

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TYRVAYA safely and effectively. See full prescribing information for TYRVAYA.

TYRVAYA® (varenicline solution) nasal spray
Initial U.S. Approval: 2006

-----**INDICATIONS AND USAGE**-----

TYRVAYA (varenicline solution) nasal spray is a cholinergic agonist indicated for the treatment of the signs and symptoms of dry eye disease. (1)

-----**DOSAGE AND ADMINISTRATION**-----

- One spray in each nostril twice daily (approximately 12 hours apart). (2.1)
- Prime with seven (7) actuations before initial use. Re-prime with 1 actuation if not used for more than five (5) days. (2.2)

-----**DOSAGE FORMS AND STRENGTHS**-----

Nasal spray delivering 0.03 mg of varenicline in each spray (0.05 mL). (3)

-----**CONTRAINDICATIONS**-----

None.

-----**ADVERSE REACTIONS**-----

The most common adverse reaction reported in 82% of patients was sneezing. Events that were reported in 5-16% of patients were cough, throat irritation, and instillation-site (nose) irritation. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Oyster Point Pharma at 1-877-EYE-0123 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA approved patient labeling.

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

TYRVAYA (varenicline solution) nasal spray is indicated for the treatment of the signs and symptoms of dry eye disease.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

Spray TYRVAYA once in each nostril twice daily (approximately 12 hours apart). If a dose is missed, resume regular dosing at the next scheduled dose time.

2.2 Priming Instructions

Priming: Prime TYRVAYA before initial use by pumping seven (7) actuations into the air away from the face. When TYRVAYA has not been used for more than 5 days, re-prime with 1 spray into the air. Do not shake.

3 DOSAGE FORMS AND STRENGTHS

Nasal spray delivering 0.03 mg of varenicline in each spray (0.05 mL).

4 CONTRAINDICATIONS

None

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In three clinical studies of dry eye disease conducted with varenicline solution nasal spray, 349 patients received at least 1 dose of TYRVAYA. The majority of patients had 31 days of treatment exposure, with a maximum exposure of 105 days.

The most common adverse reactions reported in 82% of TYRVAYA treated patients was sneezing. Other common adverse reactions that were reported in >5% of patients include cough (16%), throat irritation (13%), and instillation-site (nose) irritation (8%).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on TYRVAYA use in pregnant women to inform any drug associated risks. In animal reproduction studies, varenicline did not produce malformations at clinically relevant doses.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

Pregnant rats and rabbits received varenicline succinate during organogenesis at oral doses up to 15 and 30 mg/kg/day, respectively. While no fetal structural abnormalities occurred in either species, maternal toxicity, characterized by reduced body weight gain, and reduced fetal weights occurred in rabbits at the highest dose (4864 times the MRHD on a mg/m² basis).

In a pre- and postnatal development study, pregnant rats received up to 15 mg/kg/day of oral varenicline succinate from organogenesis through lactation. Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day (1216 times the MRHD on a mg/m² basis). Decreased fertility and increased auditory startle response occurred in offspring at the highest maternal dose of 15 mg/kg/day.

8.2 Lactation

Risk Summary

There are no data on the presence of varenicline in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies varenicline was present in milk of lactating rats. However, due to species-specific differences in lactation physiology, animal data may not reliably predict drug levels in human milk.

The lack of clinical data during lactation precludes a clear determination of the risk of TYRVAYA to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for TYRVAYA and any potential adverse effects on the breastfed child from TYRVAYA.

8.4 Pediatric Use

Safety and efficacy of TYRVAYA in pediatric patients have not been established.

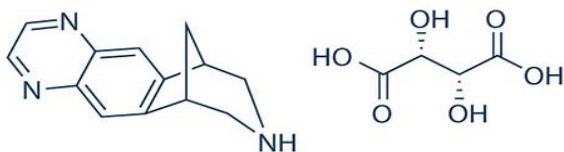
8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION

TYRVAYA nasal spray contains varenicline which is a partial nicotinic acetylcholine receptor agonist of $\alpha 4\beta 2$, $\alpha 4\alpha 6\beta 2$, $\alpha 3\beta 4$, and $\alpha 3\alpha 5\beta 4$ receptors and a full $\alpha 7$ receptor agonist.

