (CV= 24%) hours.

Correlation table between Desmopressin in Tablet and Melt forms:

| Tablet | Tablet | Melt | Melt |
|----------------------|------------------------|------------------------|-------------------------|
| Desmopressin acetate | Desmopressin free base | Desmopressin free base | Desmopressin acetate |
| 0.1mg | 89 micrograms | 60 micrograms | Approx. 67 micrograms* |
| 0.2mg | 178 micrograms | 120 micrograms | Approx. 135 micrograms* |
| 0.4mg | 356 micrograms | 240 micrograms | Approx. 270 micrograms* |

*calculated for comparative purposes

The distribution volume of desmopressin after intravenous administration is 33 L (0.41 L/kg). Desmopressin does not cross the blood-brain barrier. Desmopressin exhibits a moderate to high variability in bioavailability, both within and between subjects. Concomitant use of food decreases the rate and extent of absorption by 40%.

In vitro, in human liver microsome preparations, it has been shown that no significant amount of desmopressin is metabolised in the liver and thus human liver metabolism *in vivo* is not likely to occur.

It is unlikely that desmopressin will interact with drugs affecting hepatic metabolism, since desmopressin has been shown not to undergo significant liver metabolism in *in vitro* studies with human microsomes. However, formal *in vivo* interaction studies have not been performed.

5.3. Preclinical safety data

There are no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Gelatin
Mannitol
Citric acid, anhydrous

6.2. Incompatibilities

Not applicable

6.3. Shelf life

24 months

6.4. Special precautions for storage

MHRA PAR

DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

Store in the original package.

6.5. Nature and contents of container

PVC/Polyamide/Aluminium/Polyamide/PVC blisters. Top foil consists of Paper/Polyester terephthalate/Aluminium/heat seal lacquer. Strips of 10 oral lyophilisates in packs of 10, 30 and 100 oral lyophilisates.

Not all pack sizes may be marketed.

6.6. Instruction for use and handling (, and disposal)

None.

7. MARKETING AUTHORISATION HOLDER

Ferring Pharmaceuticals Ltd.
The Courtyard
Waterside Drive
Langley
Berkshire SL3 6EZ
United Kingdom

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/01/2006

10. DATE OF REVISION OF THE TEXT

MHRA PAR

DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

DDAVP MELT 60, 120 AND 240 MICROGRAMS ORAL LYOPHILISATE PL 03194/0091, PL03194/0092, PL 03194/0093

PRODUCT INFORMATION LEAFLET

DDAVP^{*} Melt
oral lyophilisate
desmopressin (as acetate)

PATIENT INFORMATION

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet, you may need to use it again
- If you have further questions, please ask your doctor or pharmacist
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Your medicine is called DDAVP Melt oral lyophilisate. The lyophilisates look like tablets, but are much softer and lighter. They are intended for sublingual use (to be placed under the tongue where they will dissolve completely). They are referred to as DDAVP Melt or melt(s) in this leaflet.

- This medicine contains the active ingredient, desmopressin (as acetate). It is available in three strengths: 60, 120 or 240 micrograms of desmopressin (as acetate).
- Other ingredients in this medicine are gelatin, mannitol and citric acid.
- The melts are flat, round and white. Each melt is marked on one side with one, two or three drops, indicating a strength of 60, 120 or 240 micrograms respectively.
- Each carton contains 10, 30 or 100 melts in blister strips of 10 melts per strip.

Marketing Authorisation Holder:
Ferring Pharmaceuticals Ltd., The Courtyard, Waterside Drive,
Langley, Berkshire SL3 6EZ (UK).

Manufacturer:
Ferring GmbH, Wittland 11, D 24109 Kiel, Germany.

1. What DDAVP Melt is and what it is used for

This medicine is intended for sublingual use (under the tongue). It is available in three strengths: 60, 120 or 240 micrograms of desmopressin (as acetate), an antidiuretic (reduces urine production).

This medicine is used to treat:

- diabetes insipidus (extreme thirst and the continuous production of large volumes of dilute urine). *IMPORTANT: This should not be confused with diabetes mellitus (sugar diabetes)*
- post-hypophysectomy polyuria/polydipsia (extreme thirst and the continuous production of large volumes of dilute urine following surgical removal of the pituitary gland).

