

DESMOPRESSIN ACETATE 100 MICROGRAM TABLET

PL 10622/0235

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET

PL 10622/0236

UKPAR

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DESMOPRESSIN ACETATE 100 MICROGRAM TABLET

PL 10622/0235

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET

PL 10622/0236

LAY SUMMARY

The MHRA today granted PLIVA Pharma limited Marketing Authorisations (licences) for the medicinal products Desmopressin 100microgram and 200microgram Tablets (PL 10622/0235-6). These are prescription-only medicines (POM).

Desmopressin is similar to the hormone Vasopressin (an antidiuretic), which temporarily reduces the amount of urine produced by the body.

Desmopressin is used for the treatment of:

- Some types of diabetes insipidus (a condition that causes frequent passing of water).
- Primary nocturnal enuresis (bedwetting).
- Excessive thirst or frequent passing of water when caused by surgery (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.

DESMOPRESSIN ACETATE 100 MICROGRAM TABLET

PL 10622/0235

DESMOPRESSIN ACETATE 200 MICROGRAM TABLET

PL 10622/0236

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 100microgram and Desmopressin 200microgram Tablets (PL 10622/0235-6) on 10th April 2007. 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 DDAVP tablets 0.1mg (PL 03194/0040) 0.2mg (PL 03194/0041) and Desmotabs tablets 0.2mg (PL 03194/0046). The licences were granted on the 13th January 1993 and are held by Ferring Pharmaceuticals Limited. These products are also marketed in the EU under the brand names Desmotabs, Minrin and Minrin DDAVP. 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: *1-desamino-8-D-arginine vasopressin*

Molecular formula: C₄₆H₆₄N₄O₁₂S₂

Molecular Mass: 1069.22g/mol

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 hydrate 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 lactose monohydrate, maize starch, povidone 25 and magnesium stearate.

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.

There were no novel excipients used and no overages.

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 to the originator products DDAVP tablets 0.1mg and 0.2mg tablets and Desmotabs 0.2 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 a polypropylene cap and child-resistant closure. 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 “Store below 25 degree C”, “Keep container in the outer carton”, “Keep container tightly closed” and “Store in the original package” 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.

The PIL is in compliance with current guidelines. The marketing authorisation holder has provided a commitment to update the marketing authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the

leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

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 (PL10622/0235) and Desmopressin 200 microgram Tablets (PL10622/0236). These applications are made under article 10.1 of EC Directive 2001/83.

The application for Desmopressin 100 microgram Tablets is cross-referring to DDAVP Tablets 0.1 mg (PL 03194/0040) and Desmotabs 0.2 mg (PL 03194/0046) as the intended indications are covered by these two products. The application for Desmopressin 200 microgram Tablets is cross-referred to DDAVP Tablets 0.2 mg (PL 03194/0041) and Desmotabs 0.2 mg (PL 03194/0046) as the intended indications are also covered by these two products. DDAVP Tablets 0.2 mg and Desmotabs 0.2 mg are the same product and belong to the same Marketing Authorisation Holder and were both licensed more than 10 years ago. They differed only in the indications.

2. BACKGROUND

Desmopressin is a synthetic analogue of the natural hormone arginine vasopressin. It was first synthesised in 1966 and it exhibits a longer duration of action with more potent antidiuretic activity than vasopressin but less pressor activity. Due to its action it has been widely used for the treatment of central diabetes insipidus and enuresis. It is currently licensed for intravenous, intranasal and oral administration.

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.

Treatment of Diabetes Insipidus:

Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200micrograms to 1200micrograms. A suitable starting dose in adults and children is 100micrograms 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 100micorograms to 200micrograms 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 200micorgrams at bedtime and only if needed should the dose be increased to 400micrograms.

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

6.1 PHARMACOKINETICS

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.

6.2 PHARMACODYNAMICS

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.