Varenicline, as the tartrate salt, is a powder which is a white to off-white to slightly yellow solid whose chemical name is 7,8,9,10-tetrahydro-6,10-methano-6*H*-pyrazino[2,3-*h*][3]benzazepine, (2*R*,3*R*)-2,3-dihydroxybutanedioate (1:1). It is highly soluble in water. Varenicline tartrate has a molecular weight of 361.35 Daltons and a molecular formula of C₁₃H₁₃N₃ · C₄H₆O₆. The chemical structure is:



TYRVAYA (varenicline solution) nasal spray is formulated for intranasal use as a clear 0.6 mg/mL strength solution, at pH 6.4. After priming [see *Dosage and Administration (2.2)*], each actuation delivers a 0.05 mL spray containing 0.03 mg varenicline free base, equivalent to 0.05 mg of varenicline tartrate. The formulation also contains the following inactive ingredients: sodium phosphate dibasic heptahydrate, monobasic sodium phosphate anhydrous, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The efficacy of TYRVAYA in dry eye disease is believed to be the result of varenicline's activity at heteromeric sub-type(s) of the nicotinic acetylcholine (nACh) receptor where its binding produces agonist activity and activates the trigeminal parasympathetic pathway resulting in increased production of basal tear film as a treatment for dry eye disease. Varenicline binds with high affinity and selectivity at human $\alpha 4\beta 2$, $\alpha 4\alpha 6\beta 2$, $\alpha 3\beta 4$, $\alpha 3\alpha 5\beta 4$ and $\alpha 7$ neuronal nicotinic acetylcholine receptors. The exact mechanism of action is unknown at this time.

12.3 Pharmacokinetics

Absorption/Distribution

Following administration of 0.12 mg (0.06 mg per 50- μ L spray in each nostril), a strength of varenicline that is higher than the labeled concentration, varenicline can be detected in plasma by 5 minutes, generally achieves peak concentration within 2 hours, with a mean C_{max} of 0.34 ng/mL, and has an AUC_{0-inf} of 7.46 h*ng/mL. The systemic exposure (AUC_{0-inf}) following this intranasal dose was approximately 7.5% of the exposure observed following a 1 mg oral dose of varenicline.

Metabolism/Elimination

The mean \pm SD elimination half-life of varenicline after intranasal administration is approximately 19 ± 10 hours. Varenicline undergoes minimal metabolism with 92% excreted as unchanged drug in the urine.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were performed in CD-1 mice and Sprague-Dawley rats. There was no evidence of a carcinogenic effect in mice administered varenicline by oral gavage for 2 years at doses up to 20 mg/kg/day (810 times the maximum recommended human dose [MRHD], on a mg/m² basis). Rats were administered varenicline (1, 5, and 15 mg/kg/day) by oral gavage for 2 years. In male rats (n = 65 per sex per dose group), incidences of hibernoma

(tumor of the brown fat) were increased at the mid dose (1 tumor, 5 mg/kg/day, 405 times the MRHD on a mg/m² basis) and maximum dose (2 tumors, 15 mg/kg/day, 1216 times the MRHD on a mg/m² basis). The clinical relevance of this finding to humans has not been established. There was no evidence of carcinogenicity in female rats.

Mutagenesis

Varenicline was not genotoxic, with or without metabolic activation, in the following assays: Ames bacterial mutation assay; mammalian CHO/HGPRT assay; and tests for cytogenetic aberrations *in vivo* in rat bone marrow and *in vitro* in human lymphocytes.

