CSL Behring

Stimate®

(desmopressin acetate)

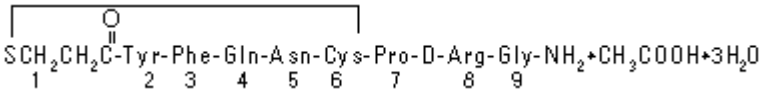
Nasal Spray, 1.5 mg/mL

R_x only

DESCRIPTION

Stimate® (**desmopressin acetate**) is a synthetic analogue of the natural pituitary hormone 8-arginine vasopressin (ADH), an antidiuretic hormone affecting renal water conservation. **Stimate® Nasal Spray** contains 1.5 mg/mL desmopressin acetate in an aqueous solution at a pH of approximately 5. **Stimate® Nasal Spray's** compression pump delivers 0.1 mL (150 mcg) of solution per spray. It is chemically defined as follows:

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



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

Stimate® Nasal Spray is provided as an aqueous solution for intranasal use.

Each mL contains:

Active ingredient:	
Desmopressin acetate	1.5 mg
Inactive ingredients:	
Sodium chloride	7.5 mg
Buffer:	
Citric acid monohydrate	1.7 mg
Disodium phosphate dihydrate	3 mg
Preservative:	
Benzalkonium chloride	0.1 mg
Purified water	To 1 mL

CLINICAL PHARMACOLOGY

Stimate® Nasal Spray contains as active substance, desmopressin acetate, which is a synthetic analogue of the natural hormone arginine vasopressin. One spray or 0.1 mL (150 mcg) of **Stimate® Nasal Spray** solution has an antidiuretic activity of about 600 International Units.

Desmopressin acetate has been shown to be more potent than arginine vasopressin in increasing plasma levels of Factor VIII activity in patients with hemophilia and von Willebrand's disease Type I.

Dose-response studies were performed in healthy persons using doses of 150 to 450 mcg, administered as one to three sprays. The response to **Stimate® Nasal Spray** is dose-related, with maximal plasma levels of 150 to 250 percent of initial concentrations achieved for both Factor VIII and von Willebrand factor. The increase is rapid and evident within 30 minutes, reaching a maximum at about 1.5 hours.

The percentage increase of Factor VIII and von Willebrand factor levels in patients with mild hemophilia A and von Willebrand's disease was not notably different from that observed in normal healthy individuals when treated with 300 mcg of **Stimate® Nasal Spray**. In patients with von Willebrand's disease, levels of Factor VIII coagulant activity and von Willebrand factor antigen remained greater than 30 U/dL for 8 hours after a 300 mcg dose of **Stimate® Nasal Spray**. After 300 mcg of **Stimate® Nasal Spray**, the percentage increase of Factor VIII and von Willebrand factor levels in patients with mild hemophilia A and von Willebrand's disease was less than observed after 0.3 mcg/kg of intravenous desmopressin acetate.

Plasminogen activator activity increases rapidly after intravenous desmopressin acetate infusion, but there has been no clinically significant fibrinolysis in patients treated with desmopressin acetate.

The effect of repeated intravenous desmopressin acetate administration when doses were given every 12 to 24 hours has generally shown a diminution of the Factor VIII activity increase noted after a single dose. It is possible to reproduce the initial response in some patients after an interval of one week, but other patients may require as long as 6 weeks.

The half-life of **Stimate® Nasal Spray** was between 3.3 and 3.5 hours, over the range of intranasal doses, 150 to 450 mcg. Plasma concentrations of **Stimate® Nasal Spray** were maximal approximately 40 to 45 minutes after dosing.

The bioavailability of **Stimate® Nasal Spray** when administered by the intranasal route as a 1.5 mg/mL solution is between 3.3 and 4.1 percent.

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.

INDICATIONS AND USAGE

Before the initial therapeutic administration of **Stimate® Nasal Spray**, the physician should establish that the patient shows an appropriate change in the coagulation profile following a test dose of intranasal administration of **Stimate® Nasal Spray**.

Desmopressin acetate is also available as a solution for injection (DDAVP® 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.

Hemophilia A

Stimate® Nasal Spray is indicated for patients with hemophilia A with Factor VIII coagulant activity levels greater than 5%.

Desmopressin acetate will also stop bleeding in patients with hemophilia A with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas or mucosal bleeding.