2. Before you take DDAVP Melt

Do not take this medicine:

- if you have a serious heart or kidney disease
- if you are taking diuretics (water tablets)
- if you are allergic to any of the ingredients listed.

Please consult your doctor before taking this medicine:

- if you are on medication for depression or epilepsy
- if you are taking a medicine for pain and/or inflammation containing non-steroidal anti-inflammatory drugs (also known as NSAIDs) e.g. indometacin
- if you are taking a medicine containing loperamide, for diarrhoea
- if you have a medical condition causing fluid and/or electrolyte imbalance
- if you have a medical condition that could be made worse by fluid and/or electrolyte disturbance.

Before you commence treatment with this medicine, you should have received appropriate advice concerning fluid intake, from a doctor or nurse. Excessive fluid intake may lead to a build up of water in the body.

Pregnancy:

If you are pregnant or planning a pregnancy, please inform your doctor before you take this medicine, as blood pressure monitoring is recommended due to the increased risk of pre-eclampsia. Symptoms of pre-eclampsia include high blood pressure, oedema (swelling due to the build up of fluid) and proteinuria (protein in the urine).

Breast-feeding:

If you are breast-feeding ask your doctor or pharmacist for advice before taking this medicine.

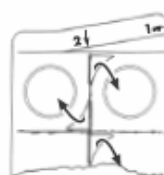
Taking/using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken or used any other medicines - even those not prescribed.

3. How to take DDAVP Melt

It is important that you do not take more than the prescribed dose in any 24 hour period.

If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor or pharmacist.



1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.

2. Now remove one blister from the strip by tearing along the perforations.

3. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow.

4. Carefully take a melt out of its blister. Place the melt under the tongue and allow it to dissolve.

5. If a melt breaks into more than two pieces while you are taking it out of its blister, do not take the broken pieces. Take a melt from another blister.

Treatment of diabetes insipidus:

Your doctor will prescribe the dose most suitable for you. The total daily dose normally lies in the range of 120 micrograms to 720 micrograms. A suitable starting dose in adults and children is one DDAVP Melt 60 micrograms taken sublingually (under the tongue) three times a day. The most common doses in adults and children are either one DDAVP Melt 60 micrograms or one DDAVP Melt 120 micrograms taken sublingually (under the tongue) three times a day.

Post-hypophysectomy polyuria/polydipsia:

Your doctor will prescribe the most suitable dose for you based on the concentration of your urine.

If you take more of this medicine than you should:

If you take more of this medicine than you should, talk to your doctor or pharmacist immediately.

If you forget to take this medicine:

If you forget to take this medicine, please consult your doctor or pharmacist for advice.

4. Possible side effects

Most people taking this medicine find it causes them no problems. However, like all medicines, this medicine can have side effects. Excessive fluid intake may lead to a build up of water which dilutes the salt in the body in severe cases. This can become a serious problem and may lead to convulsions. Early symptoms may include an unusually bad or prolonged headache, confusion, unexplained weight gain, nausea or vomiting. If you experience one or more of these symptoms, stop taking this medicine. Tell your doctor immediately or go to your nearest casualty department.

Side effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disturbances in children have been reported.

If you experience one or more of these side effects or any other undesirable effects, please inform your doctor or pharmacist.

5. Storing DDAVP Melt

Keep this medicine out of the reach and sight of children.

Store in the original package.

Do not take this medicine after the expiry date on the packaging.

If you are unsure about the storage, ask your pharmacist. It is best to return all old and unused medicines to your pharmacist for safe disposal.

DDAVP Melt 60 micrograms oral lyophilisate PL 03194/0091

DDAVP Melt 120 micrograms oral lyophilisate PL 03194/0092

DDAVP Melt 240 micrograms oral lyophilisate PL 03194/0093

This leaflet was revised in July 2005.

*DDAVP is a trademark of Ferring BV.

