PACKAGE INSERT (48XXFEX)

MINIRIN™

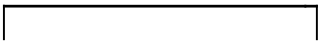
(desmopressin acetate)

NASAL SPRAY

DESCRIPTION

Minirin is 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. 1183.34 Empirical formula: $C_{46}H_{64}N_{14}O_{12}S_2 \cdot C_2H_4O_2 \cdot 3H_2O$



SCH_2CH_2CO-Tyr-Phe-Gln-Asn-Cys-Pro-D-Arg-Gly-$NH_2 \bullet CH_3COOH \bullet 3H_2O$

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

Minirin nasal spray is provided as an aqueous solution for intranasal use.

Each mL contains:
Desmopressin acetate 0.1 mg
Chlorobutanol 5.0 mg
Sodium Chloride 9.0 mg
Hydrochloric acid to adjust pH to approximately 4

The **Minirin nasal spray** compression pump delivers 0.1 mL (10 µg) of desmopressin acetate per spray.

CLINICAL PHARMACOLOGY

Minirin nasal spray contains as active substance 1-(3-mercaptopropionic acid)-8-D-arginine vasopressin, which is a synthetic analogue of the natural hormone arginine vasopressin. One mL (0.1 mg) of intranasal desmopressin acetate nasal spray has an antidiuretic activity of about 400 IU; 10 µg of desmopressin acetate is equivalent to 40 IU.

The change in structure of arginine vasopressin to desmopressin acetate has resulted in a decreased vasopressor action and decreased actions on visceral smooth muscle relative to the enhanced antidiuretic activity, so that clinically effective antidiuretic doses are usually below threshold levels for effects on vascular or visceral smooth muscle.

Minirin nasal spray administered intranasally has an antidiuretic effect about one-tenth that of an equivalent dose administered by injection.

Pharmacokinetics
Minirin nasal spray is absorbed rapidly from the nasal mucosa. Desmopressin acetate exhibits a biphasic elimination profile, with half-lives of 7.8 and 75.5 minutes for the initial and terminal phases, respectively, in contrast with lysine vasopressin, which has initial and terminal phase half-lives of 2.5 and 14.5 minutes, respectively.

INDICATIONS AND USAGE

Primary Nocturnal Enuresis: Minirin nasal spray is indicated for the management of primary nocturnal enuresis. It may be used alone or adjunctive to behavioral conditioning or other nonpharmacological intervention. It has been shown to be effective in some cases that are refractory to conventional therapies.

Central Cranial Diabetes Insipidus: Minirin nasal spray is indicated as antidiuretic replacement therapy in the management of central cranial diabetes insipidus and for management of the temporary polyuria and polydipsia following head trauma or surgery in the pituitary region. It is ineffective for the treatment of nephrogenic diabetes insipidus.

The use of **Minirin nasal spray** in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.
Patients are selected for therapy by establishing the diagnosis by means of the water deprivation test, the hypertonic saline infusion test, and/or the response to antidiuretic hormone. Continued response to intranasal desmopressin acetate can be monitored by urine volume and osmolality.
Desmopressin acetate is also available as a solution for injection when the intranasal route may be compromised. These situations include nasal congestion and blockage, nasal discharge, atrophy of nasal mucosa, and severe atrophic rhinitis. Intranasal delivery may also be inappropriate where there is an impaired level of consciousness. In addition, cranial surgical procedures, such as transsphenoidal hypophysectomy create situations where an alternative route of administration is needed as in cases of nasal packing or recovery from surgery.

CONTRAINDICATIONS

Minirin nasal spray is contraindicated in individuals with known hypersensitivity to desmopressin acetate or to any of the components of **Minirin nasal spray**.

WARNINGS

1. For intranasal use only.

2. In very young and elderly patients in particular, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia. 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.

PRECAUTIONS

General: Minirin nasal spray at high dosage has infrequently produced a slight elevation of blood pressure, which disappeared with a reduction in dosage. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease because of possible rise in blood pressure.

Minirin nasal spray should be used with caution in patients with conditions associated with fluid and electrolyte imbalance, such as cystic fibrosis, because these patients are prone to hyponatremia.

Rare severe allergic reactions have been reported with desmopressin acetate. Anaphylaxis has been reported with intravenous administration of desmopressin acetate injection, but not with Minirin nasal spray.

Central Cranial Diabetes Insipidus: Since **Minirin nasal spray** is used intranasally, changes in the nasal mucosa such as scarring, edema, or other disease may cause erratic, unreliable absorption in which case intranasal Minirin should not be used. For such situations, desmopressin acetate injection should be considered.

