CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 077414/S-008

Name: Desmopressin Acetate Tablets

Sponsor: Apotex Corporation

Approval Date: March 7, 2006

Indication: Antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077414/S-008

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077414/S-008

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 077414/S-007 and S-008

Changes Being Effected in 30 Days
APPROVAL

Apotex Corp.
U.S. Agent for Apotex Inc.
2400 North Commerce Parkway
Suite 400
Weston, FL 33326

Attention: Kiran Krishnan
VP of US Regulatory Affairs

Dear Sir:

Please refer to your Supplemental Abbreviated New Drug Applications (sANDAs) dated November 28, 2008, received November 28, 2008, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application (ANDA) for Desmopressin Acetate Tablets, 0.1 mg and 0.2 mg.

The supplemental ANDAs, submitted as "Changes Being Effected in 30 Days," provides for:

S-007: 1. Removal of lower limit for the water content in the drug substance (change from (b) (4) due to a confirmation that the physical form of the drug substance is the (b) (4)

2. Claim USP grade for the drug substance.

S-008: Corresponding labeling changes.

We have completed our review of these sANDAs, and they are approved.

We remind you that you must comply with the requirements for the approved ANDA described in 21 CFR 314.80-81.

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1 of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the Federal Register notice announcing facility fee amounts. All finished dosage

forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

The material submitted is being retained in our files.

Sincerely yours,

William P. Rickman -S

Digitally signed by William P. Rickman -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300043242, cn=William P. Rickman -S
Date: 2015.01.23 10:21:25 -05'00'

For Carol A. Holquist, RPh
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077414/S-008

LABELING

(b) (4)

(b) (4)

(b) (4)

(b) (4)

COMPOSITE

(b) (4)

Clear Laminate

(b) (4)

(b) (4)

Each tablet contains 0.1 mg of desmopressin acetate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Avoid exposure to excessive heat or light.

Dispense in a tight, light-resistant container [see USP].

Usual dosage: See package insert.

277474

NDC 60505-0257-8

Desmopressin Acetate Tablets

0.1 mg

1000 Tablets

℞ Only

APOTEX CORP.

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

3 N 60505-0257-8 7

Open Here

(b) (4)

NON PRINTING AREA (GLUE PANEL)

DESMOPRESSIN ACETATE TABLETS 0.1 mg and 0.2 mg

℞ Only

DESCRIPTION

Desmopressin Acetate Tablets are a syn hetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1129.27
Empirical Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2$

SCH_2CH_2C(=O)-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH_2•xCH_3COOH

where 1<x<1.5

1-(3-mercaptop opionic acid)-8-D-arginine vasopressin monoacetate (salt).

Desmopressin acetate tablets, for oral administration, contain ei her 0.1 or 0.2 mg desmopressin acetate. In addition, each tablet contains he following inactive ingredients: anhyd ous lactose, co n starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Desmopressin acetate tablets contain as active substance, desmopressin acetate, a syn hetic analogue of he natural hormone arginine vasopressin.

Central Diabetes Insipidus
Dose response studies in patients wi h diabetes insipidus have demonstrated that oral doses of 0.025 mg to 0.4 mg p oduced clinically significant antidiuretic effects. In most patients, doses of 0.1 mg to 0.2 mg produced optimal antidiuretic effects lasting up to eight hours. Wi h doses of 0.4 mg, antidiuretic effects were observed for up to 12 hours; measurements beyond 12 hours were not recorded. Increasing oral doses produced dose dependent increases in the plasma levels of desmopressin acetate.

The plasma half-life of desmopressin acetate followed a monoexponential time course with $t_{1/2}$ values of 1.5 to 2.5 hours which was independent of dose.

The bioavailability of desmopressin acetate oral tablets is about 5% compared to intranasal desmopressin acetate, and about 0.16% compared to intravenous desmopressin acetate. The time to reach maximum plasma desmopressin acetate levels ranged f om 0.9 to 1.5 hours following oral or intranasal administration, respectively. Following administration of desmopressin acetate tablets, he onset of antidiuretic effect occurs at a ound 1 hour, and it reaches a maximum at about 4 to 7 hours based on the measurement of increased urine osmolality.

The use of desmopressin acetate tablets in patients wi h an established diagnosis will result in a reduction in urinary output wi h an accompanying increase in urine osmolality. These effects usually will allow resumption of a more normal life style, wi h a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response to he intranasal formulations of desmopressin acetate. Usually, he change occurred over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to a local inactivation of the peptide. No lessening of effect was observed in the 46 patients who were treated wi h desmopressin acetate tablets for 12 to 44 mon hs and no serum antibodies to desmopressin were detected.

The change in structure of arginine vasopressin to desmopressin acetate resulted in less vasopressor activity and decreased action on visceral smoo h muscle relative to enhanced antidiuretic activity. Consequently, clinically effective antidiuretic doses are usually below the hreshold for effects on vascular or visceral smoo h muscle. In he four long-term studies of desmopressin acetate tablets, no increases in blood pressure in 46 patients receiving desmopressin acetate tablets for periods of 12 to 44 mon hs were reported.

In one study, he pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulation were compared during an 8-hour dosing interval at steady state. The doses administered to 36 hydrated (water loaded) healthy male adult volunteers every 8 hours were 0.1, 0.2, 0.4 mg orally and 0.01 mg intranasally by hinal tube. The results are shown in the following table:

Mean Changes from Baseline (SE) in Pharmacodynamic Parameters in Normal Healthy Adult Volunteers

Treatment	Total Urine Volume in mL	Maximum Urine Osmolality in mOsm/kg
0.1 mg PO q8h	-3689.3 (149.6)	514.8 (21.9)
0.2 mg PO q8h	-4429.9 (149.6)	686.3 (21.9)
0.4 mg PO q8h	-4998.8 (149.6)	769.3 (21.9)
0.01 mg IN q8h	-4844.9 (149.6)	754.1 (21.9)

(SE) = Standard er or of he mean

W th respect to he mean values of total urine volume decrease and maximum urine osmolality increase f om baseline, the 90% confidence limits estimated hat he 0.4 mg and 0.2 mg oral dose p oduced between 95% and 110% and 84% to 99% of pharmacodynamic activity, respectively, when compared to he 0.01 mg intranasal dose.

While both the 0.2 mg and 0.4 mg oral doses are considered pharmacodynamically similar to he 0.01 mg intranasal dose, he pharmacodynamic data on an inter-subject basis was highly variable and, herefore, individual dosing is recommended.

In another study in diabetes insipidus patients, he pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulations were compared over a 12-hour period. Ten fluid-cont olled patients under age 18 were administered tablet doses of 0.2 mg and 0.4 mg, and intranasal doses of 0.01 mg and 0.02 mg.

Mean Peak Pharmacodynamic Parameters (SD) in Pediatric and Adolescent Diabetes Insipidus Patients

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
0.01 mg IN	0.3 (0.15)	717.0 (224.63)
0.02 mg IN	0.3 (0.25)	761.8 (298.82)
0.2 mg PO	0.3 (0.12)	678.3 (147.91)
0.4 mg PO	0.2 (0.15)	787.2 (73.34)

(SD) = Standard Deviation

All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, p onounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, mean urine volume was 4 mL/min and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over he time course recorded (0 to 12 hours). A statistical separation f om baseline did not occur at any dose or time point. In hese patients, he 0.2 mg tablets and he 0.01 mg intranasal spray exhibited similar pharmacodynamic p ofiles as did he 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In ano her study of adult diabetes insipidus patients previously cont olled on desmopressin acetate intranasal spray, after one week of self-titration f om spray to tablets, patients' diuresis was cont olled wi h 0.1 mg desmopressin acetate tablets hree times a day.

Primary Nocturnal Enuresis
Two double-blind, randomized, placebo-cont olled studies were conducted in 340 patients w th primary noctu nal enuresis. Patients were 5 to 17 years old, and 72% were males. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period in which the average number of wet nights was 10 (range 4 to 14). Patients were hen randomized to receive 0.2, 0.4, or 0.6 mg of desmopressin acetate or placebo. The pooled results after two weeks are shown in he following table:

Response to Desmopressin Acetate and Placebo at Two Weeks of Treatment Mean (SE) Number of Wet Nights/2 Weeks

	Placebo (n = 85)	0.2 mg/day (n = 79)	0.4 mg/day (n = 82)	0.6 mg/day (n = 83)
Baseline	10 (0 3)	11 (0 3)	10 (0 3)	10 (0 3)
Reduction from Baseline	1 (0 3)	3 (0.4)	3 (0.4)	4 (0.4)
Pe cen Reduction from Baseline	10%	27%	30%	40%
p-value vs. placebo	—	<0 05	<0 05	<0 05

Patients treated wi h desmopressin acetate tablets showed a statistically significant reduction in he number of wet nights compared to placebo-treated patients. A greater response was observed wi h increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing he placebo-cont olled studies were started on 0.2 mg/day desmopressin acetate, and he dose was p ogressively increased until he optimal response was achieved (maximum dose 0.6 mg/day). A total of 230 patients were evaluated for efficacy; he average number of wet nights/2 weeks during he untreated baseline period was 10 (range 4 to 14), and the average duration (SD) of treatment was 4.2 (1.8) mon hs. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to he 0.6 mg/day dose. The majority of patients (198 of 230, 86%) were titrated to he highest dose. When all dose g oups were combined, 128 (56%) showed at least a 50% reduction f om baseline in he number of wet nights/2 weeks, while 87 (38%) patients achieved a complete or near complete response.

Human Pharmacokinetics
Desmopressin acetate is mainly excreted in he urine. A pharmacokinetic study conducted in heal hy volunteers and patients wi h mild, moderate, and severe renal impairment (n=24, 6 subjects in each g oup) receiving single dose desmopressin acetate (2 mcg) injection demonstrated a difference in desmopressin acetate terminal half-life. Terminal half-life significantly increased f om 3 hours in normal heal hy patients to 9 hours in patients wi h severe renal impairment. (See **CONTRAINDICATIONS.**)

INDICATIONS AND USAGE

Central Diabetes Insipidus
Desmopressin acetate tablets are indicated as antidiuretic replacement herapy in the management of central diabetes insipidus and for he management of he temporary polyuria and polydipsia following head trauma or surgery in he pituitary region. Desmopressin acetate is ineffective for he treatment of neph ogenic diabetes insipidus.

Patients were selected for herapy based on he diagnosis by means of he water deprivation test, he hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate can be monitored by measuring urine volume and osmolality.

Primary Nocturnal Enuresis
Desmopressin acetate tablets are indicated for he management of primary noctu nal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals w th known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

Desmopressin acetate tablets are contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).

Desmopressin acetate is contraindicated in patients wi h hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported f om world-wide postmarketing experience in patients treated desmopressin acetate. Desmopressin acetate is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless p operly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When desmopressin acetate tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS, Pediatric Use and Geriatric Use.**) All patients receiving desmopressin acetate tablets herapy should be observed for the following signs of symptoms associated wi h hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, le hargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. Particular attention should be paid to he possibility of he rare occurrence of an extreme decrease in plasma osmolality hat may result in seizures which could lead to coma.

