DESMOPRESSIN ACETATE 100 MICROGRAM TABLET
PL 24668/0177

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET
PL 24668/0178

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LAY SUMMARY

On the 4th December 2009 the MHRA granted Caduceus Pharma Limited Marketing Authorisations (licences) for the medicinal products Desmopressin 100microgram and 200microgram Tablets (PL 24668/0177-8). These are prescription-only medicines (POM).

Desmopressin is an antidiuretic, which reduces the amount of urine produced by the kidneys.

Desmopressin is used to treat:
- a chronic disease called diabetes insipidus which causes extreme thirst and continuous production of large volumes of dilute urine. Important: not to be confused with diabetes mellitus (sugar diabetes)
- bedwetting in children (involuntary nightly urination)
- excessive thirst or frequent urination when caused by certain medical procedures (hypophysectomy)

No new or unexpected safety concerns arose from these applications and it was therefore judged that the benefits of taking Desmopressin 100microgram and Desmopressin 200microgram Tablets outweigh the risks, hence Marketing Authorisations have been granted.
DESMPRESSIN ACETATE 100 MICROGRAM TABLET
PL 24668/0177

DESMPRESSIN ACETATE 200 MICROGRAM TABLET
PL 24668/0178

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 medicinal products Desmopressin 100 microgram and Desmopressin 200 microgram Tablets (PL 24668/0177-8) on 4th December 2009. The products are prescription-only medicine (POM).

These are abridged applications for Marketing Authorisations in the UK submitted under Article 10.1 of Directive 2001/83 (as amended) for products claiming to be a generic medicinal product to Minirin 0.1mg and 0.2mg Tablets authorised in Denmark. In the UK the product is licensed as DDAVP tablets 0.1mg and 0.2mg Tablets (PL 03194/0040-1). The licences were granted on the 13th January 1993 and are held by Ferring Pharmaceuticals Limited. The medicinal product used for bioequivalence was Minrin 0.2mg tablets sourced from The Netherlands.

Desmopressin acetate Tablets are indicated for:

• the treatment of vasopressin-sensitive cranial diabetes insipidus.
• the treatment of post-hypophysectomy polyuria/polydipsia.
• the treatment of primary nocturnal enuresis.
**PHARMACEUTICAL ASSESSMENT**

**DRUG SUBSTANCE**

Nomenclature

rINN: Desmopressin acetate hydrate

CAS: 16679-58-6

Chemical name: (3-Sulphanylpropanoyl)-l-tyrosyl-l-phenylalanyl-l-glutaminyl-l-asparaginyl-l-cysteinyl-l-prolyl-d-arginyln-glycinamide cyclic (1→6)-disulfide

Molecular formula: C_{46}H_{64}N_{14}0_{12}S_{2}

Molecular Mass: 1069.22g/mol

Appearance: White or almost white, fluffy powder

Solubility: Soluble in water, in ethanol (96 per cent) and in glacial acetic acid.

A valid Certificate of Suitability has been provided.

An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active desmopressin acetate is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data has been provided.

**DRUG PRODUCT**

**Other ingredients**

Other ingredients consist of pharmaceutical excipients, namely povidone 30, lactose monohydrate, magnesium stearate and potato starch.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

Confirmation has been given that the magnesium stearate used in the tablets is of vegetable origin. The lactose used is from Meggle and appropriate documentation regarding sourcing has been supplied.
Pharmaceutical development
The objective of the pharmaceutical development programme was to produce products containing 100mcg and 200mcg Desmopressin acetate tablets that are tolerable and which could be considered as generic products of Minirin 0.1mg and 0.2mg Tablets

The rationale for the type of pharmaceutical form developed and formulation variables evaluated during development have been stated and are satisfactory.

Dissolution and impurity profiles
Dissolution and impurity profiles for the drug product were found to be similar to that for the reference product.

Manufacture
A description and flow-chart of the manufacturing method has been provided.

In-process controls are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on batches. The results are satisfactory.