Impairment of Fertility

There was no evidence of impairment of fertility in either male or female Sprague-Dawley rats administered varenicline succinate up to 15 mg/kg/day (1216 times the MRHD on a mg/m² basis). Maternal toxicity, characterized by a decrease in body weight gain, was observed at 15 mg/kg/day. A decrease in fertility was noted in the offspring of pregnant rats administered varenicline succinate at an oral dose of 15 mg/kg/day. The decrease in fertility in the offspring of treated female rats was not evident at an oral dose of 3 mg/kg/day (243 times the MRHD, on a mg/m² basis).

14 CLINICAL STUDIES

The efficacy of TYRVAYA for the treatment of dry eye disease was supported by two randomized, multi-center, double-masked, vehicle-controlled studies (ONSET-1 and ONSET-2). In the ONSET-1 study, 182 patients were randomized in a 1:1:1:1 ratio to receive one spray in each nostril twice daily of varenicline solution 0.006 mg (N=47), TYRVAYA 0.03 mg (N=48), varenicline solution 0.06 mg (N=44), or vehicle (N=43). In the ONSET-2 study, 758 patients were randomized in a 1:1:1 ratio to receive one spray in each nostril twice daily of TYRVAYA 0.03 mg (N=260), varenicline solution 0.06 mg (N=246), or vehicle (N=252).

The majority of patients were female (74%), the mean (standard deviation [SD]) age was 61 (12.5) years, the mean (SD) baseline anesthetized Schirmer's score was 5.1 mm (2.9), and the mean (SD) baseline eye dryness score (EDS) was 59.3 (21.6). Use of artificial tears was allowed during the studies. Enrollment criteria included minimal signs [i.e., anesthetized Schirmer's test score (range, 0-10 mm) and corneal fluorescein staining (range, 2-14)] and was not limited by baseline EDS (range, 2-100).

Efficacy

Tear film production was measured by anesthetized Schirmer's score assessed using a Schirmer's strip (0-35 mm). The average baseline Schirmer's score was 5.0 mm in the ONSET-1 study and 5.1 mm in the ONSET-2 study. Of the patients treated with TYRVAYA, 52% achieved ≥ 10 mm increase in Schirmer's score from baseline in the ONSET-1 study and 47% achieved ≥ 10 mm increase in Schirmer's score from baseline in the ONSET-2 study, compared to 14% and 28% of vehicle-treated patients in the ONSET-1 study and the ONSET-2 study, respectively at Day 28 (see Table 1). Of the patients treated with TYRVAYA, the mean change in Schirmer's score was 11.7 mm and 11.3 mm as compared to 3.2 mm and 6.3 mm in the vehicle treated patients in the ONSET-1 study and ONSET-2 study, respectively at Day 28.

Table 1: Percent of Patients Achieving ≥ 10 mm Improvement from Baseline in Schirmer's Score in 28-day Studies in Patients with Dry Eye Disease

	ONSET-1		ONSET-2	
	TYRVAYA N=48	Vehicle N=43	TYRVAYA N=260	Vehicle N=252
≥ 10 -mm increase in tear production (% of eyes) at Day 28	52%	14%	47%	28%
Proportion Difference (95% CI)	38% (21%, 56%)		20% (11%, 28%)	
p-value versus control	<0.01		<0.01	

Cochran-Mantel-Haenszel (CMH) test controlling for study site, baseline Schirmer's test score (STS), and baseline EDS. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TYRVAYA (varenicline solution) nasal spray is available in a carton containing two (2) nasal spray amber glass Type I bottles. Each bottle consists of a white nasal pump and blue dust cover, delivering 0.03 mg varenicline per spray (0.05 mL). Each bottle delivers one spray in each nostril twice daily for 15 days.

Two nasal spray bottles in each carton, containing 60 sprays per bottle, equivalent to 30-days' supply with one spray in each nostril twice daily (NDC 73521-030-02).

16.2 Storage and Handling

- Store TYRVAYA nasal spray at 20°C to 25°C (68°F to 77°F). Do not freeze.
- Discard TYRVAYA nasal spray bottle 30 days after opening bottle.