3. Desmopressin acetate tablets should be used wi h caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General
Intranasal formulations of desmopressin acetate at high doses and intravenous desmopressin acetate have infrequently p oduced a slight elevation of blood pressure which disappears wi h a reduction of dosage. Al hough this effect has not been observed when single oral doses up to 0.6 mg have been administered, he drug should be used wi h caution in patients wi h co onary artery insufficiency and/or hypertensive cardiovascular disease, because of a possible rise in blood pressure.

Desmopressin acetate should be used wi h caution in patients with conditions associated with fluid and elect olyte imbalance, such as cystic fib osis, heart failure and renal disorders because hese patients are p one hyponatremia.

Rare severe allergic reactions have been reported wi h desmopressin acetate. Anaphylaxis has been reported rarely wi h intravenous and intranasal administration of desmopressin acetate but not with desmopressin acetate tablets.

Laboratory Tests
Central Diabetes Insipidus
Laboratory tests for monitoring the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions
Al hough he pressor activity of desmopressin acetate is very low compared to its antidiuretic activity, large doses of desmopressin acetate tablets should be used wi h o her pressor agents only wi h careful patient monitoring. The concomitant administration of drugs that may increase he risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective se otonin re-uptake inhibitors, chlorp omazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed wi h caution.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy
Category B
Fertility studies have not been done. Teratology studies in rats and rabbits at doses f om 0.05 to 10 *mcg*/kg/day (approximately 0.1 times he maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to he fetus due to desmopressin acetate. There are, however, no adequate and well-cont olled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low bir h weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year Swedish epidemiologic study of he use of desmopressin acetate in pregnant women with diabetes insipidus found he rate of birth defects to be no greater han that in he general population; however, the statistical power of this study is low. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no ute otonic action and the physician wil have to weigh he possible herapeutic advantages against he possible risks in each case.

Nursing Mothers
There have been no cont olled studies in nursing mo hers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable desmopressin acetate in breast milk following an intranasal dose of 0.01 mg.

It is not known whe her he drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to nursing mo hers.

Pediatric Use
Central Diabetes Insipidus
Desmopressin acetate tablets have been used safely in pediatric patients, age 4 years and older, wi h diabetes insipidus for periods up to 44 mon hs. In younger pediatric patients he dose must be individually adjusted in order to prevent an excessive decrease in plasma osmolality leading to hyponatremia and possible convulsions; dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). Use of desmopressin acetate tablets in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient and/or guardian. (See **WARNINGS.**)

Primary Nocturnal Enuresis
Desmopressin acetate tablets have been safely used in pediatric patients age 6 years and older with primary noctu nal enuresis for up to 6 mon hs. Some patients respond to a dose of 0.2 mg; however, increasing responses are seen at doses of 0.4 mg and 0.6 mg. No increase in he frequency or severity of adverse reactions or decrease in efficacy was seen wi h an increased dose or duration. The dose should be individually adjusted to achieve he best results. Treatment with desmopressin for primary noctu nal enuresis should be interrupted during acute intercurrent illness characterized by fluid and/or elect olyte imbalance (e.g., systemic infections, fever, recurrent vomiting or diar hea) or under conditions of extremely hot wea her, vigo ous exercise or o her conditions associated wi h increased water intake.

Geriatric Use
Clinical studies of desmopressin acetate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently f om younger subjects.

O her reported clinical experience has not identified differences in responses between he elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting he greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or o her drug herapy.

This drug is known to be substantially excreted by he kidney, and he risk of toxic reactions to his drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Desmopressin acetate is contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).

(See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics** and **CONTRAINDICATIONS.**)

Use of desmopressin acetate tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient. (See **WARNINGS.**)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of desmopressin acetate tablets and injection have p oduced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared w th reduction in dosage.

Central Diabetes Insipidus
In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 mon hs of desmopressin acetate tablet herapy, transient increases in AST (SGOT) no higher han 1.5 times he upper limit of normal were occasionally observed. Elevated AST (SGOT) retu ned to he normal range despite continued use of desmopressin acetate tablets.

Primary Nocturnal Enuresis
The only adverse event occurring in ≥3% of patients in cont olled clinical trials with desmopressin acetate tablets hat was p obably, possibly, or remotely related to study drug was headache (4% desmopressin acetate, 3% placebo).

Other
The following adverse events have been reported; however heir relationship to desmopressin acetate has not been established: abnormal hinking, diar hea, and edema-weight gain.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

Post Marketing
There have been rare reports of hyponatremic convulsions associated wi h concomitant use wi h he following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, d owsiness, continuing headache, p oblems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS.**) In case of overdose, he dose should be reduced, frequency of administration decreased, or the drug withdrawn according to he severity of he condition. There is no known specific antidote for desmopressin acetate. The patient should be observed and treated wi h app opriate symptomatic herapy.

An oral LD_{50} has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months wi hout any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to he diu nal patte n of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water tu nover. Patients previously on intranasal desmopressin acetate herapy should begin tablet herapy twelve hours after he last intranasal dose. During he initial dose titration period, patients should be observed closely and app opriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during he course of desmopressin acetate tablet herapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water tu nover. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

Adults and Children
It is recommended hat patients be started on doses of 0.05 mg (1/2 of he 0.1 mg tablet) two times a day and individually adjusted to heir optimum therapeutic dose. Most patients in clinical trials found hat he optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diu nal hythm of water tu nover. Total daily dosage should be increased or decreased in the range of 0.1 mg to 1.2 mg divided into two or three daily doses as needed to obtain adequate antidiuresis.

See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

Geriatric Use
This drug is known to be substantially excreted by the kidney, and he risk of toxic reactions to his drug may be greater in patients wi h impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics, CONTRAINDICATIONS,** and **PRECAUTIONS, Geriatric Use.)**

Primary Nocturnal Enuresis
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to response. Patients previously on intranasal desmopressin acetate herapy can begin tablet herapy he night following (24 hours after) he last intranasal dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve he desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum f om 1 hour before desmopressin administration, until he next mo ning, or at least 8 hours after administration. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

HOW SUPPLIED

Desmopressin Acetate Tablets 0.1 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.1" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0257-3)
Bottles of 100 (NDC 60505-0257-1)
Bottles of 1000 (NDC 60505-0257-8)

Desmopressin Acetate Tablets 0.2 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.2" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0258-3)
Bottles of 100 (NDC 60505-0258-1)
Bottles of 1000 (NDC 60505-0258-8)

Store 20° to 25°C (68° to 77°F) [see USP Cont olled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Keep out of the reach of children.

APOTEX INC.
DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg

Manufactured by:	Manufactured for:
Apotex Inc.	Apotex Corp.
To onto, Ontario	Weston, Florida
Canada M9L 1T9	33326

(APO-DESMOPRESSIN-R03-51X138-LFLT-10/30/08)

Revised: October 2008

Rev. 4

(b) (4)

COMPOSITE

Clear Laminate

(b) (4)

Open Here

NDC 60505-0257-1

Desmopressin Acetate Tablets

0.1 mg

100 Tablets

℞ Only

APOTEX CORP.

Each tablet contains 0.1 mg of desmopressin acetate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Avoid exposure to excessive heat or light.

Dispense in a tight, light-resistant container [see USP].

Usual dosage: See package insert.

271473

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

N 3 60505-0257-1 8

NON PRINTING AREA (GLUE PANEL)

DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg
℞ Only

DESCRIPTION

Desmopressin Acetate Tablets are a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1129.27

Empirical Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2$

SCH₂CH₂C(O)-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-NH₂•xCH₃COOH

where 1<x<1.5

1-(3-mercaptopropionic acid)-8-D-arginine vasopressin monoacetate (salt).

Desmopressin acetate tablets, for oral administration, contain either 0.1 or 0.2 mg desmopressin acetate. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, corn starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Desmopressin acetate tablets contain as active substance, desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin.

Central Diabetes Insipidus

Dose response studies in patients with diabetes insipidus have demonstrated that oral doses of 0.025 mg to 0.4 mg produced clinically significant antidiuretic effects. In most patients, doses of 0.1 mg to 0.2 mg produced optimal antidiuretic effects lasting up to eight hours. With doses of 0.4 mg, antidiuretic effects were observed for up to 12 hours; measurements beyond 12 hours were not recorded. Increasing oral doses produced dose dependent increases in the plasma levels of desmopressin acetate.

The plasma half-life of desmopressin acetate followed a monoexponential time course with $t_{1/2}$ values of 1.5 to 2.5 hours which was independent of dose.

The bioavailability of desmopressin acetate oral tablets is about 5% compared to intranasal desmopressin acetate, and about 0.16% compared to intravenous desmopressin acetate. The time to reach maximum plasma desmopressin acetate levels ranged from 0.9 to 1.5 hours following oral or intranasal administration, respectively. Following administration of desmopressin acetate tablets, the onset of antidiuretic effect occurs at around 1 hour, and it reaches a maximum at about 4 to 7 hours based on the measurement of increased urine osmolality.

The use of desmopressin acetate tablets in patients with an established diagnosis will result in a reduction in urinary output with an accompanying increase in urine osmolality. These effects usually will allow resumption of a more normal life style, with a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response to the intranasal formulations of desmopressin acetate. Usually, the change occurred over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to a local inactivation of the peptide. No lessening of effect was observed in the 46 patients who were treated with desmopressin acetate tablets for 12 to 44 months and no serum antibodies to desmopressin were detected.

The change in structure of arginine vasopressin to desmopressin acetate resulted in less vasopressor activity and decreased action on visceral smooth muscle relative to enhanced antidiuretic activity. Consequently, clinically effective antidiuretic doses are usually below the threshold for effects on vascular or visceral smooth muscle. In the four long-term studies of desmopressin acetate tablets, no increases in blood pressure in 46 patients receiving desmopressin acetate tablets for periods of 12 to 44 months were reported.

In one study, the pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulation were compared during an 8-hour dosing interval at steady state. The doses administered to 36 hydrated (water loaded) healthy male adult volunteers every 8 hours were 0.1, 0.2, 0.4 mg orally and 0.01 mg intranasally by rhinal tube. The results are shown in the following table:

Mean Changes from Baseline (SE) in Pharmacodynamic Parameters in Normal Healthy Adult Volunteers

Treatment	Total Urine Volume in mL	Maximum Urine Osmolality in mOsm/kg
0.1 mg PO q8h	-3689.3 (149.6)	514.8 (21.9)
0.2 mg PO q8h	-4429.9 (149.6)	686.3 (21.9)
0.4 mg PO q8h	-4998.8 (149.6)	769.3 (21.9)
0.01 mg IN q8h	-4844.9 (149.6)	754.1 (21.9)

(SE) = Standard error of the mean

With respect to the mean values of total urine volume decrease and maximum urine osmolality increase from baseline, the 90% confidence limits estimated that the 0.4 mg and 0.2 mg oral dose produced between 95% and 110% and 84% to 99% of pharmacodynamic activity, respectively, when compared to the 0.01 mg intranasal dose.