6.3 BIOEQUIVALENCE

A bioequivalence study was performed. This was a comparative, randomised, open label, single-dose, 2-way crossover study comparing Desmopressin 200 microgram tablets (Test product) with Minrin 0.2mg tablets (Sourced from The Netherlands) from Ferring BV (Reference product), in healthy adult under fasting conditions at a dose of 0.8mg.

The study was conducted in line with GCP regulations.

Subjects were enrolled in the study and data was analysed.

In each period, subjects were housed from at least 10 hours pre-dosing until the 12 hour blood draw. The 2 doses of four 200 microgram tablets each were separated by a washout period of 7 days. Samples were taken predose (0hours) and 0.25, 0.5, 0.67, 0.83, 1, 1.167, 1.33, 1.5, 1.75, 2, 3, 4, 6, 7.5, 9, 10.5 and 12 hours post dose.

Statistical analyses were performed using ANOVA model. Bioequivalence was determined using the 90% confidence interval of the relative mean AUC 0-t, AUC_∞ and C_{max} of the test to reference formulation which should be 80% to 125%.

Safety was also assessed by evaluation of vital signs, physical and laboratory results and adverse events monitoring.

The batch of Desmopressin 200microgram tablets is at least 1/10 of the proposed maximum batch size.

The pharmacokinetic results are summarised in Table 1.

Table 1 Summary of pharmacokinetic results

	TEST (mean/SD) (N=38)	REFERENCE (mean/SD) (N=38)	90% CI
AUC _{0-t} (pg*h/mL)	258.81 (160.258)	250.59 (185.078)	106.9% (94.5-121%)
AUC _{inf} (pg*h/mL)	277.12 (171.061)	268.28 (198.408)	107.0% (94.7-120.8%)
C _{max} (pg/mL)	76.271 (46.945)	71.134 (42.930)	107.6% (95.1-121.7%)
T _{max} (h)	1.094 (0.441)	1.362 (1.068)	
T _{1/2} (h)	2.879 (0.580)	2.708 (0.548)	

The sample schedule is adequate as the AUC derived from measurements is at least 80% of the AUC extrapolated to infinity in line with current guidelines.

The confidence intervals derived are within the 80% to 125% acceptance range of the Notes for Guidance on Bioavailability and Bioequivalence. Desmopressin 200 microgram tablets were therefore considered to be bioequivalent to Minrin 0.2mg tablets under fasting conditions following administration of a 0.8mg dose.

During the study there was no cause of safety concern.

Conclusion

The two dosage strengths of 0.1 mg and 0.2 mg are manufactured with the same process and the same type and quantity of ingredients, the amount of active substance being the only difference. For both strengths the in vitro dissolution matches the requirement of at least 85% dissolved in 15 minutes, similarly to the reference product. It is therefore considered appropriate to perform the bioequivalence study on the 0.2 mg dosage strength only. In conclusion, the applicant's products Desmopressin 100 micrograms Tablets and Desmopressin 200 micrograms Tablets are considered bioequivalent to the reference product.

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

These are national abridged applications for marketing authorisations for Desmopressin 100 microgram & 200 microgram Tablets claiming to be a generic medicinal product of DDAVP Tablets 0.1mg and 0.2 mg and Desmotabs Tablets 0.2mg licensed in the UK to Ferring Pharmaceuticals Ltd in 1993 and 1994.

Desmopressin is a synthetic analogue of the natural hormone arginine vasopressin. It exhibits a longer duration of action with more potent antidiuretic activity than vasopressin but less pressor activity. Due to its action it has been widely used for the treatment of central diabetes insipidus and enuresis.