DESMOMELT 120 AND 240 MICROGRAMS ORAL LYOPHILISATE

PL 03194/0094, PL 03194/0095

PRODUCT INFORMATION LEAFLET

DesmoMelt*
oral lyophilisate
desmopressin (as acetate)

PATIENT INFORMATION

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet, you may need to use it again
- If you have further questions, please ask your doctor or pharmacist
- This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

Your medicine is called DesmoMelt oral lyophilisate. The lyophilisates look like tablets, but are much softer and lighter. They are intended for sublingual use (to be placed under the tongue where they will dissolve completely). They are referred to as DesmoMelt or melt(s) in this leaflet.

- This medicine contains the active ingredient, desmopressin (as acetate). It is available in two strengths: 120 or 240 micrograms of desmopressin (as acetate).
- Other ingredients in the melts are gelatin, mannitol and citric acid.
- The melts are flat, white and round. Each melt is marked on one side with two or three drops, indicating a strength of 120 or 240 micrograms respectively.
- Each carton contains 10, 30 or 100 melts in blister strips of 10 melts per strip.

Marketing Authorisation Holder: Ferring Pharmaceuticals Ltd., The Courtyard, Waterside Drive, Langley, Berkshire SL3 6EZ (UK).

Manufacturer: Ferring GmbH, Wittland 11, D 24109 Kiel, Germany.

1. What DesmoMelt is and what it is used for

This medicine is intended for sublingual use. It is available in two strengths: 120 or 240 micrograms of desmopressin (as acetate), an antidiuretic (reduces urine production).

This medicine is used to treat primary nocturnal enuresis (bedwetting) in children (from 5 years of age) and adults (up to 65 years of age).

2. Before you take DesmoMelt

Do not take this medicine:

- if you are under 5 or over 65 years old
- if you have a serious heart or kidney disease
- if you are taking diuretics (water tablets)
- if you are taking medication for high blood pressure or have been told that your blood pressure is abnormal
- if you drink unusually large quantities of fluids, including alcohol
- if you are allergic to any of the ingredients listed.

Please consult your doctor before taking this medicine:

- if you have cystic fibrosis
- if you are on medication for depression or epilepsy
- if you are taking a medicine for pain and/or inflammation containing non-steroidal anti-inflammatory drugs (also known as NSAIDs) e.g. indometacin
- if you are taking a medicine containing loperamide, for diarrhoea
- if you have a medical condition causing fluid and/or electrolyte imbalance
- if you have a medical condition that could be made worse by fluid and/or electrolyte disturbance.

Before you commence treatment with this medicine, you should have received appropriate advice concerning fluid intake, from a doctor or nurse. Excessive fluid intake may lead to a build up of water in the body. While you are on treatment with this medicine:

- fluid intake must be limited to a minimum from 1 hour before until 8 hours after a dose
- stop taking this medicine when suffering from vomiting and/or diarrhoea until you are better
- swallowing water while swimming should be avoided because it could lead to a build up of water in the body.

Pregnancy:

If you are pregnant or planning a pregnancy, please inform your doctor before you take this medicine, as blood pressure monitoring is recommended due to the increased risk of pre-eclampsia. Symptoms of pre-eclampsia include high blood pressure, oedema (swelling due to the build up of fluid) and proteinuria (protein in the urine).

Breast-feeding:

If you are breast-feeding ask your doctor or pharmacist for advice before taking this medicine.

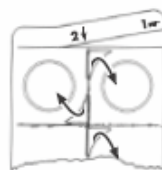
Taking/using other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken or used any other medicines - even those not prescribed.

3. How to take DesmoMelt

It is important that you do not take more than the prescribed dose in any 24 hour period.

If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor or pharmacist.



1. Completely remove the end tab of a blister strip by tearing along the perforations, starting from the corner with the hand symbol.

2. Now remove one blister from the strip by tearing along the perforations.

3. Remove the foil on each blister, starting at the corner with the printed arrow, by peeling off the foil in the direction of the arrow.

4. Carefully take a melt out of its blister. Place the melt under the tongue and allow it to dissolve.

5. If a melt breaks into more than two pieces while you are taking it out of its blister, do not take the broken pieces. Take a melt from another blister.

Bedwetting from the age 5 years:

The usual starting dose is one DesmoMelt 120 micrograms sublingually (under the tongue) at bedtime. Depending on how well the bedwetting is controlled, your doctor may increase the dose to either two DesmoMelts 120 micrograms or one DesmoMelt 240 micrograms sublingually (under the tongue) at bedtime. The need for continued treatment is normally checked every three months.