While both the 0.2 mg and 0.4 mg oral doses are considered pharmacodynamically similar to the 0.01 mg intranasal dose, the pharmacodynamic data on an inter-subject basis was highly variable and, therefore, individual dosing is recommended.

In another study in diabetes insipidus patients, the pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulations were compared over a 12-hour period. Ten fluid-controlled patients under age 18 were administered tablet doses of 0.2 mg and 0.4 mg, and intranasal doses of 0.01 mg and 0.02 mg.

Mean Peak Pharmacodynamic Parameters (SD) in Pediatric and Adolescent Diabetes Insipidus Patients

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
0.01 mg IN	0.3 (0.15)	717.0 (224.63)
0.02 mg IN	0.3 (0.25)	761.8 (298.82)
0.2 mg PO	0.3 (0.12)	678.3 (147.91)
0.4 mg PO	0.2 (0.15)	787.2 (73.34)

(SD) = Standard Deviation

All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, pronounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, mean urine volume was 4 mL/min and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over the time course recorded (0 to 12 hours). A statistical separation from baseline did not occur at any dose or time point. In these patients, the 0.2 mg tablets and the 0.01 mg intranasal spray exhibited similar pharmacodynamic profiles as did the 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In another study of adult diabetes insipidus patients previously controlled on desmopressin acetate intranasal spray, after one week of self-titration from spray to tablets, patients' diuresis was controlled with 0.1 mg desmopressin acetate tablets three times a day.

Primary Nocturnal Enuresis

Two double-blind, randomized, placebo-controlled studies were conducted in 340 patients with primary nocturnal enuresis. Patients were 5 to 17 years old, and 72% were males. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period in which the average number of wet nights was 10 (range 4 to 14). Patients were then randomized to receive 0.2, 0.4, or 0.6 mg of desmopressin acetate or placebo. The pooled results after two weeks are shown in the following table:

Response to Desmopressin Acetate and Placebo at Two Weeks of Treatment Mean (SE) Number of Wet Nights/2 Weeks

	Placebo (n = 85)	0.2 mg/day (n = 79)	0.4 mg/day (n = 82)	0.6 mg/day (n = 83)
Baseline	10 (0.3)	11 (0.3)	10 (0.3)	10 (0.3)
Reduction from Baseline	1 (0.3)	3 (0.4)	3 (0.4)	4 (0.4)
Percent Reduction from Baseline	10%	27%	30%	40%
p-value vs. placebo	—	<0.05	<0.05	<0.05

Patients treated with desmopressin acetate tablets showed a statistically significant reduction in the number of wet nights compared to placebo-treated patients. A greater response was observed with increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing the placebo-controlled studies were started on 0.2 mg/day desmopressin acetate, and the dose was progressively increased until the optimal response was achieved (maximum dose 0.6 mg/day). A total of 230 patients were evaluated for efficacy; the average number of wet nights/2 weeks during the untreated baseline period was 10 (range 4 to 14), and the average duration (SD) of treatment was 4.2 (1.8) months. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to the 0.6 mg/day dose. The majority of patients (198 of 230, 86%) were titrated to the highest dose. When all dose groups were combined, 128 (56%) showed at least a 50% reduction from baseline in the number of wet nights/2 weeks, while 87 (38%) patients achieved a complete or near complete response.

Human Pharmacokinetics

Desmopressin acetate is mainly excreted in the urine. A pharmacokinetic study conducted in healthy volunteers and patients with mild, moderate, and severe renal impairment (n=24, 6 subjects in each group) receiving single dose desmopressin acetate (2 mcg) injection demonstrated a difference in desmopressin acetate terminal half-life. Terminal half-life significantly increased from 3 hours in normal healthy patients to 9 hours in patients with severe renal impairment. (See **CONTRAINDICATIONS.**)

INDICATIONS AND USAGE

Central Diabetes Insipidus

Desmopressin acetate tablets are indicated as antidiuretic replacement therapy in the management of central diabetes insipidus and for the management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. Desmopressin acetate is ineffective for the treatment of nephrogenic diabetes insipidus.

Patients were selected for therapy based on the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate can be monitored by measuring urine volume and osmolality.

Primary Nocturnal Enuresis

Desmopressin acetate tablets are indicated for the management of primary nocturnal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

Desmopressin acetate tablets are contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).

Desmopressin acetate is contraindicated in patients with hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated desmopressin acetate. Desmopressin acetate is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When desmopressin acetate tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS, Pediatric Use and Geriatric Use.**) All patients receiving desmopressin acetate tablets therapy should be observed for the following signs of symptoms associated with hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, lethargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. Particular attention should be paid to the possibility of the rare occurrence of an extreme decrease in plasma osmolality that may result in seizures which could lead to coma.

3. Desmopressin acetate tablets should be used with caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General

Intranasal formulations of desmopressin acetate at high doses and intravenous desmopressin acetate have infrequently produced a slight elevation of blood pressure which disappears with a reduction of dosage. Although this effect has not been observed when single oral doses up to 0.6 mg have been administered, the drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease, because of a possible rise in blood pressure.

Desmopressin acetate should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, heart failure and renal disorders because these patients are prone hyponatremia.

Rare severe allergic reactions have been reported with desmopressin acetate. Anaphylaxis has been reported rarely with intravenous and intranasal administration of desmopressin acetate but not with desmopressin acetate tablets.

Laboratory Tests

Central Diabetes Insipidus

Laboratory tests for monitoring the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions

Although the pressor activity of desmopressin acetate is very low compared to its antidiuretic activity, large doses of desmopressin acetate tablets should be used with other pressor agents only with careful patient monitoring. The concomitant administration of drugs that may increase the risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective serotonin re-uptake inhibitors, chlorpromazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed with caution.

Carcinogenicity, Mutagenicity, Impairment of Fertility

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy

Category B

Fertility studies have not been done. Teratology studies in rats and rabbits at doses from 0.05 to 10 *mcg*/kg/day (approximately 0.1 times the maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to the fetus due to desmopressin acetate. There are, however, no adequate and well-controlled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low birth weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year Swedish epidemiologic study of the use of desmopressin acetate in pregnant women with diabetes insipidus found the rate of birth defects to be no greater than that in the general population; however, the statistical power of this study is low. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no uterotonic action and the physician will have to weigh the possible therapeutic advantages against the possible risks in each case.

Nursing Mothers

There have been no controlled studies in nursing mothers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable desmopressin acetate in breast milk following an intranasal dose of 0.01 mg.

It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to nursing mothers.

Pediatric Use

Central Diabetes Insipidus

Desmopressin acetate tablets have been used safely in pediatric patients, age 4 years and older, with diabetes insipidus for periods up to 44 months. In younger pediatric patients the dose must be individually adjusted in order to prevent an excessive decrease in plasma osmolality leading to hyponatremia and possible convulsions; dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). Use of desmopressin acetate tablets in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient and/or guardian. (See **WARNINGS.**)

Primary Nocturnal Enuresis

Desmopressin acetate tablets have been safely used in pediatric patients age 6 years and older with primary nocturnal enuresis for up to 6 months. Some patients respond to a dose of 0.2 mg; however, increasing responses are seen at doses of 0.4 mg and 0.6 mg. No increase in the frequency or severity of adverse reactions or decrease in efficacy was seen with an increased dose or duration. The dose should be individually adjusted to achieve the best results. Treatment with desmopressin for primary nocturnal enuresis should be interrupted during acute intercurrent illness characterized by fluid and/or electrolyte imbalance (e.g., systemic infections, fever, recurrent vomiting or diarrhea) or under conditions of extremely hot weather, vigorous exercise or other conditions associated with increased water intake.

Geriatric Use

Clinical studies of desmopressin acetate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Desmopressin acetate is contraindicated in patients with moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).

(See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics** and **CONTRAINDICATIONS.**)

Use of desmopressin acetate tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed with the patient. (See **WARNINGS.**)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of desmopressin acetate tablets and injection have produced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared with reduction in dosage.

Central Diabetes Insipidus

In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 months of desmopressin acetate tablet therapy, transient increases in AST (SGOT) no higher than 1.5 times the upper limit of normal were occasionally observed. Elevated AST (SGOT) returned to the normal range despite continued use of desmopressin acetate tablets.

Primary Nocturnal Enuresis

The only adverse event occurring in ≥3% of patients in controlled clinical trials with desmopressin acetate tablets that was probably, possibly, or remotely related to study drug was headache (4% desmopressin acetate, 3% placebo).

Other

The following adverse events have been reported; however their relationship to desmopressin acetate has not been established: abnormal thinking, diarrhea, and edema-weight gain.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

Post Marketing

There have been rare reports of hyponatremic convulsions associated with concomitant use with the following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, drowsiness, continuing headache, problems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS.**) In case of overdose, the dose should be reduced, frequency of administration decreased, or the drug withdrawn according to the severity of the condition. There is no known specific antidote for desmopressin acetate. The patient should be observed and treated with appropriate symptomatic therapy.

An oral LD_{50} has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months without any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to the diurnal pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water turnover. Patients previously on intranasal desmopressin acetate therapy should begin tablet therapy twelve hours after the last intranasal dose. During the initial dose titration period, patients should be observed closely and appropriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during the course of desmopressin acetate tablet therapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water turnover. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

Adults and Children

It is recommended that patients be started on doses of 0.05 mg (1/2 of the 0.1 mg tablet) two times a day and individually adjusted to their optimum therapeutic dose. Most patients in clinical trials found that the optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diurnal rhythm of water turnover. Total daily dosage should be increased or decreased in the range of 0.1 mg to 1.2 mg divided into two or three daily doses as needed to obtain adequate antidiuresis.

See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

Geriatric Use

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics, CONTRAINDICATIONS,** and **PRECAUTIONS, Geriatric Use.)**

Primary Nocturnal Enuresis

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to response. Patients previously on intranasal desmopressin acetate therapy can begin tablet therapy the night following (24 hours after) the last intranasal dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve the desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum from 1 hour before desmopressin administration, until the next morning, or at least 8 hours after administration. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

HOW SUPPLIED

Desmopressin Acetate Tablets 0.1 mg are available for oral administration as white to off-white, round shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.1" on the other side. They are supplied as follows:

Bottles of 30 (NDC 60505-0257-3)
Bottles of 100 (NDC 60505-0257-1)
Bottles of 1000 (NDC 60505-0257-8)

Desmopressin Acetate Tablets 0.2 mg are available for oral administration as white to off-white, round shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.2" on the other side. They are supplied as follows:

Bottles of 30 (NDC 60505-0258-3)
Bottles of 100 (NDC 60505-0258-1)
Bottles of 1000 (NDC 60505-0258-8)

Store 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Keep out of the reach of children.