Finished product specification
The finished product specification is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System
Product is packaged in a high-density polyethylene bottle with HDPE/LDPE cap and desiccant insert. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. All primary product packaging complies with EU legislation regarding contact with food.

Stability
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 2 years with storage conditions “Do not store above 30 degree C”, “Store in the original bottle” and “Keep the bottle tightly closed” have been set. These are acceptable.

Bioequivalence/bioavailability
Satisfactory certificates of analysis have been provided for the test and reference batches used in the bioequivalence study. Bio-analytical methods used have been satisfactorily validated.

SPC, PIL, Labels
The SPC, PIL and labels are pharmaceutically acceptable.
Conclusion
It is recommended that Marketing Authorisations are granted for these applications.

The proposed products are considered to be generic medicinal products to the reference product with respect to qualitative and quantitative content of the active substance, pharmaceutical form and bioequivalence.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none are required for an application of this type.
CLINICAL ASSESSMENT

1. INTRODUCTION
These are national abridged standard applications for marketing authorisations for Desmopressin 100 microgram Tablets (PL 24668/0177) and Desmopressin 200 microgram Tablets (PL 24668/0178). These applications are made under article 10.1 of EC Directive 2001/83.

The application for Desmopressin Tablets is cross-referring to Minirin 0.1mg and 0.2mg Tablets by Ferring Laegemidler A/S, Denmark, which have had a licence in the EEA since 6 December 1972. This is appropriate in the case of a generic product. Desmopressin is well known, and in the case of a generic product containing a widely used, well known active substance, no further clinical trials are required and none are submitted by the applicant. The UK reference medicinal products are DDVAMP 0.1mg and 0.2mg tablets by Ferring Pharmaceuticals Ltd.

2. BACKGROUND
Desmopressin is a synthetic analogue of arginine vasopressin. It has greater antidiuretic activity and a more prolonged action than vasopressin or lypressin. It also stimulates factor VIII and plasminogen activator activity in the blood, but has little pressor activity. Antidiuresis or oliguria is the principal action of desmopressin. In the kidneys desmopressin binds to the V2 receptor linked to an adenyl cyclase system in the collecting tubule to increase water permeability to the luminal membrane. Since there is an osmotic gradient between the hypotonic luminal fluid and the hypertonic renal interstitial medulla, the effect of desmopressin allows water to flow along the gradient and thus concentrate the luminal fluid. Urinary concentration and reduction in urine flow will occur in normal healthy individuals irrespective of their state of hydration and in patients with vasopressin deficiency.

3. INDICATIONS
Desmopressin Tablets are indicated for:
- the treatment of vasopressin-sensitive cranial diabetes insipidus.
- the treatment of post-hypophysectomy polyuria/polydipsia.
- the treatment of primary nocturnal enuresis.

4. DOSE & DOSE SCHEDULE
For oral use.

Diabetes Insipidus:
Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200 micrograms to 1200 micrograms. A suitable starting dose in adults and children is 100 micrograms three times daily. This dosage regimen should then be adjusted in accordance with the patient’s response. For the majority of patients, the maintenance dose is 100 micrograms to 200 micrograms three times daily.

Post-hypophysectomy polyuria/polydipsia:
The dose of Desmopressin acetate Tablets should be controlled by measurement of urine osmolality.

Primary nocturnal enuresis:
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 200 micrograms at bedtime and only if needed should the dose be increased to 400 micrograms.

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

5. TOXICOLOGY
No new preclinical data have been submitted and none are required for these applications.

6. CLINICAL PHARMACOLOGY
The applicant submits a randomised, 2-way, single dose, cross-over, bioequivalence study of the test Desmopressin 0.2mg x 2 (0.4mg) tablets versus the reference Minirin 0.2mg x 2 (0.4mg) tablets in healthy adult male subjects under fasting conditions.