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 10622/0235****DESMOPRESSIN ACETATE 200 MICROGRAM TABLET****PL 10622/0236****STEPS TAKEN FOR ASSESSMENT**

1	The MHRA received the marketing authorisation applications on 24 th February 2004
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 8 th March 2004
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 5 th November 2004 and to the quality dossiers on 14 th September 2004
4	The applicant responded to the MHRA's requests, providing further information to the clinical sections on 8 th June 2005 and on the quality section on 8 th June 2005
5	The applications were determined on 10 th April 2007

DESMOPRESSIN ACETATE 100 MICROGRAM TABLET**PL 10622/0235****DESMOPRESSIN ACETATE 200 MICROGRAM TABLET****PL 10622/0236****STEPS TAKEN AFTER AUTHORISATION - SUMMARY**

Date submitted	Application type	Scope	Outcome
18/06/2007	TYPE 1A	To register a certificate of suitability for the active substance	02/07/2007 Approved
12/07/2007	Type 1A	To add a primary and secondary packager	14/08/2007 Approved

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 hydrate (equivalent to 89 micrograms desmopressin).

Excipients: lactose monohydrate

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

Round, white, scored tablets marked with 0.1 on one side.

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use.

Treatment of Diabetes Insipidus:

Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200micrograms to 1200micrograms. A suitable starting dose in adults and children is 100micrograms 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 100micrograms to 200micrograms 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 200micrograms at bedtime and only if needed should the dose be increased to 400micrograms.

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: posterior pituitary lobe hormones

ATC code: H01BA02

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 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.

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

Lactose monohydrate

Maize starch

Povidone

Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

30ml High Density Polyethylene (HDPE) bottle with a tamper-proof, twist-off polypropylene (PP) closure with a silica gel desiccant insert. Each bottle contains either 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

None.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd

Vision House

Bedford Road

Petersfield

Hampshire

GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0235

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2007

10 DATE OF REVISION OF THE TEXT

10/04/2007

1 NAME OF THE MEDICINAL PRODUCT

Desmopressin acetate 200 microgram Tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200 micrograms of Desmopressin acetate hydrate (equivalent to 178 micrograms desmopressin). Excipients: lactose monohydrate For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet.

Round, white, scored tablets marked with 0.2 on one side

4 CLINICAL PARTICULARS**4.1 THERAPEUTIC INDICATIONS**

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.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

For oral use.

Treatment of Diabetes Insipidous:

Dosage is individual in diabetes insipidus but clinical experience has shown that the total daily dose normally lies in the range of 200micrograms to 1200micrograms. A suitable starting dose in adults and children is 100micrograms 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 100micrograms to 200micrograms 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 200micrograms at bedtime and only if needed should the dose be increased to 400micrograms.

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 Tablets should only be used in patients with normal blood pressure.

Before prescribing Desmopressin 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- galactosemalabsorption 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: posterior pituitary lobe hormones
ATC code: H01BA02

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 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.

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**

Lactose monohydrate

Maize starch

Povidone

Magnesium stearate

6.2 INCOMPATIBILITIES

Not applicable

6.3 SHELF LIFE

2 years

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton.

6.5 NATURE AND CONTENTS OF CONTAINER

30ml High Density Polyethylene (HDPE) bottle with a tamper-proof, twist-off polypropylene (PP) closure with a silica gel desiccant insert. Each bottle contains either 30 or 90 tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

None.

7 MARKETING AUTHORISATION HOLDER

PLIVA Pharma Ltd

Vision House

Bedford Road

Petersfield

Hampshire

GU32 3QB

8 MARKETING AUTHORISATION NUMBER(S)

PL 10622/0236

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10/04/2007

10 DATE OF REVISION OF THE TEXT

10/04/2007

PATIENT INFORMATION LEAFLET

PATIENT INFORMATION LEAFLET

Desmopressin acetate 100 microgram Tablets and Desmopressin acetate 200 microgram Tablets

Please read this leaflet carefully before you start to take your tablets.

- This leaflet contains important information about your tablets. If you have any doubts or questions, or you are not sure about anything, ask your doctor or pharmacist.
- Keep this leaflet. You may need to read it again.
- Your 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.

This leaflet contains the following information:

1. What Desmopressin acetate Tablets are and what they are used for.
2. Information to read BEFORE taking Desmopressin acetate Tablets.
3. How to take your medicine.
4. Possible side-effects.
5. Storing your medicine.