APOTEX INC.
DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

(APO-DESMOPRESSIN-R03-51X138-LFLT-10/30/08)

Revised: October 2008

Rev. 4

(b) (4)

COMPOSITE

Clear Laminate

(b) (4)

NDC 60505-0257-3

Desmopressin Acetate Tablets

0.1 mg

30 Tablets

℞ Only

APOTEX CORP.

Each tablet contains 0.1 mg of desmopressin acetate.

Store at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].

Avoid exposure to excessive heat or light.

Dispense in a tight, light-resistant container [see USP].

Usual dosage: See package insert.

277472

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

N 3 60505-0257-3 2

Open Here

NON PRINTING AREA (GLUE PANEL)

DESMOPRESSIN ACETATE TABLETS 0.1 mg and 0.2 mg

℞ Only

DESCRIPTION

Desmopressin Acetate Tablets are a syn hetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1129.27
Empirical Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2$

SCH_2CH_2C-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot xCH_3COOH$

where 1<x<1.5

1-(3-mercaptop opionic acid)-8-D-arginine vasopressin monoacetate (salt).

Desmopressin acetate tablets, for oral administration, contain ei her 0.1 or 0.2 mg desmopressin acetate. In addition, each tablet contains he following inactive ingredients: anhyd ous lactose, co n starch, and magnesium stearate.

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The plasma half-life of desmopressin acetate followed a monoexponential time course with $t_{1/2}$ values of 1.5 to 2.5 hours which was independent of dose.

The bioavailability of desmopressin acetate oral tablets is about 5% compared to intranasal desmopressin acetate, and about 0.16% compared to intravenous desmopressin acetate. The time to reach maximum plasma desmopressin acetate levels ranged f om 0.9 to 1.5 hours following oral or intranasal administration, respectively. Following administration of desmopressin acetate tablets, he onset of antidiuretic effect occurs at a ound 1 hour, and it reaches a maximum at about 4 to 7 hours based on the measurement of increased urine osmolality.

The use of desmopressin acetate tablets in patients wi h an established diagnosis will result in a reduction in urinary output wi h an accompanying increase in urine osmolality. These effects usually will allow resumption of a more normal life style, wi h a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response to he intranasal formulations of desmopressin acetate. Usually, he change occurred over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to a local inactivation of the peptide. No lessening of effect was observed in the 46 patients who were treated wi h desmopressin acetate tablets for 12 to 44 mon hs and no serum antibodies to desmopressin were detected.

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All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, p onounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, mean urine volume was 4 mL/min and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over he time course recorded (0 to 12 hours). A statistical separation f om baseline did not occur at any dose or time point. In hese patients, he 0.2 mg tablets and he 0.01 mg intranasal spray exhibited similar pharmacodynamic p ofiles as did he 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In ano her study of adult diabetes insipidus patients previously cont olled on desmopressin acetate intranasal spray, after one week of self-titration f om spray to tablets, patients' diuresis was cont olled wi h 0.1 mg desmopressin acetate tablets hree times a day.

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Baseline	10 (0 3)	11 (0 3)	10 (0 3)	10 (0 3)
Reduction from Baseline	1 (0 3)	3 (0.4)	3 (0.4)	4 (0.4)
Pe cen Reduction from Baseline	10%	27%	30%	40%
p-value vs. placebo	—	<0 05	<0 05	<0 05

Patients treated wi h desmopressin acetate tablets showed a statistically significant reduction in he number of wet nights compared to placebo-treated patients. A greater response was observed wi h increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing he placebo-cont olled studies were started on 0.2 mg/day desmopressin acetate, and he dose was p ogressively increased until he optimal response was achieved (maximum dose 0.6 mg/day). A total of 230 patients were evaluated for efficacy; he average number of wet nights/2 weeks during he untreated baseline period was 10 (range 4 to 14), and the average duration (SD) of treatment was 4.2 (1.8) mon hs. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to he 0.6 mg/day dose. The majority of patients (198 of 230, 86%) were titrated to he highest dose. When all dose g oups were combined, 128 (56%) showed at least a 50% reduction f om baseline in he number of wet nights/2 weeks, while 87 (38%) patients achieved a complete or near complete response.

Human Pharmacokinetics
Desmopressin acetate is mainly excreted in he urine. A pharmacokinetic study conducted in heal hy volunteers and patients wi h mild, moderate, and severe renal impairment (n=24, 6 subjects in each g oup) receiving single dose desmopressin acetate (2 mcg) injection demonstrated a difference in desmopressin acetate terminal half-life. Terminal half-life significantly increased f om 3 hours in normal heal hy patients to 9 hours in patients wi h severe renal impairment. (See **CONTRAINDICATIONS.**)

INDICATIONS AND USAGE

Central Diabetes Insipidus
Desmopressin acetate tablets are indicated as antidiuretic replacement herapy in the management of central diabetes insipidus and for he management of he temporary polyuria and polydipsia following head trauma or surgery in he pituitary region. Desmopressin acetate is ineffective for he treatment of neph ogenic diabetes insipidus.

Patients were selected for herapy based on he diagnosis by means of he water deprivation test, he hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate can be monitored by measuring urine volume and osmolality.

Primary Nocturnal Enuresis
Desmopressin acetate tablets are indicated for he management of primary noctu nal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals w th known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

Desmopressin acetate tablets are contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).

Desmopressin acetate is contraindicated in patients wi h hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported f om world-wide postmarketing experience in patients treated desmopressin acetate. Desmopressin acetate is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless p operly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When desmopressin acetate tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS, Pediatric Use and Geriatric Use.**) All patients receiving desmopressin acetate tablets herapy should be observed for the following signs of symptoms associated wi h hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, le hargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. Particular attention should be paid to he possibility of he rare occurrence of an extreme decrease in plasma osmolality hat may result in seizures which could lead to coma.

3. Desmopressin acetate tablets should be used wi h caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General
Intranasal formulations of desmopressin acetate at high doses and intravenous desmopressin acetate have infrequently p oduced a slight elevation of blood pressure which disappears wi h a reduction of dosage. Al hough this effect has not been observed when single oral doses up to 0.6 mg have been administered, he drug should be used wi h caution in patients wi h co onary artery insufficiency and/or hypertensive cardiovascular disease, because of a possible rise in blood pressure.

Desmopressin acetate should be used wi h caution in patients with conditions associated with fluid and elect olyte imbalance, such as cystic fib osis, heart failure and renal disorders because hese patients are p one hyponatremia.

Rare severe allergic reactions have been reported wi h desmopressin acetate. Anaphylaxis has been reported rarely wi h intravenous and intranasal administration of desmopressin acetate but not with desmopressin acetate tablets.

Laboratory Tests
Central Diabetes Insipidus
Laboratory tests for monitoring the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions
Al hough he pressor activity of desmopressin acetate is very low compared to its antidiuretic activity, large doses of desmopressin acetate tablets should be used wi h o her pressor agents only wi h careful patient monitoring. The concomitant administration of drugs that may increase he risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective se otonin re-uptake inhibitors, chlorp omazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed wi h caution.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy
Category B
Fertility studies have not been done. Teratology studies in rats and rabbits at doses f om 0.05 to 10 *mcg*/kg/day (approximately 0.1 times he maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to he fetus due to desmopressin acetate. There are, however, no adequate and well-cont olled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low bir h weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year Swedish epidemiologic study of he use of desmopressin acetate in pregnant women with diabetes insipidus found he rate of birth defects to be no greater han that in he general population; however, the statistical power of this study is low. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no ute otonic action and the physician wil have to weigh he possible herapeutic advantages against he possible risks in each case.

Nursing Mothers
There have been no cont olled studies in nursing mo hers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable desmopressin acetate in breast milk following an intranasal dose of 0.01 mg.

It is not known whe her he drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to nursing mo hers.

Pediatric Use
Central Diabetes Insipidus
Desmopressin acetate tablets have been used safely in pediatric patients, age 4 years and older, wi h diabetes insipidus for periods up to 44 mon hs. In younger pediatric patients he dose must be individually adjusted in order to prevent an excessive decrease in plasma osmolality leading to hyponatremia and possible convulsions; dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). Use of desmopressin acetate tablets in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient and/or guardian. (See **WARNINGS.**)

Primary Nocturnal Enuresis
Desmopressin acetate tablets have been safely used in pediatric patients age 6 years and older with primary noctu nal enuresis for up to 6 mon hs. Some patients respond to a dose of 0.2 mg; however, increasing responses are seen at doses of 0.4 mg and 0.6 mg. No increase in he frequency or severity of adverse reactions or decrease in efficacy was seen wi h an increased dose or duration. The dose should be individually adjusted to achieve he best results. Treatment with desmopressin for primary noctu nal enuresis should be interrupted during acute intercurrent illness characterized by fluid and/or elect olyte imbalance (e.g., systemic infections, fever, recurrent vomiting or diar hea) or under conditions of extremely hot wea her, vigo ous exercise or o her conditions associated wi h increased water intake.

Geriatric Use
Clinical studies of desmopressin acetate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently f om younger subjects.

O her reported clinical experience has not identified differences in responses between he elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting he greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or o her drug herapy.

This drug is known to be substantially excreted by he kidney, and he risk of toxic reactions to his drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Desmopressin acetate is contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).

(See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics** and **CONTRAINDICATIONS.**)

Use of desmopressin acetate tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient. (See **WARNINGS.**)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of desmopressin acetate tablets and injection have p oduced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared w th reduction in dosage.

Central Diabetes Insipidus
In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 mon hs of desmopressin acetate tablet herapy, transient increases in AST (SGOT) no higher han 1.5 times he upper limit of normal were occasionally observed. Elevated AST (SGOT) retu ned to he normal range despite continued use of desmopressin acetate tablets.

Primary Nocturnal Enuresis
The only adverse event occurring in ≥3% of patients in cont olled clinical trials with desmopressin acetate tablets hat was p obably, possibly, or remotely related to study drug was headache (4% desmopressin acetate, 3% placebo).

Other
The following adverse events have been reported; however heir relationship to desmopressin acetate has not been established: abnormal hinking, diar hea, and edema-weight gain.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

Post Marketing
There have been rare reports of hyponatremic convulsions associated wi h concomitant use wi h he following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, d owsiness, continuing headache, p oblems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS.**) In case of overdose, he dose should be reduced, frequency of administration decreased, or the drug withdrawn according to he severity of he condition. There is no known specific antidote for desmopressin acetate. The patient should be observed and treated wi h app opriate symptomatic herapy.