For the treatment of central diabetes insipidus a starting dose of 0.1 mg three times daily for both adults and children is recommended. To ensure detectable plasma concentrations over a pharmacokinetically acceptable period, it was deemed desirable to administer 0.4 mg desmopressin acetate as a single dose. The dosage of desmopressin acetate in this study was a single dose of 0.4 mg (2 x 0.2 mg tablets) per treatment phase, under fasting conditions.

Study protocol
70 healthy adult volunteers aged 18 - 56 years, were included in this study. There were three withdrawals and 67 subjects completed the study. Two subjects withdrew their consent from the study and another experienced vomiting prior to dosing in Period II and was withdrawn.

Each subject received a single dose (0.4mg tablet) of one of the two Desmopressin formulations. For each subject there were two dosing periods, with a washout period of 14 days. The washout periods are considered sufficiently long and this is confirmed with a Period II pre-dose plasma desmopressin concentration of 0.00 pg/ml. A randomisation scheme was included in the report. The following formulations were administered:

Test : Desmopressin Acetate 2 x 0.2mg tablets
Reference : Minirin 2 x 0.2mg tablets

The reference is the same product as that registered in UK. The tablet was administered with 240ml water following a >10hr fast. Standard meals were
administered from 4 hours post-dose. Blood samples for analysis were taken pre dose and at 0.25, 0.5, 0.75, 1, 1.33, 1.67, 2, 3, 4, 5, 6, and 8 hours following dosing. There followed a 14 day washout period before cross over and repeat, except for three subjects who had a washout period of 10 days.

Plasma samples were analysed for Desmopressin concentration using a validated LC/MS/MS method. The lower limit of detection for was 2.5 pg/ml. A validation report has been provided.

\[ \text{AUC}_{0-\infty}, \text{AUC}_{0-t}, C_{\max}, t_{\max} \text{ and } t_{1/2} \] were calculated according normal standard procedures.

Statistical evaluation was performed for \( \text{AUC}_{0-t}, \text{AUC}_{\infty} \) and \( C_{\max} \) with ANOVA and the 90% confidence intervals for the ratio of test formulation over the reference formulation were calculated.

The study was conducted in accordance with GCP and GLP. The report is of good quality.

The 90% confidence intervals of the ratios for \( \text{AUC}_{0-t}, \infty \) and \( C_{\max} \) were within the accepted limits of 80 – 125%:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Ratio (%)</th>
<th>90% Confidence Interval</th>
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<tbody>
<tr>
<td>C(_{\max})</td>
<td>98.43</td>
<td>89.99 – 107.66</td>
</tr>
<tr>
<td>(\text{AUC})(_{0-t})</td>
<td>103.98</td>
<td>92.79 – 116.52</td>
</tr>
<tr>
<td>(\text{AUC})(_{0-\infty})</td>
<td>101.00</td>
<td>90.91 – 112.21</td>
</tr>
</tbody>
</table>

There were no serious adverse events recorded.

The multiple strengths exemption criterion for linear pharmacokinetics over the therapeutic range is met and the results from the bioequivalence study at the 0.2mg strength can be expected to apply to the 0.1mg strength tablet also:

a. The pharmacokinetics are linear

b. The qualitative composition is the same

c. The ratio between active substance and the excipients in both strengths of the test product is the same

d. The dissolution rate of the highest strength of the test product in-vitro is similar to that of the lower strength, and the dissolution rate of both of the strengths of the test product in vitro is similar to the dissolution rates of the corresponding strengths of the reference product.

The claim that bioequivalence has been demonstrated is endorsed.
7. **EFFICACY**
   No new efficacy data have been submitted and none are required for these applications.

8. **SAFETY**
   No new safety data have been submitted and none are required for these applications.

9. **EXPERT REPORT**
   A clinical expert report has been written by clinical consultant to the pharmaceutical industry. The report is satisfactory.

10. **SUMMARY OF PRODUCT CHARACTERISTICS**
    Clinically satisfactory

11. **PATIENT INFORMATION LEAFLET**
    This is satisfactory

12. **LABELLING**
    These are satisfactory.