If you take more of this medicine than you should:

If you take more of this medicine than you should, talk to your doctor or pharmacist immediately.

If you forget to take this medicine:

Do not take double doses to make up for forgotten doses. Take the next dose at the usual time.

4. Possible side effects

Most people taking this medicine find it causes them no problems. However, like all medicines, this medicine can have side effects. Excessive fluid intake may lead to a build up of water which dilutes the salt in the body in severe cases. This can become a serious problem and may lead to convulsions. Early symptoms may include an unusually bad or prolonged headache, confusion, unexplained weight gain, nausea or vomiting. If you experience one or more of these symptoms, stop taking this medicine. Tell your doctor immediately or go to your nearest casualty department.

Side effects include headache, stomach pain and nausea. Isolated cases of allergic skin reactions and more severe general allergic reactions have been reported. Very rare cases of emotional disturbances in children have been reported.

If you experience one or more of these side effects or any other undesirable effects, please inform your doctor or pharmacist.

5. Storing DesmoMelt

Keep this medicine out of the reach and sight of children.

Store in the original package.

Do not take this medicine after the expiry date on the packaging.

If you are unsure about the storage, ask your pharmacist. It is best to return all old and unused medicines to your pharmacist for safe disposal.

DesmoMelt 120 micrograms oral lyophilisate PL 03194/0094

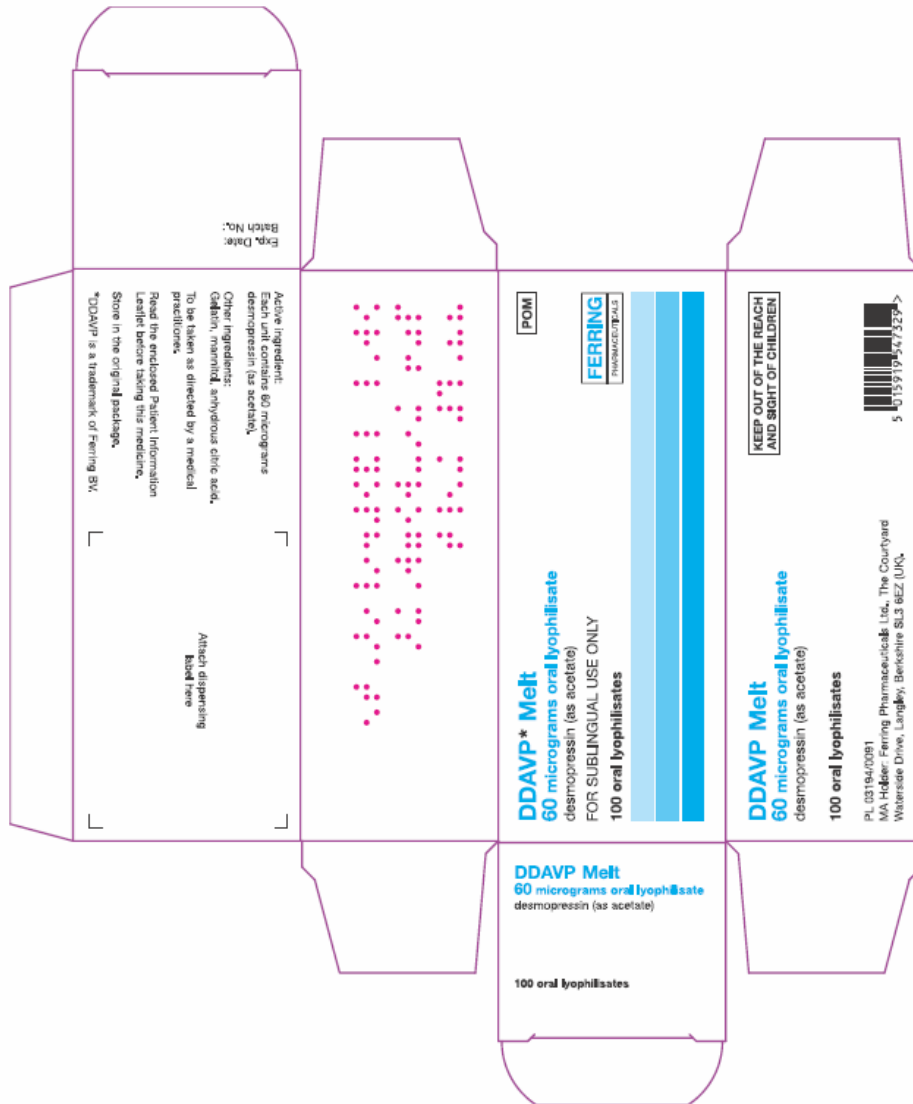
DesmoMelt 240 micrograms oral lyophilisate PL 03194/0095