Primary Nocturnal Enuresis: If changes in the nasal mucosa have occurred, unreliable absorption may result. **Minirin nasal spray** should be discontinued until the nasal problems resolve.

Information for Patients: Patients should be informed that the **Minirin nasal spray** bottle accurately delivers 50 doses of 10 µg each. Any solution remaining after 50 doses should be discarded since the amount delivered thereafter may be substantially less than 10 µg of drug. No attempt should be made to transfer remaining solution to another bottle. Patients should be instructed to read accompanying directions on use of the spray pump carefully before use.

Laboratory Tests: Laboratory tests for following the patient with central cranial diabetes insipidus or post-surgical or head trauma-related polyuria and polydipsia include urine volume and osmolality. In some cases plasma osmolality measurements may be required. For the healthy patient with primary nocturnal enuresis, serum electrolytes should be checked at least once if therapy is continued beyond 7 days.

Drug Interactions: Although the pressor activity of Minirin is very low compared to the antidiuretic activity, use of large doses of intranasal Minirin with other pressor agents should only be done with careful patient monitoring.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Studies with Minirin 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 µg/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 reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.
Several publications of desmopressin acetate's use 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 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 10 µg. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when desmopressin acetate is administered to a nursing woman.

Pediatric Use: *Primary Nocturnal Enuresis:* **Minirin nasal spray** has been used in childhood nocturnal enuresis. Short-term (4-8 weeks) **Minirin nasal spray** administration has been shown to be safe and modestly effective in pediatric patients aged 6 years or older with severe childhood nocturnal enuresis. Adequately controlled studies with intranasal Minirin in primary nocturnal enuresis have not been conducted beyond 4-8 weeks. The dose should be individually adjusted to achieve the best results.

Central Cranial Diabetes Insipidus: **Minirin nasal spray** has been used in children with diabetes insipidus. Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. The dose must be individually adjusted to the patient with attention in the very young to the danger of an extreme decrease in plasma osmolality with resulting convulsions. Dose should start at 0.05 mL or less.
Since the spray cannot deliver less than 0.1 mL (10 μg), smaller doses should be administered using the rhinal tube delivery system. Do not use the nasal spray in pediatric patients requiring less than 0.1 mL (10 μg) per dose.
There are reports of an occasional change in response with time, usually greater than 6 months. Some patients may show a decreased responsiveness, others a shortened duration of effect. There is no evidence this effect is due to the development of binding antibodies but may be due to a local inactivation of the peptide.

ADVERSE REACTIONS

Infrequently, high dosages of intranasal Minirin have produced transient headache and nausea. Nasal congestion, rhinitis and flushing have also been reported occasionally along with mild abdominal cramps. These symptoms disappeared with reduction in dosage. Nosebleed, sore throat, cough and upper respiratory infections have also been reported.

The following table lists the percent of patients having adverse experiences without regard to relationship to study drug from the pooled pivotal study data for nocturnal enuresis.

ADVERSE REACTION	PLACEBO (N=59) %	Desmopressin acetate 20 µg (N=60) %	Desmopressin acetate 40 µg (N=61) %
BODY AS A WHOLE			
Abdominal Pain	0	2	2
Asthenia	0	0	2
Chills	0	0	2
Headache	0	2	5
Throat Pain	2	0	0
NERVOUS SYSTEM			
Depression	2	0	0
Dizziness	0	0	3
RESPIRATORY SYSTEM			
Epistaxis	2	3	0
Nostril Pain	0	2	0
Respiratory Infection	2	0	0
Rhinitis	2	8	3
CARDIOVASCULAR SYSTEM			
Vasodilation	2	0	0
DIGESTIVE SYSTEM			
Gastrointestinal Disorder	0	2	0
Nausea	0	0	2
SKIN & APPENDAGES			
Leg Rash	2	0	0
Rash	2	0	0
SPECIAL SENSES			
Conjunctivitis	0	2	0
Edema Eyes	0	2	0
Lachrymation Disorder	0	0	2

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

OVERDOSAGE

See **ADVERSE REACTIONS** above. In case of overdosage, 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 or **Minirin nasal spray.**
An oral LD_{50} has not been established. An intravenous dose of 2 mg/kg in mice demonstrated no effect.

DOSAGE AND ADMINISTRATION

Primary Nocturnal Enuresis: Dosage should be adjusted according to the individual. The recommended initial dose for those 6 years of age and older is 20 µg or 0.2 mL solution intranasally at bedtime. Adjustment up to 40 µg is suggested if the patient does not respond. Some patients may respond to 10 µg and adjustment to that lower dose may be done if the patient has shown a response to 20 µg. It is recommended that one-half of the dose be administered per nostril. Adequately controlled studies with intranasal Minirin in primary nocturnal enuresis have not been conducted beyond 4-8 weeks.