17 PATIENT COUNSELING INFORMATION

- Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).
- Instruct patients that TYRVAYA works to increase tear production in the eye after being sprayed in the nose.
- Instruct patients to prime the bottle before using it for the first time by pumping seven (7) sprays into the air away from the face and to re-prime it by pumping 1 spray into the air away from the face if the bottle has not been used in more than five (5) days.
- Instruct patients to wipe the nasal applicator with a clean tissue after each use.
- Instruct patients to not shake or freeze the bottle.

Manufactured for: Oyster Point Pharma, Inc., a Viatris company, 202 Carnegie Center, Suite 106, Princeton, NJ 08540

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TYRVAYA® and/or the use of TYRVAYA® in a method may be covered by one or more patents or patent applications, available at www.oysterpointrx.com/patent-notices.

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Patient Information
TYRVAYA® (Teer-vye-ah)
 (varenicline solution)
 nasal spray, for intranasal use

What is TYRVAYA?

TYRVAYA is a prescription nasal spray used to treat the signs and symptoms of dry eye disease.

Before you use TYRVAYA, tell your healthcare provider about all of your medical conditions, including if you:

- are pregnant or plan to become pregnant. It is not known if TYRVAYA will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if TYRVAYA passes into your breast milk. You and your healthcare provider should decide if you will use TYRVAYA if you plan to breastfeed.

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

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

How should I use TYRVAYA?

- See the Instructions for Use at the end of this Patient Information leaflet for information about the right way to use TYRVAYA.
- TYRVAYA increases tear production in the eye after being sprayed in the nose.
- Use TYRVAYA exactly as your healthcare provider tells you to use it.
- Do not shake the bottles.
- Spray TYRVAYA 1 time in each nostril, 2 times daily (about 12 hours apart).
- A 1-month supply of TYRVAYA consists of 2 nasal spray bottles. Finish 1 bottle before opening the second. TYRVAYA comes in glass bottles with a white nasal pump and blue dust cover.
- If you miss a dose of TYRVAYA, skip that dose and take your next dose at your regular scheduled time. Do not take an extra dose to make up for a missed dose.

What are the possible side effects of TYRVAYA?

The most common side effects of TYRVAYA include sneezing, cough, and throat and nose irritation.

These are not the only possible side effects of TYRVAYA. 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 TYRVAYA?

- Store TYRVAYA at room temperature between 68°F to 77°F (20°C to 25°C).
- Do not freeze.
- Throw away (discard) TYRVAYA nasal spray bottle 30 days after first use.

Keep TYRVAYA and all medicines out of the reach of children.

General information about the safe and effective use of TYRVAYA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use TYRVAYA for a condition for which it was not prescribed. Do not give TYRVAYA to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TYRVAYA that is written for health professionals.

What are the ingredients in TYRVAYA?

Active ingredient: varenicline tartrate

Inactive ingredients: sodium phosphate dibasic heptahydrate, monobasic sodium phosphate anhydrous, sodium chloride, sodium hydroxide and/or hydrochloric acid (to adjust pH) and water for injection.

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TYRVAYA® and/or the use of TYRVAYA® in a method may be covered by one or more patents or patent applications, available at www.oysterpointrx.com/patent-notice.
 Manufactured for: Oyster Point Pharma, Inc., 202 Carnegie Center, Suite 106, Princeton, NJ 08540

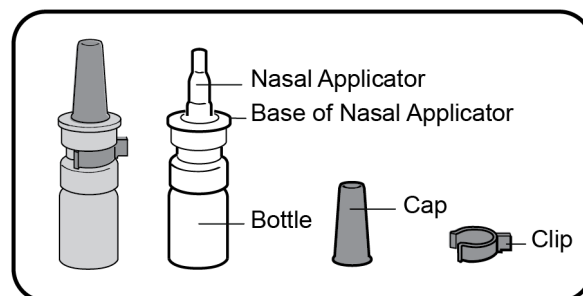
Instructions for Use
TYRVAYA® (Teer-vye-ah)
(varenicline solution)
nasal spray, for intranasal use

Read this Instructions for Use before you start using TYRVAYA 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.