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, **Stimate® Nasal Spray** provided effective hemostasis 100% of the time in 2 of the 5 patients. For those patients not responding in 100% of bleeding occasions, 45% (14 of 31) of bleeding episodes were effectively controlled with **Stimate® Nasal Spray**.

Desmopressin acetate is not indicated for the treatment of hemophilia A with Factor VIII coagulant activity levels equal to or less than 5%, or for the treatment of hemophilia B, or in patients who have Factor VIII antibodies.

von Willebrand's Disease (Type I)

Stimate® Nasal Spray is indicated for patients with mild to moderate classic von Willebrand's disease (Type I) with Factor VIII levels greater than 5%.

Desmopressin acetate will also stop bleeding in mild to moderate von Willebrand's disease patients with episodes of spontaneous or trauma-induced injuries such as hemarthroses, intramuscular hematomas, mucosal bleeding or menorrhagia.

In the outpatient setting during two clinical trials where patients recorded bleeding episodes, **Stimate® Nasal Spray** provided effective hemostasis 100% of the time in 75% of the patients (n=16). For those patients not responding in 100% of bleeding occasions, 78% (64 of 82) of bleeding episodes were effectively controlled with **Stimate® Nasal Spray**.

Patients may respond in a variable fashion depending on the type of molecular defect they have. Bleeding time and Factor VIII coagulant activity, ristocetin cofactor activity, and von Willebrand factor antigen should be checked after initial administration of **Stimate® Nasal Spray** to ensure that adequate levels have been achieved.

Stimate® Nasal Spray is not indicated for the treatment of severe classic von Willebrand's disease (Type I) and when there is evidence of an abnormal molecular form of Factor VIII antigen. See ***WARNINGS***.

CONTRAINDICATIONS

None.

WARNINGS

For intranasal use only.

Very rare cases of hyponatremia have been reported from world-wide postmarketing experience in patients treated with Stimate (desmopressin acetate). Stimate 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.

When Stimate Nasal Spray is administered, in particular in pediatric and geriatric patients, fluid intake should be adjusted downward in order to decrease the potential occurrence of water intoxication and hyponatremia (See ***PRECAUTIONS, Pediatric Use*** and ***Geriatric Use***.) All patients receiving Stimate therapy should be observed for the following signs or 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 that could lead to coma.

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

Stimate® Nasal Spray should not be used to treat patients with Type IIB von Willebrand's disease since platelet aggregation may be induced.

PRECAUTIONS

General

Desmopressin acetate has infrequently produced changes in blood pressure causing either a slight elevation in blood pressure or a transient fall in blood pressure and a compensatory increase in heart rate. The drug should be used with caution in patients with coronary artery insufficiency and/or hypertensive cardiovascular disease.

Stimate® Nasal Spray 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 to hyponatremia.

There have been rare reports of thrombotic events (thrombosis, acute cerebrovascular thrombosis, acute myocardial infarction) following desmopressin acetate injection in patients predisposed to thrombus formation. No causality has been determined; however, the drug should be used with caution in these patients.

Severe allergic reactions have been reported rarely. Fatal anaphylaxis has been reported in one patient who received intravenous DDAVP® (desmopressin acetate). It is not known whether antibodies to desmopressin acetate are produced after repeated administration.

Since **Stimate® 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 **Stimate® Nasal Spray** should be discontinued until the nasal problems resolve. For such situations, DDAVP® Injection should be considered.

Information for Patients

Patients should be informed that the bottle accurately delivers 25 sprays of 150 mcg each. Any solution remaining after 25 sprays should be discarded since the amount delivered thereafter may be substantially less than 150 mcg 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.

Patients should also be advised that if bleeding is not controlled, the physician should be contacted.

Hemophilia A

Laboratory tests for assessing patient status include levels of Factor VIII coagulant, Factor VIII antigen and Factor VIII ristocetin cofactor (von Willebrand factor) as well as activated partial thromboplastin time. Factor VIII coagulant activity should be determined before giving **Stimate® Nasal Spray** for hemostasis. If Factor VIII coagulant activity is present at less than 5% of normal, **Stimate® Nasal Spray** should not be relied on.

von Willebrand's Disease

Laboratory tests for assessing patient status include levels of Factor VIII coagulant activity, VWF:RCo and VWF:Ag.

Drug Interactions

Although the pressor activity of desmopressin acetate is very low, its use with other pressor agents should be done 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.

DDAVP® Injection has been used with epsilon aminocaproic acid without adverse effects.