Central Cranial Diabetes Insipidus: Minirin nasal spray dosage 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 with nasal congestion and blockage have often responded well to intranasal Minirin. The usual dosage range in adults is 0.1 to 0.4 mL daily, either as a single dose or divided into two or three doses. Most adults require 0.2 mL daily in two divided doses. The morning and evening doses should be separately adjusted for an adequate diurnal rhythm of water turnover. For children aged 3 months to 12 years, the usual dosage range is 0.05 to 0.3 mL daily, either as a single dose or divided into two doses. About 1/4 to 1/3 of patients can be controlled by a single daily dose of Minirin administered intranasally.

The nasal spray pump can only deliver doses of 0.1 mL (10 µg) or multiples of 0.1 mL. If doses other than these are required, the rhinal tube delivery system may be used.

The spray pump must be primed prior to the first use. To prime pump, press down four times. The bottle will now deliver 10 µg of drug per spray. Discard Minirin nasal spray after 50 sprays since the amount delivered thereafter per spray may be substantially less than 10 µg of drug.

HOW SUPPLIED

Minirin nasal spray is available as a 5 mL bottle with spray pump delivering 50 doses of 10 µg (NDC 55566-5010-1). Store refrigerated 2 to 8°C (36 to 46°F). When traveling, product will maintain stability for 3 weeks when stored at controlled room temperature, 20 to 25°C (68 to 77°F).

Rx only

Keep out of the reach of children.

U.S. Pat. Nos. 5,500,413, 5,596,078, and 5,674,850
Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals,
Linhamn, Sweden

6043-01
Rev 9/02

PATIENT INFORMATION
MINIRIN NASAL SPRAY

Read this information carefully before you begin treatment. Read the information you get whenever you get more medicine. There may be new information. This information does not take the place of talking with your doctor about your medical condition or your treatment. If you have any questions about Minirin, ask your doctor. Only your doctor can determine if Minirin is right for you.

What is Minirin?

Minirin is a medicine used to treat people who

- have trouble controlling their urine at night (frequent urination)
- do not have enough vasopressin hormone. Vasopressin hormone controls urination.

You take Minirin by spraying it in your nose

.

Who should not useMinirin?

Do not use Minirin if you are allergic to any of its ingredients.
Desmopressin acetate is the active ingredient. Ask your doctor or pharmacist if you need to know the other ingredients.

Tell your doctor about

- all the medicines you take. Your doctor may have to check your condition more carefully if you take certain medicines.
- all your medical conditions, especially
  - high blood pressure
  - coronary artery or heart disease
  - cystic fibrosis or other conditions that involve fluid or electrolyte (salt) imbalance

Tell your doctor if you

- have scarring, swelling, or other conditions in your nose. Minirin Nasal Spray may not be right for you.
- are pregnant or breast-feeding. Your doctor will discuss with you if Minirin is right for you.

How should I take Minirin?

If you take Minirin to reduce night-time urination, you should take it at bedtime. When you take Minirin, your doctor may ask you to drink less liquid.

Complete instructions for using Minirin Nasal Spray are at the end of this leaflet.

What should I avoid while taking Minirin?

While you are treated with Minirin, do not drink a lot of liquid.

What are the possible side effects of Minirin?

The most common side effects are short-term headache and nausea, nose bleed, sore throat, cough, and colds.

Sometimes Minirin causes stuffy or irritated nose, mild stomach cramps or flushing (warm skin, usually on your face and neck). Tell your doctor if you have these side effects. Your doctor may reduce your dose of Minirin.

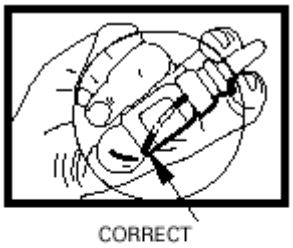
Tell your doctor if your nose feels irritated or you have other changes in your nose. You may need to stop taking Minirin for a while.

General advice about prescription medicines
Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use Minirin for a condition for which it was not prescribed. Do not give Minirin to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about Minirin. If you would like more information, talk with your doctor. You can ask your pharmacist or doctor for information about Minirin that is written for health professionals.

Instructions for using Minirin Nasal Spray

1. Remove the protective cap from the spray bottle.
2. **The spray pump must be primed before the first use.** To prime the pump, press down 4 times.
3. Once primed, the spray pump delivers 10 micrograms of medicine each time it is pressed. To be sure you get the right amount of medicine, tilt the bottle so that the dip tube inside the bottle is in the deepest part of the medicine. (See figures below.)