An oral LD_{50} has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months wi hout any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to he diu nal patte n of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water tu nover. Patients previously on intranasal desmopressin acetate herapy should begin tablet herapy twelve hours after he last intranasal dose. During he initial dose titration period, patients should be observed closely and app opriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during he course of desmopressin acetate tablet herapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water tu nover. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

Adults and Children
It is recommended hat patients be started on doses of 0.05 mg (1/2 of he 0.1 mg tablet) two times a day and individually adjusted to heir optimum therapeutic dose. Most patients in clinical trials found hat he optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diu nal hythm of water tu nover. Total daily dosage should be increased or decreased in the range of 0.1 mg to 1.2 mg divided into two or three daily doses as needed to obtain adequate antidiuresis.

See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

Geriatric Use
This drug is known to be substantially excreted by the kidney, and he risk of toxic reactions to his drug may be greater in patients wi h impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics, CONTRAINDICATIONS,** and **PRECAUTIONS, Geriatric Use.**)

Primary Nocturnal Enuresis
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to response. Patients previously on intranasal desmopressin acetate herapy can begin tablet herapy he night following (24 hours after) he last intranasal dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve he desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum f om 1 hour before desmopressin administration, until he next mo ning, or at least 8 hours after administration. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

HOW SUPPLIED

Desmopressin Acetate Tablets 0.1 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.1" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0257-3)
Bottles of 100 (NDC 60505-0257-1)
Bottles of 1000 (NDC 60505-0257-8)

Desmopressin Acetate Tablets 0.2 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.2" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0258-3)
Bottles of 100 (NDC 60505-0258-1)
Bottles of 1000 (NDC 60505-0258-8)

Store 20° to 25°C (68° to 77°F) [see USP Cont olled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Keep out of the reach of children.

APOTEX INC.
DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg

Manufactured by: Apotex Inc. To onto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

(APO-DESMOPRESSIN-R03-51X138-LFLT-10/30/08)

Revised: October 2008

Rev. 4

(b) (4)

COMPOSITE

Color Lavender

NDC 60505-0258-1

Desmopressin Acetate Tablets 0.2 mg

100 Tablets

Rx Only

APOTEX CORP.

Each tablet contains: 0.2 mg of desmopressin acetate.

Dispense in a tight, light-resistant container (see USP).

Store 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature].

60505-0258-1

Manufactured for: Apotex Corp. Weston, Florida 33326

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

APO-DESMOPRESSIN-FLD-2.0/13R-L/LT-1/3/DS/0

Revised: October 2008

Rev. 4

NON PRINTING AREA (GLUE PANEL)

NDC 60505-0258-4

Desmopressin Acetate Tablets 0.2 mg

100 Tablets

Rx Only

APOTEX CORP.

Each tablet contains: 0.2 mg of desmopressin acetate.

Dispense in a tight, light-resistant container (see USP).

Store at 20°C to 25°C (68°F to 77°F) [see USP Controlled Room Temperature].

Manufactured for: Apotex Corp. Weston, Florida 33326

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

APO-DESMOPRESSIN-FLD-2.0/13R-L/LT-1/3/DS/0

Revised: October 2008

Rev. 4

60505-0258-1

DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg
Rx Only

DESCRIPTION

Desmopressin Acetate Tablets are a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1128.27
Empirical Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2$

where 1-cys-3-cys

1-(3-mercapto propionic acid)-8-D-arginine vasopressin monoacetate (salt).

Desmopressin acetate tablets, for oral administration, contain 0.1 mg or 0.2 mg desmopressin acetate. In addition, each tablet contains the following inactive ingredients: anhydrous lactose, corn starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Desmopressin acetate tablets contain as active substance, desmopressin acetate, a synthetic analogue of the natural hormone arginine vasopressin.

Central Diabetes Insipidus

The antidiuretic response in patients with diabetes insipidus have demonstrated that oral doses of 0.025 mg to 0.4 mg e reduced clinically significant antidiuretic effects. In most patients, doses of 0.1 mg to 0.2 mg produced optimal antidiuretic effects lasting up to eight hours. With doses of 0.4 mg, antidiuretic effects were observed for up to 12 hours; measurements beyond 12 hours were not made. Oral administration of 0.4 mg produced dose dependent increases in the plasma levels of desmopressin acetate.

The plasma half-life of desmopressin acetate followed oral administration of desmopressin acetate tablets was 1.5 to 2.5 hours which was independent of dose.

The bioavailability of desmopressin acetate oral tablets is about 5% compared to intranasal desmopressin acetate, and about 0.16% compared to intravenous desmopressin acetate. The time to reach maximum plasma desmopressin concentration was observed to be 1.5 hours following oral or intranasal administration, respectively. Following administration of desmopressin acetate tablets, he onset of antidiuretic effect occurs at a ruoni t hour, and it reaches a maximum in about 4 to 5 hours based on the measurement of increased urine osmolality.

The use of desmopressin acetate tablets in patients wi h an established diagnosis will result in a reduction in urinary volume, a concomitant increase in urine osmolality. Those effects generally will allow resumption of a more normal life style, with a decrease in urinary frequency and enuresis.

There are reports of an occasional change in response to he intranasal formulations of desmopressin acetate, in which the response decreases over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies to the drug or to the carrier substance in the peptide. No increase in this effect was observed in the 40 patients who were treated wi h desmopressin acetate tablets for 12 to 44 mon ths and no serum antibodies to desmopressin were detected.

The change in structure of arginine vasopressin to desmopressin acetate results in a loss of pressor activity and decreased action on visceral smoo h muscle relative to enhanced antidiuretic activity. Consequently, clinically effective antidiuretic doses are usually below the threshold for effects on vascular smooth muscle. Clinical trials in 40 patients and studies of desmopressin acetate tablets, or increases in blood pressure in 40 patients receiving desmopressin acetate tablets for periods of 12 to 44 mon ths were reported.

In one study, he pharmacokinetic characteristics of desmopressin acetate tablets and intranasal formulation were compared during an 8-hour dosing interval at steady state. The doses administered to 36 hydrated (water loaded) healthy male adult volunteers every 8 hours were 0.1, 0.2, 0.4 mg orally and 0.01 mg intranasally by nasal tube. The results are shown in the following table:

Mean Changes from Baseline (SE) in Pharmacodynamic Parameters in Normal Healthy Adult Volunteers

Treatment	Total Urine Volume in mL	Maximum Urine Flow Rate in mL/hr	Maximum Urine Osmolality
0.1 mg PO q8h	-3089.2 (148.6)	514.8 (21.9)	
0.2 mg PO q8h	-4029.9 (148.6)	699.2 (21.9)	
0.4 mg PO q8h	-4998.8 (148.6)	769.5 (21.9)	
0.01 mg IN q8h	-4944.9 (148.6)	754.1 (21.9)	

(SE) = Standard er or of he mean

Wi th respect to he mean volume of total urine volume and maximum urine osmolality following dosing at steady baseline, the 80% confidence ibotts estimated bet ba 0.4 mg and 0.2 mg oral dose p roduced between 85% and 110% and 94% to 99% of pharmacodynamic activity, respectively, when compared to he 0.01 mg intranasal dose.

While both the 0.2 mg and 0.4 mg oral doses are considered pharmacodynamically similar to he 0.01 mg intranasal dose, he pharmacodynamic data on an inter-subject basis was highly variable and, therefore, individual dosing is recommended.

In another study in diabetes insipidus patients, he pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulations were compared over a 12-hour period. Ten fluid-cost ubted patients aede age 18 were administered tablet doses of 0.2 mg and 0.4 mg, and intranasal doses of 0.01 mg and 0.02 mg.

Mean Peak Pharmacodynamic Parameters (SD) in Pediatric and Adolescent Diabetes Insipidus Patients

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
0.01 mg IN	8.3 (0.15)	717.0 (254.87)
0.02 mg IN	8.1 (0.25)	751.0 (248.87)
0.2 mg PO	5.3 (0.15)	678.3 (142.24)
0.4 mg PO	4.2 (0.25)	797.7 (173.24)

(SD) = Standard Deviation

All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, p ronounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, urine volume was <200 mL/hr and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over he time course recorded (0 to 12 hours). A statistical sepcnstor t on baseline did not occur at any dose or time. Desmopressin acetate tablets at doses of 0.2 or 0.01 mg intranasal were exhibited similar pharmacodynamic p rofiles in dei he 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In ano her study of adult diabetes insipidus patients previously ood ollar on desmopressin acetate intranasal spray, after one week of ad-libitum f ure to desmopressin acetate tablets, patients were titrated to 0.1 mg desmopressin acetate tablets. Ione three a day.

Primary Nocturnal Enuresis

Two double-blind, randomized, placebo-cont olled studies were conducted in 329 children, 6 to 17 years of ayo, six reurosis. Patients were 5 to 17 years old, and 72% were males. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period in which the average number of wetting episodes per night for the 14 nights were determined to range from 4.2, 4.4, and 4.0 during desmopressin acetate or placebo. The pooled results after two weeks are shown in he following table:

Response to Desmopressin Acetate and Placebo at Two Weeks of Treatment Mean (SE) Number of Wet Nights/7 Weeks

	Placebo (n = 165)	0.2 mg/night desmopressin acetate (n = 164)	0.4 mg/night desmopressin acetate (n = 165)
Baseline	10.8 (0.3)	11 (0.3)	10.9 (0.3)
Reduction from Baseline	1 (0.3)	3 (0.4)	1 (0.4)	4 (0.4)
% reg. Reduction from Baseline	10%	27%	39%	40%
p-value vs. placebo	—	<0.05	<0.05	<0.05

Patients treated wit h desmopressin acetate tablets showed a statistically significant reduction in he number of wet nights compared to placebo-treated patients. A greater response was observed wi h increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing he placebo-cont olled studies were titrated to 0.6 mg desmopressin acetate tablets. The dose was p rgressively increased until he optimal response was achieved (maximum dose 0.6 mg/day). A total of 220 patients were evaluated for efficacy; he average number of wet nights/2 weeks during he desmopressin acetate tablets phase was 3.1 (SE 0.2); he average duration (SD) of treatment was 4.2 (1.6) mon ths. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to he 0.6 mg/day dose. Of the 195 patients (89%) who did not, 170 were titrated to he highest dose. When all dose g roups were combined, 128 (58%) showed at least a 50% reduction f om baseline to he number of wet nights/2 weeks, while 67 (30%) patients achieved a complete or near complete response.

Human Pharmacokinetics

Desmopressin acetate is primarily excreted in he urine. A pharmacokinetic study conducted in healt hy volunteers and patients wi h mild, moderate, and severe renal impairment (cr-Cl, 4 subjects in each g roup) receiving single dose desmopressin acetate (0.4 mg) showed that renal impairment prolonged desmopressin acetate terminal half-life. Terminal half-life significantly increased f om 3 hours in normal heal hy patients to 9 hours in patients exposed to severe renal impairment. (See **CONTRAINDICATIONS**.)

INDICATIONS AND USAGE

Central Diabetes Insipidus

Desmopressin acetate tablets are indicated as antidiuretic replacement herapy in the management of central diabetes insipidus and for he management of he temporary polyuria and polydipsia following head injury or surgery in his region. Desmopressin acetate is ineffective for he treatment of nephi ogenic diabetes insipidus.