The name of your medicine is Desmopressin acetate 100 microgram Tablets or Desmopressin acetate 200 microgram Tablets (Desmopressin acetate Tablets).

Each Desmopressin acetate 100 microgram Tablet contains 100 micrograms of the active ingredient desmopressin (as desmopressin acetate hydrate) and are round, white scored tablets marked with 0.1 on one side.

Each Desmopressin acetate 200 microgram Tablet contains 200 micrograms of the active ingredient desmopressin (as desmopressin acetate hydrate) and are round, white scored tablets marked with 0.2 on one side.

Other ingredients are lactose monohydrate, maize starch, povidone, magnesium stearate.

Desmopressin acetate Tablets are available in bottles of 30 or 90 tablets.

Marketing Authorisation Holder: PLIVA Pharma Ltd, Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB.

Manufacturer: KERN Pharma S.L., Pol. Ind. Colón II. C/. Venus, 72. 08228 Terrassa, Barcelona, Spain.

1. What Desmopressin acetate Tablets are and what they are used for.

What is Desmopressin?

Desmopressin is similar to the hormone Vasopressin (an antidiuretic), which temporarily reduces the amount of urine produced by the body.

What is it used for?

Desmopressin is used for the treatment of:

- Some types of diabetes insipidus (a condition that causes frequent passing of water).
- Primary nocturnal enuresis (bedwetting).
- Excessive thirst or frequent passing of water when caused by surgery (hypophysectomy).

2. Information to read BEFORE taking Desmopressin acetate Tablets.

When should you NOT take Desmopressin acetate Tablets?

Ask yourself the following questions:

- Have you ever taken a medicine containing desmopressin or any of the other ingredients listed above and had an unusual or allergic (hypersensitive) reaction?

Effects on your ability to drive and use machines

Desmopressin acetate Tablets should not affect your ability to drive or use machinery.

3. How to take your medicine.

It is important to take the tablets as directed by your doctor. Check the medicine label carefully. If you are not sure, ask your doctor or pharmacist.

Your doctor may check your weight and blood pressure while you are taking Desmopressin acetate Tablets.

For patients being treated for some types of diabetes insipidus (a condition that causes frequent passing of water) Important: This disease should not be confused with diabetes mellitus (sugar diabetes):

The usual daily dose is between 200 micrograms and 1200 micrograms daily. Most patients will take 100 micrograms to 200 micrograms three times daily.

For patients being treated for primary nocturnal enuresis (bedwetting):

The usual dose for children above 5 years old and adults under 65 years old is 200 micrograms taken at bedtime. This may be increased to 400 micrograms if needed. Your doctor will check that you still need to take these tablets regularly (every three months).

For patients being treated for excessive thirst or frequent passing of water when caused by certain medical procedures (hypophysectomy) or a head injury:

The dose will be decided by your doctor depending on the strength of your urine.

If you take too many tablets

It is important to stick to the dose on the label of your medicine. If you or someone else has taken more Desmopressin acetate Tablets than they should, contact your doctor, pharmacist or hospital emergency department immediately. Always take any left over tablets with you and also the box as this will allow easier identification of the tablets. An overdose of Desmopressin acetate Tablets can lead to, increase in weight, headache, feeling sick, stomach cramps, and in serious cases swelling of the brain, fits and coma.

If you forget to take your tablets

If you forget to take your tablets, take your tablets at the usual time for your next dose. **Do not** take twice the number of tablets, just carry on as before.

4. Can your tablets have any side-effects?

Like all medicines, Desmopressin acetate Tablets can have side-effects.

If you notice any of the following reactions, tell your doctor immediately or go to the casualty department at your nearest hospital before taking another dose:

- General allergic reactions including skin rash (red spots, hives, itching), chest tightness or wheeziness, swelling of the eyelids, face or lips.
- Confusion with or without fits

(It is possible that there is water intoxication or low sodium level in the blood).