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DDAVP MELT 60 MICROGRAMS ORAL LYOPHILISATE PL 03194/0091

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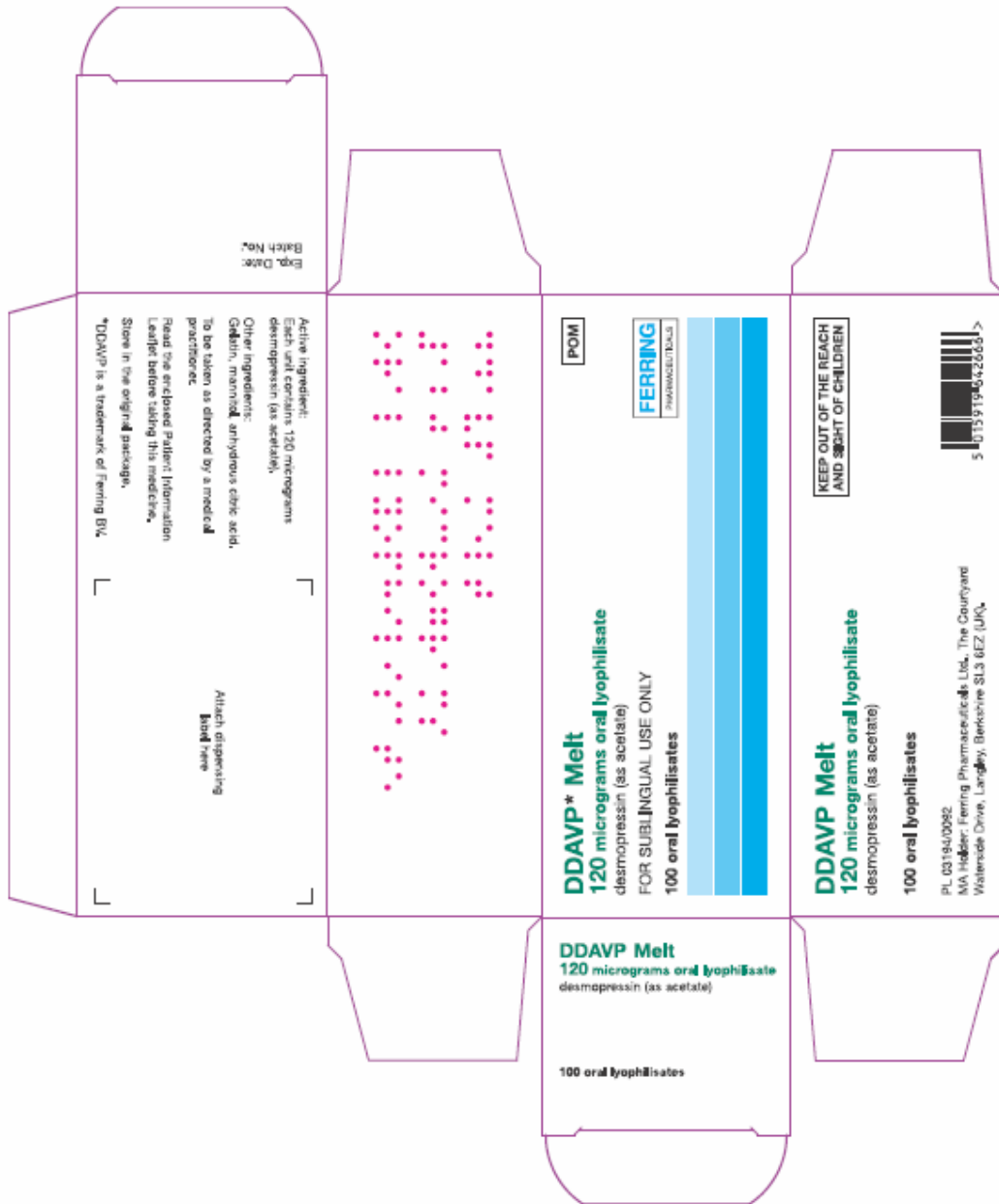
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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