Patients were selected for herapy based on he diagnosis by means of he water deprivation test, he hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate tablets is monitored by measuring urine volume and osmolality.

Primary Nocturnal Enuresis

Desmopressin acetate tablets are indicated for he treatment of primary nocturnal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals w h known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

Desmopressin acetate tablets are contraindicated in the treatment of nocturia associated with polyuria (defined as a creatinine clearance below 50mL/min).

Desmopressin acetate is contraindicated in patients wi h hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported f om world-wide postmarketing experience in patients treated desmopressin acetate. Desmopressin acetate is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless properly administered, severe hyponatremia may lead to fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When desmopressin acetate tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of hyponatremia and water intoxication. (See **PRECAUTIONS, Pediatric Use** and **Geriatric Use**.) All patients receiving desmopressin acetate tablets herapy should be observed for the following signs of symptoms hyponatremia: h adache, nausea/vomiting, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, ih harpy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental state (e.g., confusion, decreased consciousness and confusion). Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. Particular attention should be paid to he possibility of he sore occurrence of these symptoms in children and females, but may result in seizures which could lead to coma.

3. Desmopressin acetate tablets should be used wi h caution in patients with hutritual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General

Intranasal formulations of desmopressin acetate at the 10 mcg dose strength have been reported to have infrequently p roduced a slight elevation of blood pressure which disappears wit h a reduction of dose. Desmopressin acetate 0.1 mg tablets should be used when single oral doses up to 0.6 mg have been administered. he drug should be used wi h caution in patients wi h co ronary artery insufficiency and/or hypertensive cardiovascular disease, because of a possible rise in blood pressure.

Desmopressin acetate should be used wi h caution in patients with conditions associated wi h fluid and/or elect rolyte imbalance, such as cystic fib rosis, heart failure and renal disorders because these patients are p one to hyponatremia.

Rare severe allergic reactions have been reported wi h desmopressin acetate. Anaphylaxis has been reported rarely wi h intranasal and intravenous administration of desmopressin acetate but not with desmopressin acetate tablets.

Laboratory Tests

Central Diabetes Insipidus

Measurements before initiating the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine osmolality and electrolyte. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions

Although he pressor activity of desmopressin acetate is very low, the antidiuretic activity is high. Concomitant doses of desmopressin acetate tablets should be used wi h c aution in patients receiving drugs known to enhance the release of ADH or potentiate its action; these drugs may increase he risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective se rotonin re uptake inhibitors, clofibrate, vinblastine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed wi h caution.

Carcinogenesis, Mutagenicity, Impairment of Fertility

Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy

Category B

Fertility studies have not been done. Teratology studies have been performed in rats at doses of 0.1 mg/kg/day (approximately 0.1 times he maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m²) revealed no harm to he fetus due to desmopressin acetate. There are, however, no adequate and well-cont olled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used in the management of diabetes insipidus during pregnancy have been reviewed. These reports include reports of congenital anomalies and live birt h weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year livedisk epidemiologic study of he use of desmopressin acetate in pregnant women with diabetes insipidus found he rate of birth defects to be no greater than that in he general population. Similarly, he perinatal mortality rate was not h igh. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no ob stetric action and the physician will have to weigh he possible teratogenic advantages against he possible dise ks in each case.

Nursing Mothers

Limited data from women ors cont olled studies in nursing he ers, A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assurable desmopressin acetate in breast milk following an intranasal dose of 0.01 mg.

It is not known whe her he drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to nursing mo hers.

Pediatric Use

Central Diabetes Insipidus

Desmopressin acetate tablets have been used safely in pediatric patients, age 4 years and older, wi h diabetes insipidus for periods up to 44 mon ths. Desmopressin acetate tablets should be titrated to individually adjusted dr osage to prevent an excessive decrease in plasma osmolality leading to hyponatremia and water intoxication. Initiation at a liquid dose of 0.05 mg (1/4 of the 0.1 mg tablet) of desmopressin acetate tablets in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. (See **DOSAGE AND ADMINISTRATION**.) he patient and/or guardian. (See **WARNINGS**.)

Primary Nocturnal Enuresis

Desmopressin acetate tablets have been safely used in pediatric patients age 6 years and older with primary noctu nal enuresis for up to 6 mon ths. Some patients respond to a dose of 0.2 mg; however, titration between 0.2 mg and 0.4 mg, 0.4 mg and 0.6 mg, and 0.6 mg. No increase in he frequency or severity of adverse reactions or decrease in efficacy was seen wi h an increased dose or duration. The dose should be individually adjusted to achieve he best results in each patient. Desmopressin acetate tablets at doses of 0.4 mg or more should be interrupted during acute intercurrent illness characterized by fluid and/or elect rolyte imbalance, such as those with vomiting, fever, recurrent vomiting or diar hea or under conditions of extremely hot wea ther, vigo rous exercise or h eat conditions associated wi h increased water intake.

Geriatric Use

Clinical studies of desmopressin acetate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently f om younger subjects.

O her reported clinical experience has not identified differences in responses between he elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or o her drug herapy.

This drug is known to be substantially excreted by he kidney, and he risk of toxic reactions to his drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Desmopressin acetate is contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).

(See **CLINICAL PHARMACOLOGY**, **Human Pharmacokinetics** and **CONTRAINDICATIONS**.)

Use of desmopressin acetate tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. (See **PRECAUTIONS**.) he patient and/or guardian. (See **WARNINGS**.)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of desmopressin acetate have been given by injection have p roduced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared w ih reduction in dosage.

Central Diabetes Insipidus

In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 mon ths, occasional episodes of mild elevations of transient increases in AST (SGOT) no higher than 5 t imes he upper limit of normal were occasionally observed. Elevated AST (SGOT) rela ted to he normal range despite continued use of desmopressin acetate tablets.

Primary Nocturnal Enuresis

In clinical studies conducted in ng ±2% of patients he most frequent adverse events associated with desmopressin acetate tablets were (and probably, possibly, or remotely related to study drug) was headache (4% desmopressin acetate, 3% placebo).

Other

The following adverse events have been reported, although a causal relationship to desmopressin acetate has not been established: abnormal thinking, dial hea, and edema-weight gain.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

Post Marketing

There have been rare reports of hyponatremic convulsions associated wi h concomitant use wi h he following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, d rowsiness, continuous headache, p oliguria with hyponatremia, and in severe cases, coma and convulsion. (See **WARNINGS**.) In case of overdose, he dose should be reduced, frequency of administration decreased, or the drug withdrawn according to he severity of he condition. There is no known specific antidote for desmopressin acetate. The patient should be observed and treated wi h sup ortive symptomatic herapy.

An oral LD50 has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months wi hout any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg he aster demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to he dai ily satis e d response. Adequate dosage is usually indicated by a normal adequate duration of sleep and adequate, not excessive, water to esser. Patients preciously on desmopressin acetate intranasal may be converted to heir total herapy twelve hours after he last intranasal dose. During he initial dose titration period, patients should be observed closely and app ropriate safety parameters measured to assure adequate antidiuresis. Urine volume and osmolality at regular intervals during he course of desmopressin acetate tablet herapy to assure adequate antidiuretic response. Serum electrolytes and body weight should be ma intained as necessary to assure adequate water to esser. Fluid restriction should be observed. (See **WARNINGS**, **PRECAUTIONS**, **Pediatric Use** and **Geriatric Use**.)

Adults and Children

It is recommended hat patients be started on doses of 0.1 mg to 0.2 mg daily, administered in divided doses, and individually adjusted to bet optimum therapeutic dose. Most patients in clinical trials found hat he optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose may be titrated upward by 0.1 mg to 0.2 mg increments until he optimum effect is reached. Total daily dosage should be increased or decreased in the range of 0.1 mg to 0.2 mg divided tabs two or three daily doses as needed to obtain adequate antidiuresis.

See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

Geriatric Use

The dose is known to be substantially excreted by he kidney, and he risk of toxic reactions to his drug may be greater in patients wi h impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY**, **Human Pharmacokinetics**, **CONTRAINDICATIONS**, and **PRECAUTIONS, Geriatric Use**.)

Primary Nocturnal Enuresis

The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to he dai ily satis e d response. The intranasal desmopressin acetate herapy can begin tablet herapy he night following (24 hours after) he last intranasal dose. The recommended starting dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.4 mg to achieve he desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum for at least eight hours following administration, until he next mo rning, or at least 8 hours after administration. (See **WARNINGS**, **PRECAUTIONS**, **Pediatric Use** and **Geriatric Use**.)

HOW SUPPLIED

Desmopressin Acetate Tablets 0.1 mg are available for oral administration as white to off-white, round shaped, scored tablets, imprinted "APO" on one side and "DDT" bisect "0.1" on he ir bet side. They are supplied as follows:

Bottles of 100 (NDC 60505-0257-1)
Bottles of 100 (NDC 60505-0257-4)
Bottles of 1000 (NDC 60505-0257-8)

Desmopressin Acetate Tablets 0.2 mg are available for oral administration as white to off-white, round shaped, scored tablets, imprinted "APO" on one side and "DDT" bisect "0.2" on he ir bet side. They are supplied as follows:

Bottles of 30 (NDC 60505-0258-3)
Bottles of 100 (NDC 60505-0258-1)
Bottles of 1000 (NDC 60505-0258-8)

Keep out of the reach of children.

APOTEX INC
DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg

COMPOSITE

Clear Laminate

(b) (4)

Open Here

NDC 60505-0258-3

Desmopressin Acetate Tablets

0.2 mg

30 Tablets

℞ Only

APOTEX CORP.

Manufactured by: Apotex Inc. Toronto, Ontario Canada M9L 1T9

Manufactured for: Apotex Corp. Weston, Florida 33326

N 3 60505-0258-3 1

NON PRINTING AREA (GLUE PANEL)

DESMOPRESSIN ACETATE TABLETS 0.1 mg and 0.2 mg

℞ Only

DESCRIPTION

Desmopressin Acetate Tablets are a syn hetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. It is chemically defined as follows:

Mol. Wt. 1129.27
Empirical Formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2$

$SCH_2CH_2C(=O)$-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \cdot xCH_3COOH$

where 1<x<1.5

1-(3-mercaptop opionic acid)-8-D-arginine vasopressin monoacetate (salt).

Desmopressin acetate tablets, for oral administration, contain ei her 0.1 or 0.2 mg desmopressin acetate. In addition, each tablet contains he following inactive ingredients: anhyd ous lactose, co n starch, and magnesium stearate.

CLINICAL PHARMACOLOGY

Desmopressin acetate tablets contain as active substance, desmopressin acetate, a syn hetic analogue of he natural hormone arginine vasopressin.