13. **MARKETING AUTHORISATION FORM**
    These are satisfactory.

14. **DISCUSSION**
    The applicant has conducted a bioequivalent study comparing the applicant’s product with the cross referred medicinal product using the higher strength of 200 micrograms. The study has confirmed that both products are bioequivalent and therefore would exhibit the same efficacy and safety profile.

15. **CONCLUSIONS**
    The efficacy and safety of Desmopressin 100 micrograms and 200 microgram Tablets are satisfactory for the grant of product licences.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Desmopressin Acetate 100mcg and 200mcg tablets 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
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
Based on the submitted bioequivalence study Desmopressin Acetate 100mcg and 200mcg Tablets are considered bioequivalent with Minrin 0.2mg tablets.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory..

RISK BENEFIT ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The bioequivalence study supports the claim that the applicant’s product and the innovator product are interchangeable. Extensive clinical experience with Desmopressin Acetate 100mcg and 200mcg tablets is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.
DESMOPRESSIN ACETATE 100 MICROGRAM TABLET

PL 24668/0177

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET

PL 24668/0178

STEPS TAKEN FOR ASSESMENT

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<tr>
<td>1</td>
<td>The MHRA received the marketing authorisation applications on 14th April 2008</td>
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<tr>
<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 18th April 2008</td>
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<td>3</td>
<td>Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 27th June 2008 and 1st October 2008</td>
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<tr>
<td>4</td>
<td>The applicant responded to the MHRA’s requests, providing further information to the clinical sections on 29th August 2008 and 2nd April 2009</td>
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<td>The applications were determined on 4th December 2009</td>
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DESMOPRESSIN ACETATE 100 MICROGRAM TABLET

PL 24668/0177

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET

PL 24668/0177

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Desmopressin acetate 100 microgram Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 100 micrograms of desmopressin acetate (equivalent to 89 micrograms desmopressin).
Excipients: lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, round, scored on one side and marked with D1 on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
− Vasopressin-sensitive cranial diabetes insipidus.
− Post-hypophysectomy polyuria/polydipsia.
− Primary nocturnal enuresis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use.

Diabetes Insipidus:
Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200 micrograms to 1200 micrograms. A suitable starting dose in adults and children is 100 micrograms three times daily. This dosage regimen should then be adjusted in accordance with the patient’s response. For the majority of patients, the maintenance dose is 100 micrograms to 200 micrograms three times daily.

Post-hypophysectomy polyuria/polydipsia:
The dose of Desmopressin acetate Tablets should be controlled by measurement of urine osmolality.

Primary nocturnal enuresis:
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 200 micrograms at bedtime and only if needed should the dose be increased to 400 micrograms.
The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without Desmopressin acetate tablets.

4.3 CONTRAINDICATIONS
− Hypersensitivity to desmopressin or any of the excipients.
- Cardiac insufficiency and other conditions requiring treatment with diuretic agents.
- When used to control primary nocturnal enuresis Desmopressin acetate Tablets should only be used in patients with normal blood pressure.
- Before prescribing Desmopressin acetate Tablets 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.
- Hyponatraemia.
- Syndrome of inappropriate secretion of antidiuretic hormone.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

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 Desmopressin acetate Tablets would be less than normal.

When Desmopressin acetate Tablets are 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 Desmopressin acetate Tablets 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

It is important to monitor body weight and blood pressure during treatment with desmopressin.

4.5 INTERACTION 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 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. 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

Gastrointestinal tract:

Stomach pain, nausea, abdominal cramps, vomiting.

Nervous system disorders:

Headache

Very rare; emotional disturbance in children.

Skin/General:

Allergic skin reactions and more severe general allergic reactions.