Carcinogenicity, Mutagenicity, Impairment of Fertility

There have been no long-term studies in animals to assess the carcinogenic, mutagenic or impairment of fertility potential of **Stimate® Nasal Spray**.

Pregnancy Category B

Reproduction studies performed in rats and rabbits by the subcutaneous route at doses up to 10 mcg/kg/day have revealed no evidence of harm to the fetus due to desmopressin acetate. This dose is equivalent to 10 times (for Factor VIII stimulation) or 38 times (for diabetes insipidus) the systemic human dose based on a mg/M^2 surface area.

There are no adequate and well-controlled studies in pregnant women. 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 15-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. 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 DDAVP® in breast milk following an intranasal dose of 10 mcg. 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 **Stimate® Nasal Spray** is administered to a nursing woman.

Pediatric Use

Use in infants and children will require careful fluid intake restriction to prevent possible hyponatremia and water intoxication. **Stimate® Nasal Spray** should not be used in infants younger than 11 months in the treatment of hemophilia A or von Willebrand's disease; safety and effectiveness in children between 11 months and 12 years of age has been demonstrated.

Geriatric Use

Clinical studies of Stimate® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently than younger subjects. However, other post-marketing experience has indicated the occurrence of hyponatremia with the use of desmopressin acetate and fluid overload.

Therefore, in elderly patients fluid intake should be adjusted downward in an effort 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, and that could lead to coma.

Patients who do not have need of antidiuretic hormone for its antidiuretic effect should be cautioned to ingest only enough fluid to satisfy thirst, in an effort to decrease the potential occurrence of water intoxication and hyponatremia.

As for all patients, dosing for geriatric patients should be appropriate to their clinical condition.

ADVERSE REACTIONS

Infrequently, DDAVP® Injection has produced transient headache, nausea, mild abdominal cramps and vulval pain. These symptoms disappeared with reduction in dosage. Occasional facial flushing has been reported with the administration of DDAVP® Injection. Infrequently, high doses of intranasal DDAVP® 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.

In addition to those listed above, the following have also been reported in clinical trials with **Stimate® Nasal Spray**: Somnolence, dizziness, itchy or light-sensitive eyes, insomnia, chills, warm feeling, pain, chest pain, palpitations, tachycardia, dyspepsia, edema, vomiting, agitation and balanitis.

DDAVP® Injection (desmopressin acetate) has infrequently produced changes in blood pressure causing either a slight elevation or a transient fall with a compensatory increase in heart rate. Severe allergic reactions including anaphylaxis have been reported rarely with DDAVP® Injection.

Post Marketing

There have been rare reports of convulsions from hyponatremia associated with concomitant use of desmopressin and the following medications: oxybutynin and imipramine.

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

To report SUSPECTED ADVERSE REACTIONS, contact CSL Behring Pharmacovigilance at 1-866-915-6958 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

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 cases of overdosage, the dosage 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 **Stimate® 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

Hemophilia A and von Willebrand's Disease (Type I)

Stimate® Nasal Spray is administered by nasal insufflation, one spray per nostril, to provide a total dose of 300 mcg. In patients weighing less than 50 kg, 150 mcg administered as a single

spray provided the expected effect on Factor VIII coagulant activity, Factor VIII ristocetin cofactor activity and skin bleeding time. If **Stimate® Nasal Spray** is used preoperatively, it should be administered 2 hours prior to the scheduled procedure.

The necessity for repeat administration of **Stimate® Nasal Spray** or use of any blood products for hemostasis should be determined by laboratory response as well as the clinical condition of the patient. Fluid restriction should be observed, and fluid intake should be limited to a minimum, from 1 hour before desmopressin administration, until at least 24 hours after administration. The tendency toward tachyphylaxis (lessening of response) with repeated administration given more frequently than once every 48 hours should be considered in treating each patient.

The nasal spray pump can only deliver doses of 0.1 mL (150 mcg) or multiples of 0.1 mL. If doses other than these are required, DDAVP® Injection may be used.

The spray pump must be primed prior to the first use. To prime pump, press down 4 times. The bottle should be discarded after 25 sprays since the amount delivered thereafter per spray may be substantially less than 150 mcg of drug.

HOW SUPPLIED

A 2.5 mL bottle with spray pump capable of delivering 25 sprays of 150 mcg (NDC 0053-6871-00).

Store at room temperature not to exceed 25°C (77°F) for the period indicated by the expiration date on the label. Discard six months after being opened. Store bottle in upright position.