DDAVP MELT 120 MICROGRAMS ORAL LYOPHILISATE PL 03194/0092

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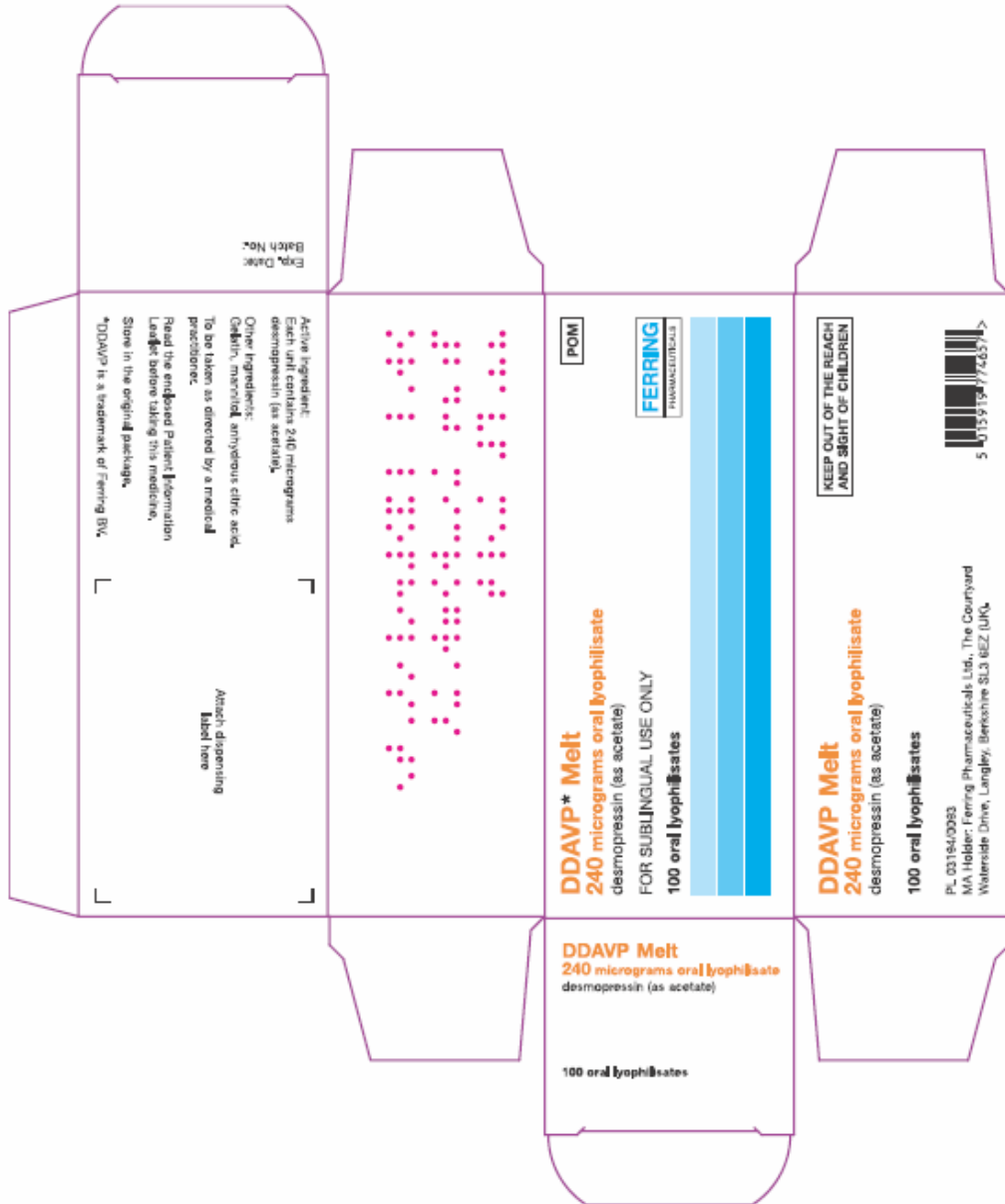
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DDAVP Melt 60, 120 and 240 micrograms oral lyophilisate