Important information you need to know before using TYRVAYA:

- **TYRVAYA is for use in the nose.**
- **Do not shake the bottles.**
- The TYRVAYA carton contains enough medicine for 30 days.
 - Each carton has 2 glass nasal spray bottles.
 - Each nasal spray bottle has enough medicine for 15 days of treatment.
 - **Do not** open the second nasal spray bottle until you have used the entire first bottle.

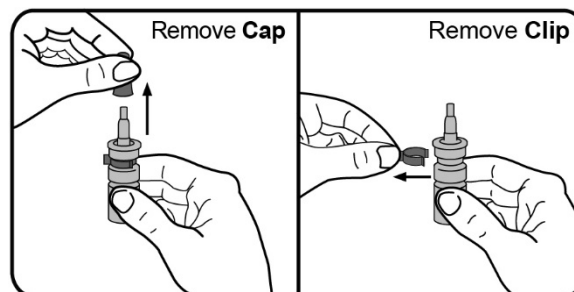
Parts of your TYRVAYA nasal spray:



Steps for priming TYRVAYA before first Use

Step 1. Remove the cap and the clip.

Do not throw away the cap or the clip. The cap and the clip will be placed back on to the nasal applicator after each use.

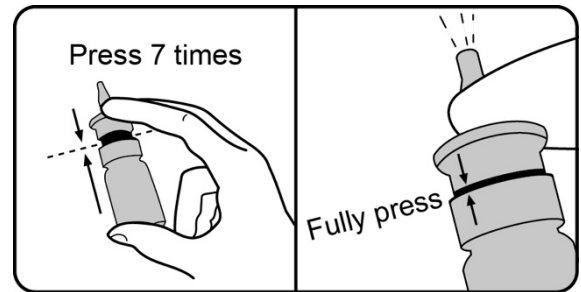


Step 2. Hold the nasal spray bottle upright and away from your face. Place 1 finger on each side of the base of the nasal applicator and place your thumb underneath the bottle.



Step 3. Prime the nasal spray bottle by **fully** pressing and releasing the nasal applicator 7 times with your thumb and fingers. **You may feel some resistance but be sure to press all the way down.** You may not see a spray released each time you press and release the nasal applicator. You should see a spray by the 7th time you press and release. Spray away from yourself and others.

TYRVAYA is now primed for use.



- **Reprime:** If you do not use TYRVAYA for more than **5 days**, you will need to reprime the nasal spray bottle with **1 spray** before you start using it. To reprime, hold the nasal spray bottle upright and away from your face and **fully** press and release the nasal spray applicator **1 time**.
- **Avoid priming the nasal spray bottle more than needed:** Priming the nasal spray bottle more than needed will reduce the amount of medicine in the nasal spray bottle.

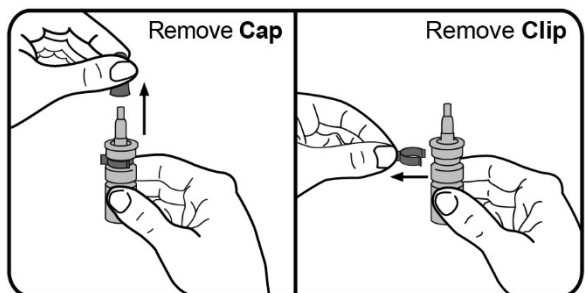
Steps for using TYRVAYA nasal spray after priming

Step 1. Blow your nose to clear your nostrils, if needed.



Step 2. Remove the cap and clip.