This is a very serious side effect; it is very rare and happens when Desmopressin acetate Tablets are taken without reducing your fluid intake.

Other possible side effects are:

- Stomach pain or cramps, feeling or being sick
- Headaches, and very rarely emotional problems in children

If you suffer from any of the side-effects listed above or if you experience any other side-effects not mentioned on this leaflet, please inform your doctor or pharmacist immediately.

5. Storing your tablets.

Store out of the reach and sight of children

- Do you have heart failure or any other conditions requiring treatment with diuretic agents (water tablets)?
- Are you being treated for primary nocturnal enuresis (bedwetting) and have high blood pressure, or are over 65 years old?
- Do you suffer from alcoholism?
- Do you drink an unusually large amount of fluid? This may be caused by a condition known as psychogenic polydipsia.
- Do you suffer from low levels of sodium in your blood (hyponatraemia)?
- Do you have a syndrome that causes your body to produce the wrong levels of antidiuretic hormone (SIADH)?

If the answer to any of these questions is YES and you have not already discussed this with your doctor, you should do so as soon as possible and before taking these tablets.

When should you take special care while taking Desmopressin acetate Tablets?

Ask yourself the following questions:

- Do you suffer from a serious heart or kidney disease?
- Do you have cardiovascular disease?
- Do you have cystic fibrosis?
- Are you pregnant, trying to become pregnant or breast-feeding?
- Do you suffer from blood pressure problems?

If the answer to any of the above questions is YES and you have not already discussed this with your doctor, you should do so as soon as possible and before taking this medicine.

Some conditions mean you are more likely to build up too much water in your body. If you have one of these conditions your doctor will advise you about how to stop this happening, as it is more likely to happen when you are taking Desmopressin acetate Tablets.

If the medicine is used for primary nocturnal enuresis (bedwetting), you should;

- stop taking Desmopressin acetate Tablets if you are being sick or have diarrhoea. Check with your doctor or pharmacist before you start to take your Desmopressin acetate Tablets again.
- try not to drink the water while swimming.
- limit the amount you drink from 1 hour before you take the tablets, to 8 hours after you have taken the tablets.

If you have been told that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Taking other medicines

It is important to check whether you are or have recently been taking other medicines before you start taking your tablets. Are you taking any of the following medicines?

- Antidepressants e.g. fluoxetine, sertraline.
- Chlorpromazine which is used to treat conditions including schizophrenia and other mental illnesses in adults and children, agitation, aggression and also to stop you feeling or being sick. .
- Carbamazepine (a medicine used to treat fits and mental illness).
- A type of pain killer called NSAIDs (Non-steroidal anti-inflammatory drugs) which include ibuprofen and aspirin.
- Medicines which are used to stop diarrhoea e.g. loperamide.

It is important that you consult your doctor or pharmacist if you are taking any other medicine. If you are not sure whether another medicine you are taking may be one of the types listed above, check with your doctor or pharmacist. Please inform your doctor or pharmacist if you are taking, or have recently taken, any other medicine including those that you have bought without a prescription.

Do not store above 25°C. Store in the original package. Keep the bottle tightly closed and keep the bottle in the outer carton to protect the tablets from light and moisture.

Do not use this medicine after the 'use by' date on the carton. If you have any tablets that are out of date, return it to your pharmacist for disposal.

Remember: this treatment is for YOU. Only a doctor can prescribe it for you. Never give it to others.