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Manufactured for:
CSL Behring LLC
King of Prussia, PA 19406-0901
US License No. 1767

By:
Ferring GmbH
Kiel, Germany

PATIENT INSTRUCTION GUIDE

Stimate® Nasal Spray
(Pronounced Stim-ate)
(desmopressin acetate)

Read this patient information leaflet before you start taking **Stimate® Nasal Spray** and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment.

What is the most important information I should know about Stimate® Nasal Spray?

All patients using Stimate® Nasal Spray are at risk for water intoxication, fluid overload and low sodium levels in the blood. You must follow your healthcare provider's instructions on limiting the amount of fluid you can drink when taking Stimate® Nasal Spray.

- Do not drink more than you need to satisfy your thirst.
- You can have serious side effects such as seizures, coma, and death from drinking too much fluid.
- Children and elderly patients are at higher risk for these conditions and must follow their healthcare provider's restrictions on drinking fluids.

Call your healthcare provider right away if you have any of the following symptoms while using Stimate® Nasal Spray. They may mean that your blood sodium level is low:

• Headache	• Loss of appetite
• Nausea	• Irritability
• Vomiting	• Muscle weakness
• Weight gain	• Muscle spasms or cramps
• Restlessness	• Hallucinations
• Tiredness	• Confusion

Using Stimate® Nasal Spray the wrong way may cause it not to work to control bleeding.

- Call your healthcare provider right away if you have any uncontrolled bleeding.

What is Stimate® Nasal Spray?

Stimate® Nasal Spray is a prescription medicine used to stop some types of bleeding in people with mild hemophilia A or mild to moderate von Willebrand's disease Type 1.

Stimate® Nasal Spray should not be used in children under 11 months of age.

What should I tell my healthcare provider before I use Stimate® Nasal Spray?

Before taking Stimate® Nasal Spray, tell your healthcare provider about all of your medical conditions, including if you:

- Have any nasal problems such as a stuffy nose, have ever had surgery on your nose, or have trouble breathing through your nose. You may need to use another form of this medicine.
- Have or have had any heart, blood circulation, or blood pressure problems.
- Have a condition that causes fluid or water imbalance problems such as:
  - Cystic fibrosis
  - Heart failure
  - Kidney problems
- Have or have had a condition that causes you to be very thirsty.
- Are pregnant or plan to become pregnant. It is not known if Stimate® Nasal Spray will harm your unborn baby.
- Are breast-feeding or plan to breast-feed. It is not known if Stimate® Nasal Spray passes into your breast milk. You and your healthcare provider should decide if you will take Stimate® Nasal Spray.

Tell your healthcare provider and pharmacist about all the medicines you take, including prescription and non-prescription medicines, such as over-the-counter medicines, vitamins, supplements and herbal remedies.

Using Stimate® Nasal Spray with certain other medicines can affect the way Stimate® Nasal Spray works.

Know the medicines you take. Keep a list of them and show it to your healthcare provider and pharmacist when you get a new medicine.

It is especially important to tell your healthcare provider if you take:

- Blood pressure or heart medicines
- Antidepressants
- Anti-anxiety medicines
- Antihistamines
- Pain relievers such as narcotics or non-steroidal anti-inflammatory medicines (NSAIDs)
- Seizure medicines
- Medicines for over-active urinary bladder

Ask your healthcare provider or pharmacist if you are not sure if your medicine is one of these.

How should I use Stimate® Nasal Spray?

- Use Stimate® Nasal Spray exactly as your healthcare provider told you. Do not use more Stimate® Nasal Spray or take it more often than your healthcare provider told you.

- The Stimate® Nasal Spray pump provides the correct dose of your medicine. For detailed instructions on how to use the nasal spray pump, see the ***Patient Instructions for Use*** at the end of this leaflet.
- The nasal spray pump delivers 25 sprays of Stimate® Nasal Spray and each spray contains a measured amount of medicine. Any medicine left in the spray pump after 25 sprays should be thrown away because, at that time, the amount of medicine in each spray may be a lot less than the correct amount. Do not put any leftover medicine into another bottle.
- If your symptoms do not improve, or if they become worse, contact your healthcare provider. Do not stop taking Stimate® Nasal Spray without talking to your healthcare provider.
- If you use too much Stimate® Nasal Spray, call your healthcare provider or go to the nearest hospital emergency department right away.

What are the possible side effects of Stimate® Nasal Spray?

Stimate® Nasal Spray may cause serious side effects that come from having too much water in the body. See **"What is the most important information I should know about Stimate® Nasal Spray?"**.