Central Diabetes Insipidus
Dose response studies in patients wi h diabetes insipidus have demonstrated that oral doses of 0.025 mg to 0.4 mg p oduced clinically significant antidiuretic effects. In most patients, doses of 0.1 mg to 0.2 mg produced optimal antidiuretic effects lasting up to eight hours. Wi h doses of 0.4 mg, antidiuretic effects were observed for up to 12 hours; measurements beyond 12 hours were not recorded. Increasing oral doses produced dose dependent increases in the plasma levels of desmopressin acetate.

The plasma half-life of desmopressin acetate followed a monoexponential time course with $t_{1/2}$ values of 1.5 to 2.5 hours which was independent of dose.

The bioavailability of desmopressin acetate oral tablets is about 5% compared to intranasal desmopressin acetate, and about 0.16% compared to intravenous desmopressin acetate. The time to reach maximum plasma desmopressin acetate levels ranged f om 0.9 to 1.5 hours following oral or intranasal administration, respectively. Following administration of desmopressin acetate tablets, he onset of antidiuretic effect occurs at a ound 1 hour, and it reaches a maximum at about 4 to 7 hours based on the measurement of increased urine osmolality.

The use of desmopressin acetate tablets in patients wi h an established diagnosis will result in a reduction in urinary output wi h an accompanying increase in urine osmolality. These effects usually will allow resumption of a more normal life style, wi h a decrease in urinary frequency and nocturia.

There are reports of an occasional change in response to he intranasal formulations of desmopressin acetate. Usually, he change occurred over a period of time greater than six months. This change may be due to decreased responsiveness, or to shortened duration of effect. There is no evidence that this effect is due to the development of binding antibodies, but may be due to a local inactivation of the peptide. No lessening of effect was observed in the 46 patients who were treated wi h desmopressin acetate tablets for 12 to 44 mon hs and no serum antibodies to desmopressin were detected.

The change in structure of arginine vasopressin to desmopressin acetate resulted in less vasopressor activity and decreased action on visceral smoo h muscle relative to enhanced antidiuretic activity. Consequently, clinically effective antidiuretic doses are usually below the hreshold for effects on vascular or visceral smoo h muscle. In he four long-term studies of desmopressin acetate tablets, no increases in blood pressure in 46 patients receiving desmopressin acetate tablets for periods of 12 to 44 mon hs were reported.

In one study, he pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulation were compared during an 8-hour dosing interval at steady state. The doses administered to 36 hydrated (water loaded) healthy male adult volunteers every 8 hours were 0.1, 0.2, 0.4 mg orally and 0.01 mg intranasally by hinal tube. The results are shown in the following table:

Mean Changes from Baseline (SE) in Pharmacodynamic Parameters in Normal Healthy Adult Volunteers

Treatment	Total Urine Volume in mL	Maximum Urine Osmolality in mOsm/kg
0.1 mg PO q8h	-3689.3 (149.6)	514.8 (21.9)
0.2 mg PO q8h	-4429.9 (149.6)	686.3 (21.9)
0.4 mg PO q8h	-4998.8 (149.6)	769.3 (21.9)
0.01 mg IN q8h	-4844.9 (149.6)	754.1 (21.9)

(SE) = Standard er or of he mean

W th respect to he mean values of total urine volume decrease and maximum urine osmolality increase f om baseline, the 90% confidence limits estimated hat he 0.4 mg and 0.2 mg oral dose p oduced between 95% and 110% and 84% to 99% of pharmacodynamic activity, respectively, when compared to he 0.01 mg intranasal dose.

While both the 0.2 mg and 0.4 mg oral doses are considered pharmacodynamically similar to he 0.01 mg intranasal dose, he pharmacodynamic data on an inter-subject basis was highly variable and, herefore, individual dosing is recommended.

In another study in diabetes insipidus patients, he pharmacodynamic characteristics of desmopressin acetate tablets and intranasal formulations were compared over a 12-hour period. Ten fluid-cont olled patients under age 18 were administered tablet doses of 0.2 mg and 0.4 mg, and intranasal doses of 0.01 mg and 0.02 mg.

Mean Peak Pharmacodynamic Parameters (SD) in Pediatric and Adolescent Diabetes Insipidus Patients

Treatment	Urine Volume in mL/min	Maximum Urine Osmolality in mOsm/kg
0.01 mg IN	0.3 (0.15)	717.0 (224.63)
0.02 mg IN	0.3 (0.25)	761.8 (298.82)
0.2 mg PO	0.3 (0.12)	678.3 (147.91)
0.4 mg PO	0.2 (0.15)	787.2 (73.34)

(SD) = Standard Deviation

All four dose formulations (0.01 mg IN, 0.02 mg IN, 0.2 mg PO and 0.4 mg PO) have a similar, p onounced pharmacodynamic effect on urine volume and urine osmolality. At two hours after study drug administration, mean urine volume was 4 mL/min and urine osmolality was >500 mOsm/kg. Mean plasma osmolality remained relatively constant over he time course recorded (0 to 12 hours). A statistical separation f om baseline did not occur at any dose or time point. In hese patients, he 0.2 mg tablets and he 0.01 mg intranasal spray exhibited similar pharmacodynamic p ofiles as did he 0.4 mg tablets and the 0.02 mg intranasal spray formulation. In ano her study of adult diabetes insipidus patients previously cont olled on desmopressin acetate intranasal spray, after one week of self-titration f om spray to tablets, patients' diuresis was cont olled wi h 0.1 mg desmopressin acetate tablets hree times a day.

Primary Nocturnal Enuresis
Two double-blind, randomized, placebo-cont olled studies were conducted in 340 patients w th primary noctu nal enuresis. Patients were 5 to 17 years old, and 72% were males. A total of 329 patients were evaluated for efficacy. Patients were evaluated over a two-week baseline period in which the average number of wet nights was 10 (range 4 to 14). Patients were hen randomized to receive 0.2, 0.4, or 0.6 mg of desmopressin acetate or placebo. The pooled results after two weeks are shown in he following table:

Response to Desmopressin Acetate and Placebo at Two Weeks of Treatment Mean (SE) Number of Wet Nights/2 Weeks

	Placebo (n = 85)	0.2 mg/day (n = 79)	0.4 mg/day (n = 82)	0.6 mg/day (n = 83)
Baseline	10 (0 3)	11 (0 3)	10 (0 3)	10 (0 3)
Reduction from Baseline	1 (0 3)	3 (0.4)	3 (0.4)	4 (0.4)
Pe cen Reduction from Baseline	10%	27%	30%	40%
p-value vs. placebo	—	<0 05	<0 05	<0 05

Patients treated wi h desmopressin acetate tablets showed a statistically significant reduction in he number of wet nights compared to placebo-treated patients. A greater response was observed wi h increasing doses up to 0.6 mg.

In a six month, open-label extension study, patients completing he placebo-cont olled studies were started on 0.2 mg/day desmopressin acetate, and he dose was p ogressively increased until he optimal response was achieved (maximum dose 0.6 mg/day). A total of 230 patients were evaluated for efficacy; he average number of wet nights/2 weeks during he untreated baseline period was 10 (range 4 to 14), and the average duration (SD) of treatment was 4.2 (1.8) mon hs. Twenty-five (25) patients (11%) achieved a complete or near complete response (≤2 wet nights/2 weeks) and did not require titration to he 0.6 mg/day dose. The majority of patients (198 of 230, 86%) were titrated to he highest dose. When all dose g oups were combined, 128 (56%) showed at least a 50% reduction f om baseline in he number of wet nights/2 weeks, while 87 (38%) patients achieved a complete or near complete response.

Human Pharmacokinetics
Desmopressin acetate is mainly excreted in he urine. A pharmacokinetic study conducted in heal hy volunteers and patients wi h mild, moderate, and severe renal impairment (n=24, 6 subjects in each g oup) receiving single dose desmopressin acetate (2 mcg) injection demonstrated a difference in desmopressin acetate terminal half-life. Terminal half-life significantly increased f om 3 hours in normal heal hy patients to 9 hours in patients wi h severe renal impairment. (See **CONTRAINDICATIONS.**)

INDICATIONS AND USAGE

Central Diabetes Insipidus
Desmopressin acetate tablets are indicated as antidiuretic replacement herapy in the management of central diabetes insipidus and for he management of he temporary polyuria and polydipsia following head trauma or surgery in he pituitary region. Desmopressin acetate is ineffective for he treatment of neph ogenic diabetes insipidus.

Patients were selected for herapy based on he diagnosis by means of he water deprivation test, he hypertonic saline infusion test, and/or response to antidiuretic hormone. Continued response to desmopressin acetate can be monitored by measuring urine volume and osmolality.

Primary Nocturnal Enuresis
Desmopressin acetate tablets are indicated for he management of primary noctu nal enuresis. Desmopressin acetate may be used alone or as an adjunct to behavioral conditioning or other non-pharmacologic intervention.

CONTRAINDICATIONS

Desmopressin acetate tablets are contraindicated in individuals w th known hypersensitivity to desmopressin acetate or to any of the components of desmopressin acetate tablets.

Desmopressin acetate tablets are contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50mL/min).

Desmopressin acetate is contraindicated in patients wi h hyponatremia or a history of hyponatremia.

WARNINGS

1. Very rare cases of hyponatremia have been reported f om world-wide postmarketing experience in patients treated desmopressin acetate. Desmopressin acetate is a potent antidiuretic which, when administered, may lead to water intoxication and/or hyponatremia. Unless p operly diagnosed and treated hyponatremia can be fatal. Therefore, fluid restriction is recommended and should be discussed with the patient and/or guardian. Careful medical supervision is required.

2. When desmopressin acetate tablets are administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward to decrease the potential occurrence of water intoxication and hyponatremia. (See **PRECAUTIONS, Pediatric Use and Geriatric Use.**) All patients receiving desmopressin acetate tablets herapy should be observed for the following signs of symptoms associated wi h hyponatremia: headache, nausea/vomiting, decreased serum sodium, weight gain, restlessness, fatigue, le hargy, disorientation, depressed reflexes, loss of appetite, irritability, muscle weakness, muscle spasms or cramps and abnormal mental status such as hallucinations, decreased consciousness and confusion. Severe symptoms may include one or a combination of the following: seizure, coma and/or respiratory arrest. Particular attention should be paid to he possibility of he rare occurrence of an extreme decrease in plasma osmolality hat may result in seizures which could lead to coma.

3. Desmopressin acetate tablets should be used wi h caution in patients with habitual or psychogenic polydipsia who may be more likely to drink excessive amounts of water, putting them at greater risk of hyponatremia.

PRECAUTIONS

General
Intranasal formulations of desmopressin acetate at high doses and intravenous desmopressin acetate have infrequently p oduced a slight elevation of blood pressure which disappears wi h a reduction of dosage. Al hough this effect has not been observed when single oral doses up to 0.6 mg have been administered, he drug should be used wi h caution in patients wi h co onary artery insufficiency and/or hypertensive cardiovascular disease, because of a possible rise in blood pressure.