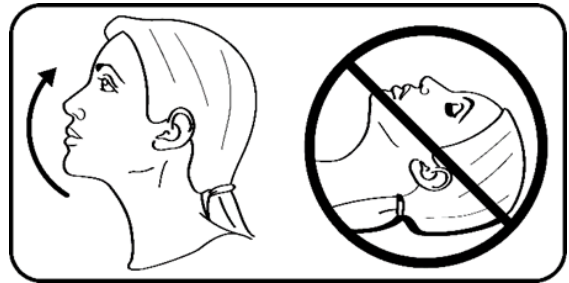
Do not throw away the cap or the clip. The cap and the clip will be placed back on to the nasal applicator after each use.



Step 3. Hold the nasal spray bottle upright. Place 1 finger on each side of the base of the nasal applicator and your thumb underneath the bottle.

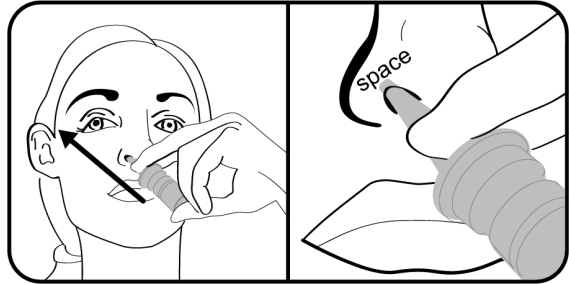


Step 4. Tilt your head back slightly without lying down.



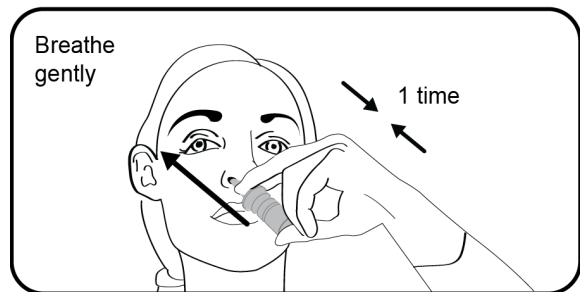
Step 5. Insert the nasal applicator into the left or right nostril. Tilt the nasal applicator and point the tip of the nasal applicator towards the top of the ear on the same side as your nostril.

Do not press the tip of the nasal applicator against the wall of the inside of your nose. Leave a space between the tip of the nasal applicator and the wall of the inside of your nose.

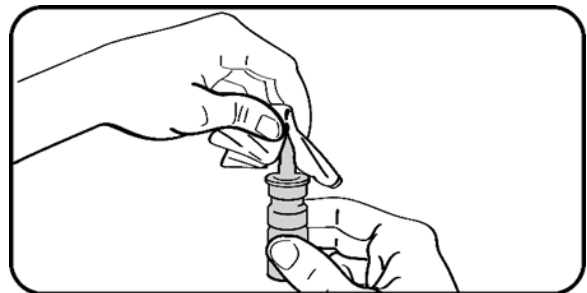


Step 6. Place your tongue to the roof of your mouth and breathe gently while **fully** pressing and releasing the nasal applicator **1-time** to release a spray into your nostril.

Repeat Steps 5 and 6 to deliver a second spray in the other nostril.

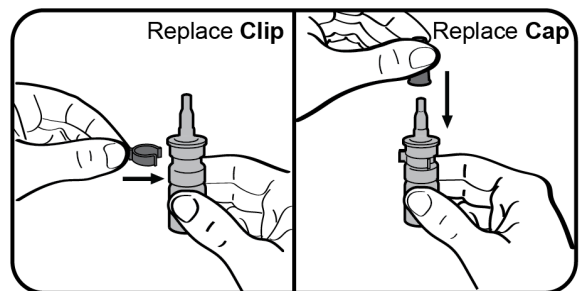


Step 7. Wipe the nasal applicator with a clean tissue.



Step 8. Replace the clip and the cap.

Repeat Steps 1 to 8 each time you use TYRVAYA.



This Instructions for Use has been approved by the U.S. Food and Drug Administration.
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