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 Desmopressin acetate Tablets 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. Therefore, symptoms such as an increase in body weight, headache, nausea, abdominal cramps and in severe cases cerebral oedema, convulsions and coma may be expected.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: vasopressin and analogues, ATC code: H01BA02

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

5.2 PHARMACOKINETIC PROPERTIES
The absolute bioavailability of orally administered desmopressin varies between 0.08% and 0.16%. Mean maximum plasma concentration is reached within 2 hours. The distribution volume is 0.2 – 0.32 l/kg. Desmopressin does not cross the blood-brain barrier. The oral terminal half-life varies between 2.0 and 3.11 hours.

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.

About 65% of the amount of desmopressin absorbed after oral administration could be recovered in the urine within 24 hours.

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
Lactose monohydrate
Potato starch
Povidone
Magnesiun stearate

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C. Store in original bottle. Keep the bottle tightly closed. The desiccant should not be removed.

6.5 NATURE AND CONTENTS OF CONTAINER
HDPE bottle with HDPE/LDPE cap and desiccant insert.
Pack sizes: 7, 10, 15, 20, 30, 60, 90, 100 and 250 tablets
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Tablets may be crushed, but must not be suspended in water.
Any unused product or waste material should be disposed of in accordance with local requirements.

7  MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8  MARKETING AUTHORISATION NUMBER(S)
PL 24668/0177

9  DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/12/2009

10  DATE OF REVISION OF THE TEXT
04/12/2009
SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT
Desmopressin acetate 200 microgram Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200 micrograms of desmopressin acetate (equivalent to 178 micrograms desmopressin).
Excipients: lactose monohydrate.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Tablet
White, round, scored on one side and marked with D2 on the other side.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS
− Vasopressin-sensitive cranial diabetes insipidus.
− Post-hypophysectomy polyuria/polydipsia.
− Primary nocturnal enuresis.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION
For oral use.

Diabetes Insipidus:
Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200 micrograms to 1200 micrograms. A suitable starting dose in adults and children is 100 micrograms three times daily. This dosage regimen should then be adjusted in accordance with the patient’s response. For the majority of patients, the maintenance dose is 100 micorograms to 200 micrograms three times daily.

Post-hypophysectomy polyuria/polydipsia:
The dose of Demopressin acetate Tablets should be controlled by measurement of urine osmolality.

Primary nocturnal enuresis:
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 200 micrograms at bedtime and only if needed should the dose be increased to 400 micrograms.
The need for continued treatment should be reassessed after 3 months by means of a period of at least 1 week without Desmopressin acetate tablets.

4.3 CONTRAINDICATIONS
− Hypersensitivity to demopressin or any of the excipients.
- Cardiac insufficiency and other conditions requiring treatment with diuretic agents.
- When used to control primary nocturnal enuresis Desmopressin acetate Tablets should only be used in patients with normal blood pressure.
- Before prescribing Desmopressin acetate Tablets 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.
- Hyponatraemia.
- Syndrome of inappropriate secretion of antidiuretic hormone.

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Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose- galactose malabsorption should not take this medicine.

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It is important to monitor body weight and blood pressure during treatment with desmopressin.

**4.5 INTERACTION 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.

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A standardised 27% fat meal significantly decreased the absorption (rate and extent) of a 0.4mg dose of oral desmopressin. 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

Gastrointestinal tract:
Stomach pain, nausea, abdominal cramps, vomiting.

Nervous system disorders:
Headache
Very rare; emotional disturbance in children.

Skin/General:
Allergic skin reactions and more severe general allergic reactions.
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 Desmopressin acetate Tablets 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. Therefore, symptoms such as an increase in body weight, headache, nausea, abdominal cramps and in severe cases cerebral oedema, convulsions and coma may be expected.

5 PHARMACOLOGICAL PROPERTIES
5.1 PHARMACODYNAMIC PROPERTIES
Pharmacotherapeutic group: vasopressin and analogues, ATC code: H01BA02

In its main biological effects, demopressin 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 absolute bioavailability of orally administered desmopressin varies between 0.08% and 0.16%. Mean maximum plasma concentration is reached within 2 hours. The distribution volume is 0.2 – 0.32 l/kg. Desmopressin does not cross the blood-brain barrier. The oral terminal half-life varies between 2.0 and 3.11 hours.