Desmopressin acetate should be used wi h caution in patients with conditions associated with fluid and elect olyte imbalance, such as cystic fib osis, heart failure and renal disorders because hese patients are p one hyponatremia.

Rare severe allergic reactions have been reported wi h desmopressin acetate. Anaphylaxis has been reported rarely wi h intravenous and intranasal administration of desmopressin acetate but not with desmopressin acetate tablets.

Laboratory Tests
Central Diabetes Insipidus
Laboratory tests for monitoring the patient with central diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases, measurements of plasma osmolality may be useful.

Drug Interactions
Al hough he pressor activity of desmopressin acetate is very low compared to its antidiuretic activity, large doses of desmopressin acetate tablets should be used wi h o her pressor agents only wi h careful patient monitoring. The concomitant administration of drugs that may increase he risk of water intoxication with hyponatremia, (e.g. tricyclic antidepressants, selective se otonin re-uptake inhibitors, chlorp omazine, opiate analgesics, NSAIDs, lamotrigine and carbamazepine) should be performed wi h caution.

Carcinogenicity, Mutagenicity, Impairment of Fertility
Studies with desmopressin acetate have not been performed to evaluate carcinogenic potential, mutagenic potential or effects on fertility.

Pregnancy
Category B
Fertility studies have not been done. Teratology studies in rats and rabbits at doses f om 0.05 to 10 *mcg*/kg/day (approximately 0.1 times he maximum systemic human exposure in rats and up to 38 times the maximum systemic human exposure in rabbits based on surface area, mg/m^2) revealed no harm to he fetus due to desmopressin acetate. There are, however, no adequate and well-cont olled studies in pregnant women. Because animal studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Several publications where desmopressin acetate was used in the management of diabetes insipidus during pregnancy are available; these include a few anecdotal reports of congenital anomalies and low bir h weight babies. However, no causal connection between these events and desmopressin acetate has been established. A fifteen year Swedish epidemiologic study of he use of desmopressin acetate in pregnant women with diabetes insipidus found he rate of birth defects to be no greater han that in he general population; however, the statistical power of this study is low. As opposed to preparations containing natural hormones, desmopressin acetate in antidiuretic doses has no ute otonic action and the physician wil have to weigh he possible herapeutic advantages against he possible risks in each case.

Nursing Mothers
There have been no cont olled studies in nursing mo hers. A single study in postpartum women demonstrated a marked change in plasma, but little if any change in assayable desmopressin acetate in breast milk following an intranasal dose of 0.01 mg.

It is not known whe her he drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to nursing mo hers.

Pediatric Use
Central Diabetes Insipidus
Desmopressin acetate tablets have been used safely in pediatric patients, age 4 years and older, wi h diabetes insipidus for periods up to 44 mon hs. In younger pediatric patients he dose must be individually adjusted in order to prevent an excessive decrease in plasma osmolality leading to hyponatremia and possible convulsions; dosing should start at 0.05 mg (1/2 of the 0.1 mg tablet). Use of desmopressin acetate tablets in pediatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient and/or guardian. (See **WARNINGS.**)

Primary Nocturnal Enuresis
Desmopressin acetate tablets have been safely used in pediatric patients age 6 years and older with primary noctu nal enuresis for up to 6 mon hs. Some patients respond to a dose of 0.2 mg; however, increasing responses are seen at doses of 0.4 mg and 0.6 mg. No increase in he frequency or severity of adverse reactions or decrease in efficacy was seen wi h an increased dose or duration. The dose should be individually adjusted to achieve he best results. Treatment with desmopressin for primary noctu nal enuresis should be interrupted during acute intercurrent illness characterized by fluid and/or elect olyte imbalance (e.g., systemic infections, fever, recurrent vomiting or diar hea) or under conditions of extremely hot wea her, vigo ous exercise or o her conditions associated wi h increased water intake.

Geriatric Use
Clinical studies of desmopressin acetate tablets did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently f om younger subjects.

O her reported clinical experience has not identified differences in responses between he elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting he greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or o her drug herapy.

This drug is known to be substantially excreted by he kidney, and he risk of toxic reactions to his drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Desmopressin acetate is contraindicated in patients wi h moderate to severe renal impairment (defined as a creatinine clearance below 50ml/min).

(See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics** and **CONTRAINDICATIONS.**)

Use of desmopressin acetate tablets in geriatric patients requires careful fluid intake restrictions to prevent possible hyponatremia and water intoxication. Fluid restriction should be discussed wi h he patient. (See **WARNINGS.**)

ADVERSE REACTIONS

Infrequently, large doses of the intranasal formulations of desmopressin acetate tablets and injection have p oduced transient headache, nausea, flushing and mild abdominal cramps. These symptoms have disappeared w th reduction in dosage.

Central Diabetes Insipidus
In long-term clinical studies in which patients with diabetes insipidus were followed for periods up to 44 mon hs of desmopressin acetate tablet herapy, transient increases in AST (SGOT) no higher han 1.5 times he upper limit of normal were occasionally observed. Elevated AST (SGOT) retu ned to he normal range despite continued use of desmopressin acetate tablets.

Primary Nocturnal Enuresis
The only adverse event occurring in ≥3% of patients in cont olled clinical trials with desmopressin acetate tablets hat was p obably, possibly, or remotely related to study drug was headache (4% desmopressin acetate, 3% placebo).

Other
The following adverse events have been reported; however heir relationship to desmopressin acetate has not been established: abnormal hinking, diar hea, and edema-weight gain.

See **WARNINGS** for the possibility of water intoxication and hyponatremia.

Post Marketing
There have been rare reports of hyponatremic convulsions associated wi h concomitant use wi h he following medications: oxybutinin and imipramine.

OVERDOSAGE

Signs of overdose may include confusion, d owsiness, continuing headache, p oblems with passing urine and rapid weight gain due to fluid retention. (See **WARNINGS.**) In case of overdose, he dose should be reduced, frequency of administration decreased, or the drug withdrawn according to he severity of he condition. There is no known specific antidote for desmopressin acetate. The patient should be observed and treated wi h app opriate symptomatic herapy.

An oral LD_{50} has not been established. Oral doses up to 0.2 mg/kg/day have been administered to dogs and rats for 6 months wi hout any significant drug-related toxicities reported. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Central Diabetes Insipidus
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to he diu nal patte n of response. Response should be estimated by two parameters: adequate duration of sleep and adequate, not excessive, water tu nover. Patients previously on intranasal desmopressin acetate herapy should begin tablet herapy twelve hours after he last intranasal dose. During he initial dose titration period, patients should be observed closely and app opriate safety parameters measured to assure adequate response. Patients should be monitored at regular intervals during he course of desmopressin acetate tablet herapy to assure adequate antidiuretic response. Modifications in dosage regimen should be implemented as necessary to assure adequate water tu nover. Fluid restriction should be observed. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

Adults and Children
It is recommended hat patients be started on doses of 0.05 mg (1/2 of he 0.1 mg tablet) two times a day and individually adjusted to heir optimum therapeutic dose. Most patients in clinical trials found hat he optimal dosage range is 0.1 mg to 0.8 mg daily, administered in divided doses. Each dose should be separately adjusted for an adequate diu nal hythm of water tu nover. Total daily dosage should be increased or decreased in the range of 0.1 mg to 1.2 mg divided into two or three daily doses as needed to obtain adequate antidiuresis.

See **Pediatric Use** subsection for special considerations when administering desmopressin acetate to pediatric diabetes insipidus patients.

Geriatric Use
This drug is known to be substantially excreted by the kidney, and he risk of toxic reactions to his drug may be greater in patients wi h impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. (See **CLINICAL PHARMACOLOGY, Human Pharmacokinetics, CONTRAINDICATIONS,** and **PRECAUTIONS, Geriatric Use.**)

Primary Nocturnal Enuresis
The dosage of desmopressin acetate tablets must be determined for each individual patient and adjusted according to response. Patients previously on intranasal desmopressin acetate herapy can begin tablet herapy he night following (24 hours after) he last intranasal dose. The recommended initial dose for patients age 6 years and older is 0.2 mg at bedtime. The dose may be titrated up to 0.6 mg to achieve he desired response. Fluid restriction should be observed, and fluid intake should be limited to a minimum f om 1 hour before desmopressin administration, until he next mo ning, or at least 8 hours after administration. (See **WARNINGS, PRECAUTIONS, Pediatric Use and Geriatric Use.**)

HOW SUPPLIED

Desmopressin Acetate Tablets 0.1 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.1" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0257-3)
Bottles of 100 (NDC 60505-0257-1)
Bottles of 1000 (NDC 60505-0257-8)

Desmopressin Acetate Tablets 0.2 mg are available for oral administration as white to off-white, ound shaped, scored tablets, imprinted "APO" on one side and "DES" bisect "0.2" on he o her side. They are supplied as follows:
Bottles of 30 (NDC 60505-0258-3)
Bottles of 100 (NDC 60505-0258-1)
Bottles of 1000 (NDC 60505-0258-8)

Store 20° to 25°C (68° to 77°F) [see USP Cont olled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

Keep out of the reach of children.

APOTEX INC.
DESMOPRESSIN ACETATE TABLETS
0.1 mg and 0.2 mg

Manufactured by:	Manufactured for:
Apotex Inc.	Apotex Corp.
To onto, Ontario	Weston, Florida
Canada M9L 1T9	33326

(APO-DESMOPRESSIN-R03-51X138-LFLT-10/30/08)

Revised: October 2008

Rev. 4

(b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 077414/S-008

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING # 1

SUPPLEMENT- CBE

EDR- FPL

DATE OF REVIEW: 2/4/09

ANDA #:77-414/SL-008, combined with SC-007

NAME OF FIRM: Apotex Pharmaceuticals

NAME OF DRUG: Desmopressin Acetate Tab 0.1 mg and 0.2 mg

DATE OF SUBMISSION: 28 NOV 2008

COMMENTS:

1. **EXTENDED CONTAINER LABELS**: 0.1 mg and 0.2 mg in 30s, 100s, and 1000s - Satisfactory in FPL as of the Nov. 28, 2008 submission.

\\Cdsesub1\evsprod\ANDA077414\0003\m1\us\114-labeling\final-labeling\final-package-insert-package-inserts

RECOMMENDATIONS: The extended label format for each of the package sizes is satisfactory for approval.

NOTE TO CHEMIST: Labels are satisfactory for approval.

FOR THE RECORD:

1. The supplement provides for a change in the drug substance from a (b) (4) molecular weight.

cc: ANDA 77-414/S-008
Dup/Division File
HFD-613/APayne/JGrace (no cc:)
V:\FIRMSAM\apotex\LTRS&REV\77414s008ap1dfslabreview.doc
Review

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Angela Payne
2/3/2009 09:38:11 AM
LABELING REVIEWER

Associated with SC-007

John Grace
2/3/2009 10:16:01 AM
LABELING REVIEWER