DesmoMelt 120 and 240 micrograms oral lyophilisate

DDAVP MELT 240 MICROGRAMS ORAL LYOPHILISATE PL 03194/0093

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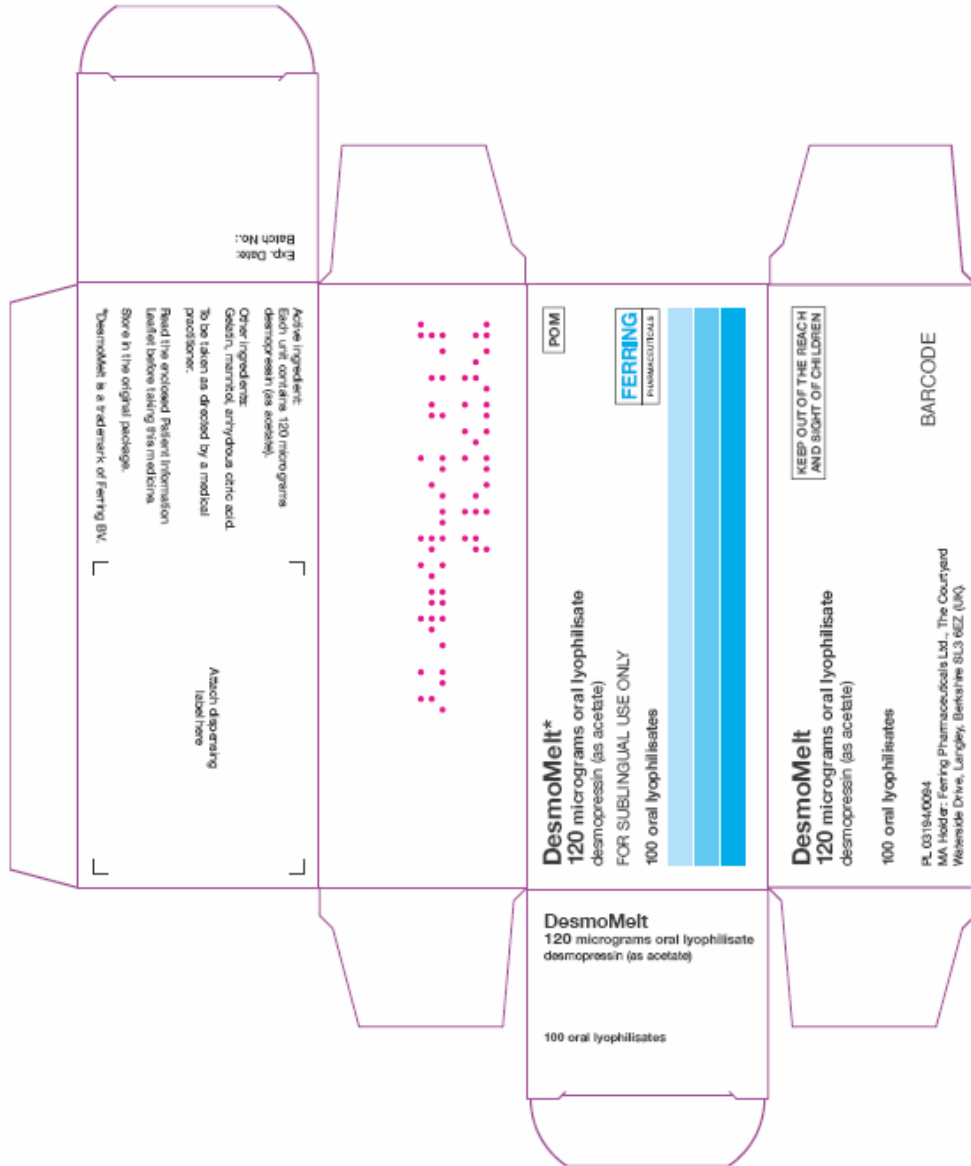
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DesmoMelt 120 and 240 micrograms oral lyophilisate