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.

About 65% of the amount of desmopressin absorbed after oral administration could be recovered in the urine within 24 hours.

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
Lactose monohydrate
Potato starch
Povidone
Magnesium stearate

6.2 INCOMPATIBILITIES
Not applicable

6.3 SHELF LIFE
2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Do not store above 30°C. Store in original bottle. Keep the bottle tightly closed. The desiccant should not be removed.

6.5 NATURE AND CONTENTS OF CONTAINER
HDPE bottle with HDPE/LDPE cap and desiccant insert.
Pack sizes: 7, 10, 15, 20, 30, 60, 90, 100 and 250 tablets
Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Tablets may be crushed, but must not be suspended in water.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER
Caduceus Pharma Limited
6th Floor
94 Wigmore Street
London
W1U 3RF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 24668/0178

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
04/12/2009

10 DATE OF REVISION OF THE TEXT
04/12/2009
Desmopressin acetate
100 microgram and 200 microgram tablets

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

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If you have any of the side effects, or if you notice any side effects not listed, please tell your doctor or pharmacist.

In this leaflet:
1. What Desmopressin is and what it is used for
2. Before you take Desmopressin acetate tablets
3. How to take Desmopressin acetate tablets
4. Possible side effects
5. How to store Desmopressin acetate tablets
6. Further information

1. WHAT Desmopressin IS AND WHAT IT IS USED FOR

The ingredient that makes the tablet work (the active substance) is called desmopressin. Desmopressin is an antidiuretic, which reduces the amount of urine produced by the kidneys.

Desmopressin acetate tablets are used to treat:
- a chronic disease called diabetes insipidus which causes extreme thirst and continuous production of large volumes of dilute urine. Important: Not to be confused with diabetes mellitus (sugar diabetes)
- bedwetting in children (involuntary nightly urination)
- excessive thirst or frequent urination when caused by certain medical procedures (hypophysectomy)

2. BEFORE YOU TAKE Desmopressin ACETATE tablets

Do not take Desmopressin acetate tablets if you:
- are allergic (hypersensitive) to desmopressin or any of the other ingredients in Desmopressin acetate tablets (see section 6)
- drink unusually large amounts of fluid
- suffer from alcoholism
- suffer from heart problems or other diseases needing treatment with diuretics (water tablets)
- suffer from reduced kidney function, cardiovascular disease or cystic fibrosis
- know you have a low level of sodium in your blood (hyponatraemia)
- suffer from “syndrome of inappropriate high secretion of antidiuretic hormone” (SIADH).

- are being treated for primary nocturnal enuresis and have high blood pressure.
- Check with your doctor or pharmacist before taking Desmopressin acetate tablets if you:
  - are elderly (over 65)
  - have a medical condition causing fluid and/or electrolyte imbalance in the body such as an infection, fever or stomach upset
  - suffer from a serious bladder problem or impaired urine outflow.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:
- tricyclic or SSRl antidepressants (used to treat depression)
- carbamazepine (used to treat epilepsy)
- chlorpromazine (used to treat psychosis or schizophrenia)
- loperamide (used to treat diarrhoea)
- medicines for pain and/or inflammation called non-steroidal anti-inflammatory drugs (NSAIDs) e.g. indometacin, ibuprofen.

Fluid Intake
- Before you start treatment with this medicine, your doctor should give you advice about fluid intake.
- When using this medicine for bedwetting or nocturia, keep your fluid intake to a minimum from 1 hour before you take a tablet until 8 hours after a dose.
- Too much fluid intake may lead to a build up of water, which dilutes the salt in the body. This can occur with or without warnings or symptoms, which include unusually bad or prolonged headache, feeling or being sick, unexplained weight gain and in serious cases, fits.
- If you have any of these symptoms, stop the treatment and contact your doctor at once.