Date of preparation: January 2007

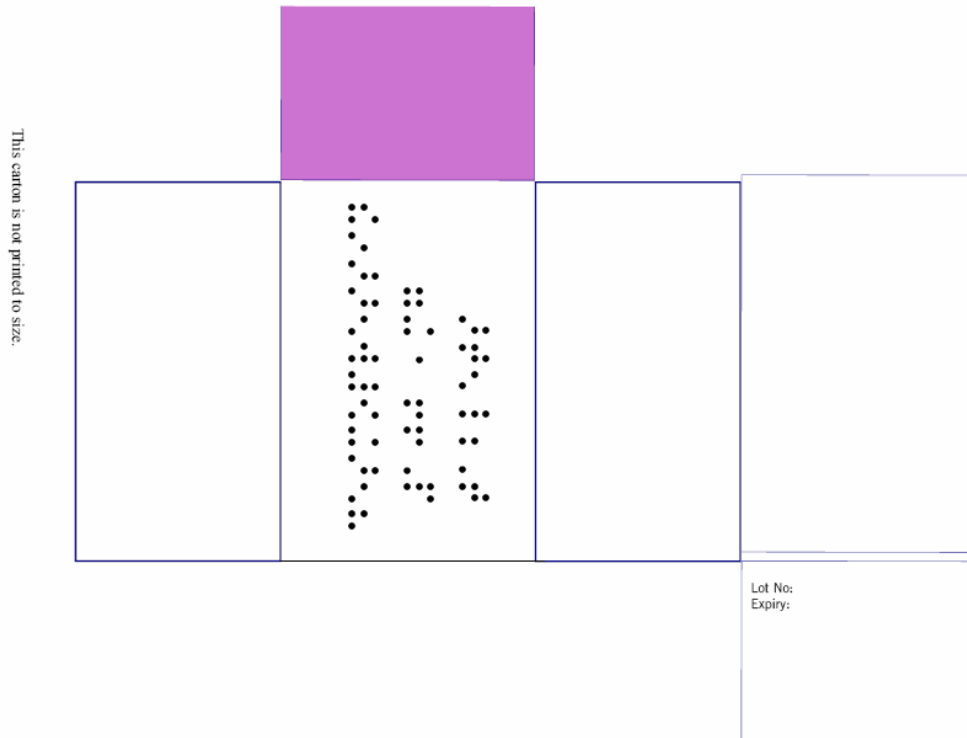
LABELLING

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Desmopressin acetate 100 microgram Tablets 30 Tablets			
<p>MA Holder: PLIVA Pharma Ltd., Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB.</p> <p>PL 10622/0235</p>	<p>Desmopressin acetate 100 microgram Tablets 30 Tablets</p> <p>Each tablet contains 100 micrograms of desmopressin acetate hydrate</p>	<p>Desmopressin acetate 100 microgram Tablets 30 Tablets</p> <p>Each tablet contains 100 micrograms of desmopressin acetate hydrate.</p>	<p>Dosage: For oral use as directed by your doctor.</p> <p>This medicinal product contains lactose. Please read enclosed package leaflet before use.</p> <p>Do not store above 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <div style="border: 1px solid black; width: 100px; height: 30px; margin: 10px auto; text-align: center;">BAR CODE</div> <p style="text-align: right; font-weight: bold;">POM</p>
		<p>Lot No: Expiry:</p>	

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Desmopressin acetate 100 microgram Tablets 90 Tablets			
<p>MA Holder: PLIVA Pharma Ltd., Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB.</p> <p>PL 10622/0235</p>	<p>Desmopressin acetate 100 microgram Tablets 90 Tablets</p> <p>Each tablet contains 100 micrograms of desmopressin acetate hydrate</p>	<p>Desmopressin acetate 100 microgram Tablets 90 Tablets</p> <p>Each tablet contains 100 micrograms of desmopressin acetate hydrate.</p>	<p>Dosage: For oral use as directed by your doctor.</p> <p>This medicinal product contains lactose. Please read enclosed package leaflet before use.</p> <p>Do not store above 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton.</p> <p>KEEP OUT OF THE REACH AND SIGHT OF CHILDREN</p> <div style="border: 1px solid black; width: 100px; height: 30px; margin: 10px auto; text-align: center;">BAR CODE</div> <p style="text-align: right; font-weight: bold;">POM</p>
		<p>Lot No: Expiry:</p>	



Desmopressin acetate 100 microgram Tablets

30 Tablets

Each tablet contains 100 micrograms of desmopressin acetate hydrate.