DESMOMELT 120 MICROGRAMS ORAL LYOPHILISATE

PL 03194/0094

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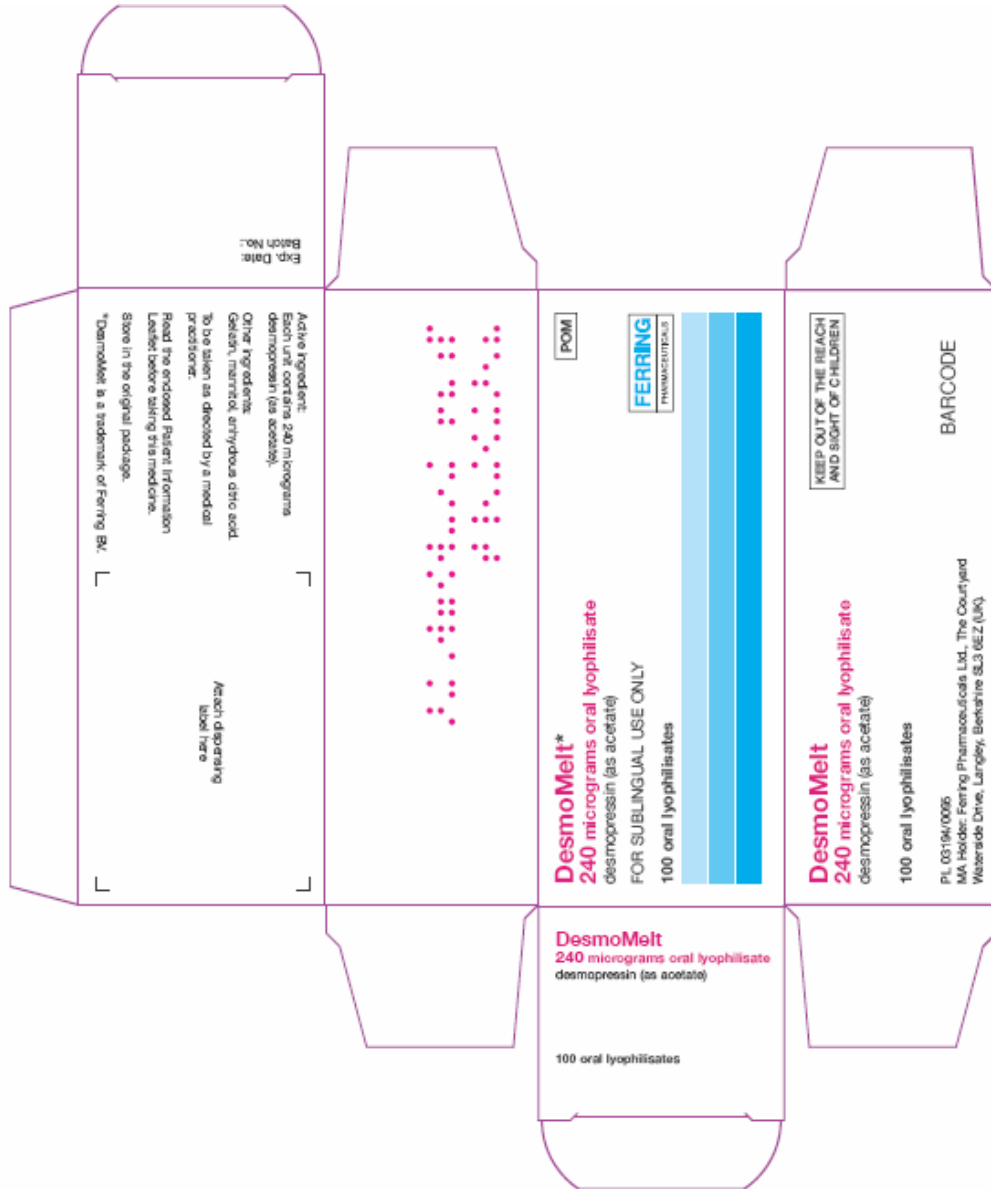
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DesmoMelt 120 and 240 micrograms oral lyophilisate

DESMOMELT 240 MICROGRAMS ORAL LYOPHILISATE

PL 03194/0095

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