Pregnancy and breastfeeding
Desmopressin acetate tablets can be used during breastfeeding but should only be used in pregnancy as directed by a doctor.
- Ask your doctor or pharmacist for advice before taking any medicine.
Driving and using machines
There is no evidence to suggest that Desmopressin acetate tablets affect the ability to drive or use machines.

Sugar Intolerance
If you have been told that you have an intolerance to some sugars, contact your doctor before taking this medicine, as it contains lactose.

3. HOW TO TAKE Desmopressin ACETATE tablets
Always take Desmopressin acetate tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.

- Divide the tablets in half or swallow whole.
- Do not take Desmopressin acetate tablets with food, as the effect of the tablets may be reduced.

Usual doses
- Diabetes insipidus
  - Adults and children - 100 micrograms three times a day.
- Bedwetting (Involuntary nightly urination)
  - Children (over 5 years) and adults up to 65 years of age - 200 micrograms at bedtime. This may be increased to 400 micrograms at bedtime depending on how well the bedwetting is controlled. The need for continued treatment is normally checked every three months by introducing a treatment free week.
- Excessive thirst or frequent urination when caused by certain medical procedures
  - The dose will be decided by your doctor depending on the strength of your urine.

When using this medicine for bedwetting keep your fluid intake to a minimum 1 hour before you take a tablet until 1 hour after a dose. Avoid swallowing water while swimming to prevent a build up of water in the body.

If you take more Desmopressin acetate tablets than you should
An overdose may lengthen the effect of desmopressin and increase the risk of water build up in the body and low blood salt. Symptoms include fits and unconsciousness. If you take more Desmopressin acetate tablets than prescribed, contact your doctor, pharmacist or the nearest hospital at once.

If you forget to take Desmopressin acetate tablets
Do not take a double dose to make up for a forgotten dose.

If you stop taking Desmopressin acetate tablets
You should only change or stop your treatment if advised by your doctor.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Desmopressin acetate tablets can cause side effects, although not everybody gets them. Stop the treatment and contact your doctor if you get any of the following and they persist or become troublesome. Tell your doctor or pharmacist if you notice any of the following other side effects, or if you notice any not listed.

- Headache.
- Abdominal pain, feeling sick, dizziness, swelling of arms and legs, weight gain, frequent urination.
- Emotional disturbances in children.

5. HOW TO STORE Desmopressin ACETATE tablets
Keep out of the reach and sight of children. Do not store Desmopressin acetate tablets above 30°C. Keep the container tightly closed in order to protect from moisture. Do not use Desmopressin acetate tablets after the expiry date, stated on the pack. Always return any left over medicine to your pharmacist.

6. Further information
What Desmopressin acetate tablets contain
- The active substance (the ingredient that makes the tablet work) is desmopressin acetate. Each tablet contains either 100 micrograms or 200 micrograms of the active substance.
- The other ingredients of the tablets are lactose monohydrate, potato starch, povidone and magnesium stearate.

What Desmopressin acetate tablets look like and contents of the pack
Desmopressin acetate tablets are white, round, and marked with a break line on one side.

The tablets are in plastic containers containing 7, 10, 15, 20, 30, 50, 100 or 250 tablets. Not all pack sizes may be available.

Marketing Authorisation Holder
Caduceus Pharma Ltd., 5th Floor, 94 Wigmore Street, London, W1U 1SR, United Kingdom

Manufacturer
Inpho AS, Gjøbbekikutten 10, 3420 Lierkogen, Norway

The leaflet was last revised in October 2008
Desmopressin acetate 200 microgram Tablets

Each tablet contains 200 microgram desmopressin acetate. Also contains lactose monohydrate.

See patient information leaflet for further information.

Read the package leaflet before use.

To be taken as directed by your doctor. For oral use.

Keep out of the reach of children.

Do not chew the tablets. Swallow the tablets whole.

Keep the bottle tightly closed.

The dosage should not be removed.

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