Dosage: For oral use as directed by your doctor.
This medicinal product contains lactose. Please read enclosed package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
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Lot no:
Expiry:

Desmopressin acetate 100 microgram Tablets


90 Tablets

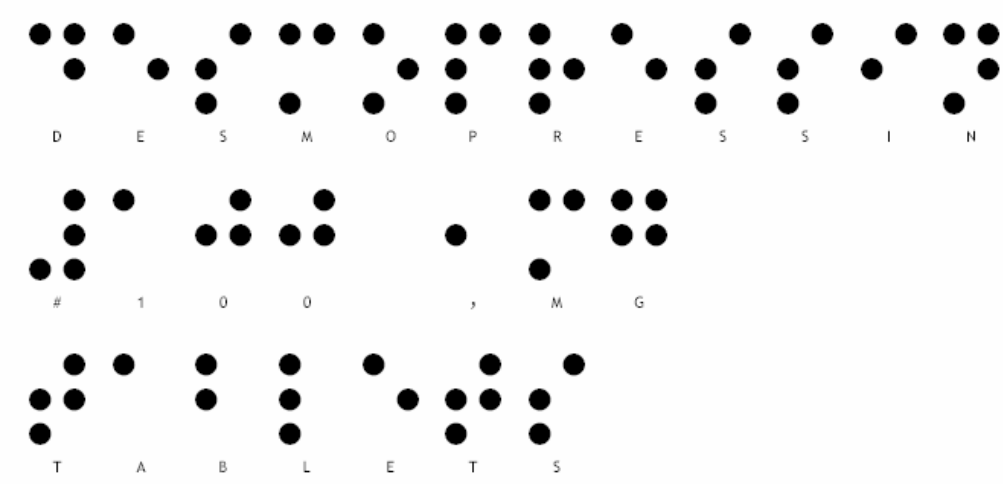
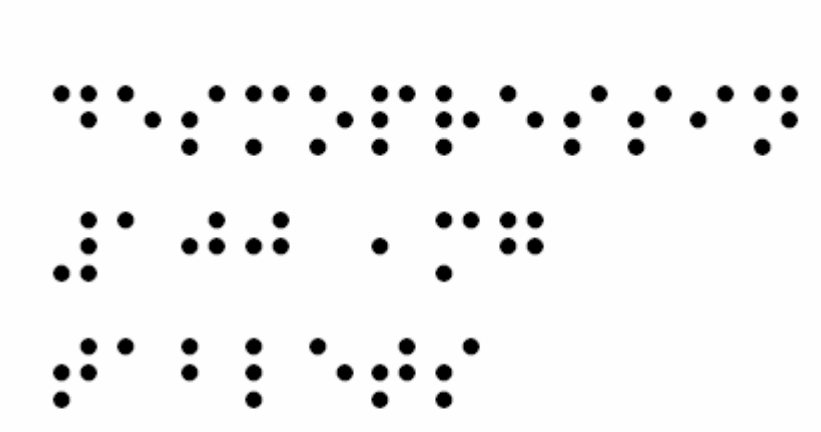
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  Lot nos. Expiry:



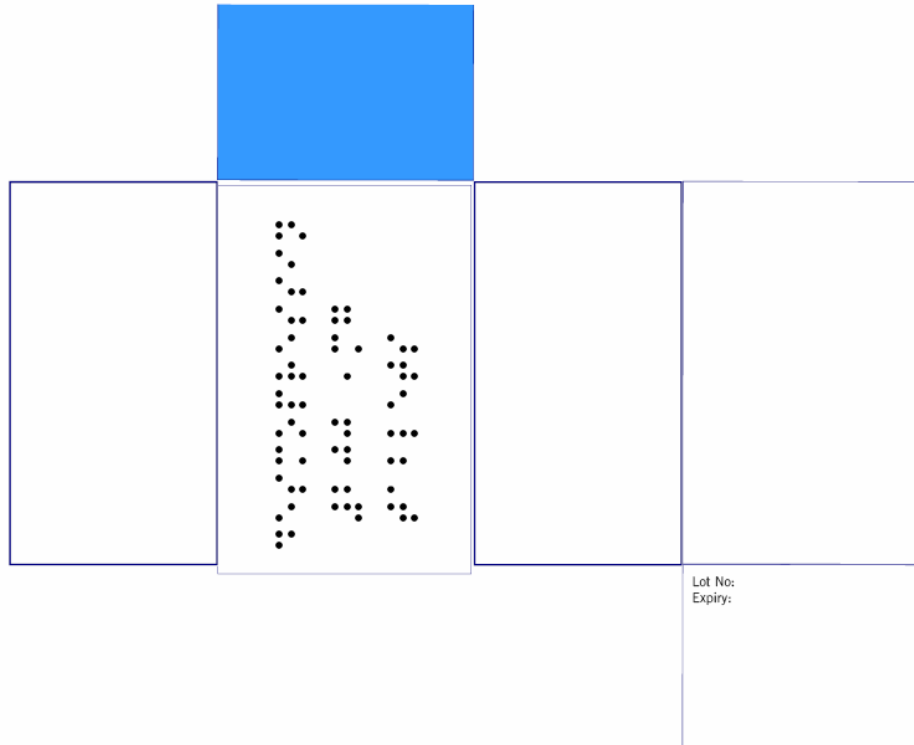
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Desmopressin acetate 200 microgram Tablets 30 Tablets			
MA Holder: PLIVA Pharma Ltd., Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB. PL 10622/0236	Desmopressin acetate 200 microgram Tablets 30 Tablets Each tablet contains 200 micrograms of desmopressin acetate hydrate	Desmopressin acetate 200 microgram Tablets 30 Tablets Each tablet contains 200 micrograms of desmopressin acetate hydrate	Dosage: For oral use as directed by your doctor. This medicinal product contains lactose Please read enclosed package leaflet before use. Do not store above 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN POM <div style="border: 1px solid black; width: 100px; height: 30px; margin: 0 auto; text-align: center;"> BAR CODE </div>
		Lot No: Expiry:	

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Desmopressin acetate 200 microgram Tablets 90 Tablets			
MA Holder: PLIVA Pharma Ltd., Vision House, Bedford Road, Petersfield, Hampshire GU32 3QB. PL 10622/0236	Desmopressin acetate 200 microgram Tablets 90 Tablets Each tablet contains 200 micrograms of desmopressin acetate hydrate	Desmopressin acetate 200 microgram Tablets 90 Tablets Each tablet contains 200 micrograms of desmopressin acetate hydrate	Dosage: For oral use as directed by your doctor. This medicinal product contains lactose Please read enclosed package leaflet before use. Do not store above 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton. KEEP OUT OF THE REACH AND SIGHT OF CHILDREN POM <div style="border: 1px solid black; width: 100px; height: 30px; margin: 0 auto; text-align: center;"> BAR CODE </div>
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Desmopressin acetate 200 microgram Tablets


30 Tablets

Each tablet contains 200 micrograms of the active ingredient desmopressin acetate hydrate.

Dosage: For oral use as directed by your doctor.
This medicinal product contains lactose. Please read enclosed package leaflet before use.

KEEP OUT OF THE REACH AND SIGHT OF CHILDREN
Do not store above 25°C. Store in the original package. Keep the bottle tightly closed. Keep the bottle in the outer carton.

MA Holder:
PLIVA Pharma Ltd., Vision House,
Bedford Road, Petersfield, Hampshire GU32 3QB.
PL 10622/0236

 **PLIVA**

POM Lot no:
Expiry:

Desmopressin acetate 200 microgram Tablets

90 Tablets

Each tablet contains 200 micrograms of desmopressin acetate hydrate.

Dosage: For oral use as directed by your doctor.
This medicinal product contains lactose. Please read enclosed package leaflet before use.

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  Lot no: Expire