Common side effects of Stimate Nasal Spray include:

- Occasional facial flushing
- Nasal congestion
- Runny nose
- Nosebleed
- Sore throat
- Cough
- Upper respiratory infections.

Tell your healthcare provider about any side effect that bothers you or does not go away. These are not all the possible side effects of Stimate® Nasal Spray. If you have questions, talk to your healthcare provider.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store Stimate® Nasal Spray?

- Store at room temperature, but not higher than 77°F (25°C).
- Throw away Stimate® Nasal Spray six months after it is opened, or when the expiration date has passed, if this date is before the six months is up.
- Store Stimate® Nasal Spray standing upright.

Keep Stimate® Nasal Spray and all medicines out of the reach of children.

General information about Stimate® Nasal Spray

Medicines are sometimes prescribed for conditions that are not mentioned in the patient leaflet. Do not use Stimate® Nasal Spray for a condition for which it was not prescribed. Do not give Stimate® Nasal Spray to other people, even if they have the same symptoms you have. It may harm them.

This patient information leaflet summarizes the most important information about Stimate® Nasal Spray. If you would like more information about Stimate® Nasal Spray, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about Stimate® Nasal Spray that is written for health professionals. For more information, go to *www.stimate.com* or call CSL Behring Medical Affairs at 1-800-504-5434.

What are the ingredients in Stimate® Nasal Spray?

Active ingredients: desmopressin acetate
Inactive ingredients: sodium chloride, citric acid monohydrate, disodium phosphate dihydrate, benzalkonium chloride, purified water.

Patient Instructions for Use

Read these instructions carefully before you use your Stimate® Nasal Spray pump. The following instructions tell you how to prepare, or prime, your Stimate® Nasal Spray pump so that it is ready to use.

Using your Stimate® Nasal Spray Pump

1. Remove the protective cap.

2. When using Stimate® Nasal Spray for the first time, the spray pump must be primed by pressing down on the ring at the top of the pump 4 times. Hold the spray tip away from your face and eyes. See Figure A.

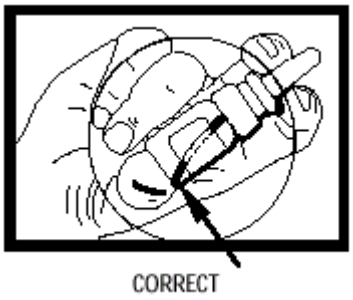


Figure A

3. When primed, the Stimate® Nasal Spray pump delivers one dose of medicine each time it is pressed. For the right dose, tilt your Stimate® Nasal Spray pump so that the tube inside the spray pump draws the medicine up from the deepest part of the medicine inside the container. See Figures A and B.

Figure B

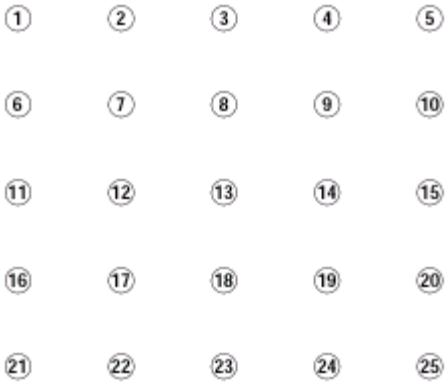
4. Put the spray nozzle tip into your nostril and press the spray pump one time for one dose (150-micrograms). If two doses are prescribed, spray each nostril one time (for a dose of 300-micrograms).

5. When you finish using your Stimate® Nasal Spray, put the cap over the tip of the pump.

6. If Stimate® Nasal Spray has not been used for one week, you will need to prime the pump again by pressing one time, or until you see a fine mist.

Use this check-off chart to help you keep track of the number of sprays used. This will help make sure that you receive 25 sprays with each bottle of Stimate® Nasal Spray. There is extra medicine in the bottle to allow for priming. When using the chart to check off sprays, do not count the priming sprays.

Stimate® Nasal Spray
25 Spray Check-off Chart



1. Keep this chart with your Stimate® Nasal Spray or put it someplace where you can easily get it.

2. Check off number 1 on the chart with your first dose of Stimate® Nasal Spray. Check off the numbers after each use of Stimate® Nasal Spray. If your healthcare provider prescribed a 2-spray dose (300-micrograms), then two numbers should be checked off.

3. Throw away the Stimate® Nasal Spray after 25 sprays.

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