Arrow indicates the dip tube and it is in the deepest part of the medicine.

Arrow indicates the dip tube and it is **NOT** in the deepest part of the medicine.

4. To give yourself a 10-microgram dose, place the spray nozzle in a nostril and press the spray pump once. If a higher dose has been prescribed, spray half the dose in each nostril. For example, if your dose is 20 micrograms, spray once in each nostril. **You cannot use the spray pump for doses less than 10 micrograms or doses that are not multiples of 10 micrograms.** If you need less than 10 micrograms of Minirin at a time, talk with your doctor about how to take the medicine so you get the right amount.

5. Replace the protective cap on the bottle after use. Store the bottle in the refrigerator. The pump will stay primed for up to 1 week in the refrigerator. **If you have not used the spray for 1 week or more, re-prime the pump by pressing once.**

6. **After you have used 50 doses, throw away the bottle**. There is not enough medicine left for a full dose. Do not try to pour the leftover medicine into another spray pump that has medicine in it. There is extra medicine in the bottle for priming.

7. We have included a convenient check-off chart to help you keep track of the doses you use. This will help assure that you get 50 full doses of medicine.

How should I store Minirin?

Store Minirin in the refrigerator 36º -46ºF (2º -8ºC). When traveling, you can keep it out of the refrigerator for up to 3 weeks if you store it at room temperature at 68º -77ºF (20º -25ºC).

Minirin Nasal Spray
50-Dose Check-off

①	②	③	④	⑤
⑥	⑦	⑧	⑨	⑩
⑪	⑫	⑬	⑭	⑮
⑯	⑰	⑱	⑲	⑳
㉑	㉒	㉓	㉔	㉕
㉖	㉗	㉘	㉙	㉚
㉛	㉜	㉝	㉞	㉟
㊱	㊲	㊳	㊴	㊵
㊶	㊷	㊸	㊹	㊺
㊻	㊼	㊽	㊾	㊿

1. Keep this chart with your medicine or in a convenient location, such as on the refrigerator.
2. Starting with #1, check off each dose as you use the medicine.
3. **Throw away the bottle after 50 doses.**

Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals,
Linhamn, Sweden

6043-01
REV 9/02

451562

NDC 55566-5010-1

MINIRIN™

(desmopressin acetate)

Nasal Spray

0.1 mg/mL

5 mL

(50 doses of 10 mcg)

Usual dosage: see package insert.

Store refrigerated 2 to 8°C (36 to 46°F).

Keep out of the reach of children.

Rx only

Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals,
Limhamn, Sweden

6042-01

EXP.

LOT

451562

NDC 55566-5010-1

MINIRIN™

(desmopressin acetate)

Nasal Spray

0.1 mg/mL

5 mL

(50 doses of 10 mcg)

Usual dosage: see package insert.

Store refrigerated 2 to 8°C (36 to 46°F).

Keep out of the reach of children.

Rx only

Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals,
Limhamn, Sweden

6042-01

EXP.

LOT

Desmopressin 5ml USA Black

100% of Black

Order No: **A-6402**	Case No: **2002-146**	Product: **451562**	Date: **2002-10-08**
Proof No: /	Replaces: 451561	Pharmacode: **424**	
Vers No: **3**	Format: **23x68**	QPP No: **101**	

☐ APPROVED Date: Sign:

☐ NEW PROOF Date: Sign:

PRINTCOM
Box 9126,
200 39 MALMÖ
Tel: 040 - 671 76 22,
Fax: 040 - 671 76 06

451572

10 x 5 mL

NDC 55566-5010-1

MINIRIN™

(desmopressin acetate)

Nasal Spray

0.1 mg/mL

Rx only

6045-01

Store refrigerated
2 to 8°C (36 to 46°F).

EXP.
LOT

Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals, Limhamn, Sweden

451572

10 x 5 mL

NDC 55566-5010-1

MINIRIN™

(desmopressin acetate)

Nasal Spray

0.1 mg/mL

Rx only

6045-01

Store refrigerated
2 to 8°C (36 to 46°F).

EXP.
LOT

Manufactured for
Ferring Pharmaceuticals Inc.
Suffern, NY 10901
By Ferring Pharmaceuticals, Limhamn, Sweden

Desmopressin 5 ml USA	Black		
100% of Black	Order No: **A-6403**	Case No: **2002-149**	Product: **451572**	Date: **2002-09-18**
	Proof No: /	Replaces: 451571	Pharmacode: **425**	
	Vers No: **2**	Format: **60x55**	QPP No: **100**	
	☐ APPROVED Date:		Sign:	
	☐ NEW PROOF Date:		Sign:	

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