PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

TEVA-NALOXONE NASAL SPRAY

naloxone hydrochloride nasal spray

4 mg/0.1 mL

Opioid Antagonist

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TEVA-NALOXONE NASAL SPRAY

naloxone hydrochloride nasal spray

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Intranasal	Solution for intranasal administration 4 mg/0.1 mL (40 mg/mL)	Benzalkonium chloride, edetate disodium, sodium chloride, hydrochloric acid and sodium hydroxide to adjust pH and purified water.

INDICATIONS AND CLINICAL USE

TEVA-NALOXONE NASAL SPRAY is a pure opioid antagonist indicated for emergency use to reverse known or suspected opioid overdose, as manifested by respiratory and/or severe central nervous system depression.

TEVA-NALOXONE NASAL SPRAY can be administered by a bystander (non-health care professional) before emergency medical assistance becomes available, but it is not intended to be a substitute for professional medical care. Emergency medical assistance (calling 911) should be requested immediately when an opioid overdose is suspected, before administering naloxone.

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Emergency medical assistance (calling 911) should be requested immediately when an opioid overdose is suspected, before using naloxone (see **WARNINGS AND PRECAUTIONS**, Rebound Opioid Toxicity).

- Individuals with a satisfactory response to an initial dose of naloxone should be kept under continued surveillance (see **WARNINGS AND PRECAUTIONS**, Rebound Opioid Toxicity).

- Caregivers administering naloxone should be prepared to act in response to or assist the patient in cases of potential adverse reactions such as aggressive reactions, convulsions and vomiting. Special attention is warranted if naloxone is administered to a neonate or a pregnant woman (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome and *Special Populations*, Pediatrics, Pregnant Women and **DOSAGE AND ADMINISTRATION**).

General

In the absence of opioids, in opioid naïve people, naloxone administration shows essentially no pharmacologic activity. In opioid dependent people, naloxone may trigger an acute opioid withdrawal syndrome (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome).

The effectiveness of naloxone has not been assessed in people with intranasal conditions such as abnormal nasal anatomy, nasal symptoms (*i.e.*, blocked and/or runny nose, nasal polyps, etc.) or in people having a product sprayed into the nasal cavity prior to naloxone administration. It is unknown if these conditions affect naloxone's effectiveness. If TEVA-NALOXONE NASAL SPRAY is procured with the intention of using it in people that may present these conditions, the pharmacist may suggest other route of administration (*e.g.* intramuscular).

Naloxone does not counteract overdoses due to: barbiturates, benzodiazepines, psychostimulants (*e.g.*, cocaine, amphetamines, methylphenidate, etc.), alcohol, or any other non-opioid drug such as non-opioid tranquilizers, anesthetics or sedatives. However, mistakenly administering naloxone to a person that is unconscious because of a non-opioid overdose or for other reasons is unlikely to create more harm.

Rebound Opioid Toxicity

Rebound opioid toxicity is the re-emergence of an opioid overdose manifestation, including respiratory depression, following the temporary reversal of the opioid overdose with naloxone. The patient who has responded satisfactorily to naloxone should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary until the emergency medical services take charge of the patient (see **DOSAGE AND ADMINISTRATION**). Repeated doses are often required as the duration of action of most opioids exceeds that of naloxone, and therefore, re-emergence of opioid overdose manifestation is likely.

Respiratory

Naloxone is not effective against respiratory depression due to non-opioid drugs (see **WARNINGS AND PRECAUTIONS**, General). A single dose of naloxone may not reverse respiratory depression (or reversal may be incomplete) if the opioid overdose is caused by certain partial agonist opioids such as buprenorphine and pentazocine or highly potent opioids such as fentanyl or its analogs. Additional doses of naloxone administered at close intervals may be required in such cases (see **DOSAGE AND ADMINISTRATION**, Recommended Dose and Dosage Adjustment). Similarly, an opioid overdose caused by very large doses of any opioid may also require administration of multiple doses of naloxone at close intervals (see **DOSAGE AND ADMINISTRATION**, Recommended Dose and Dosage Adjustment). In addition to naloxone, other resuscitative measures such as maintenance of a free airway, artificial ventilation and cardiac massage could be executed by a bystander (non-health care professionals) if the bystander knows how to perform the maneuvers. Moreover, vasopressor agents should be employed (if available) whenever necessary if a health care professional is present.

Acute Opioid Withdrawal Syndrome

TEVA-NALOXONE NASAL SPRAY should be administered with caution to persons who are known or suspected to be physically dependent on opioids. In such cases, an abrupt reversal of opioid effects may precipitate an acute opioid withdrawal syndrome. The severity of such a syndrome will depend on the degree of physical dependence, the dose and potency of the opioid that induced the overdose, and the dose of naloxone administered.

The signs and symptoms of an acute opioid withdrawal syndrome include, but are not limited to: body aches, pain, fever/pyrexia, sweating/hyperhidrosis, runny nose, sneezing, piloerection, yawning, weakness, asthenia, shivering, chills, tremor/trembling, convulsions/seizures, nervousness, restlessness, irritability, aggressive behavior, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the dependent neonate, signs also include excessive crying as well as hyperactive reflexes and the acute withdrawal may be life-threatening if not recognized and properly treated (see **WARNINGS AND PRECAUTIONS**, *Special Populations*, Pediatrics).

Emergency medical assistance (*i.e.*, calling 911) should be requested immediately when an opioid overdose is suspected. Monitor the patient for the development of the signs and symptoms of opioid withdrawal. Caregivers administering naloxone to any patient should always be prepared for potential reactions associated with acute opioid withdrawal syndrome and to assist the patient to minimize harm when experiencing these reactions. For example, a patient should be positioned in lateral decubitus to prevent choking if vomiting occurs; sharp or dangerous objects should be moved away in case of convulsions to protect the patient from injury, but the patient should not be restrained.

Cardiovascular

Rare cases of cardiac arrest, tachycardia and ventricular fibrillation have been reported after naloxone administration. These cases may have been confounded by the effects of other drugs or other effects such as prolonged hypoxia. A direct relationship to naloxone has not been

established.

Post-Operative Considerations

Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema and rare cases of cardiac arrest have been reported. Death, coma, and encephalopathy have been reported as sequelae of these events. These events have primarily occurred in post-operative patients with pre-existing cardiovascular disorders and/or other drugs may have contributed to the adverse effects. A direct relationship to naloxone has not been established.

Neurologic

Convulsions or seizures after naloxone administration have been rarely reported and the relationship between naloxone and convulsion or seizure is unclear. If convulsions or seizures occur, sharp or dangerous objects should be moved away to protect the patient from injury but the patient should not be restrained.

Psychiatric

Irritability and aggressive behavior are among the manifestations of an acute opioid withdrawal syndrome, which may be precipitated when naloxone is administered to a person who is physically dependent on opioids (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome). Caregivers administering naloxone to any patient should always be prepared to manage potential aggressive reactions.

Gastrointestinal

Naloxone administration could trigger gastrointestinal reactions including diarrhea, nausea, vomiting and abdominal cramps (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome). If vomiting occurs, the patient should be positioned in lateral decubitus to prevent choking.

Special Populations
Pregnant Women: There are no adequate and well-controlled studies in pregnant women. Reproduction studies performed in mice and rats at doses up to 12 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to naloxone. Administration of naloxone to an opioid-dependent pregnant woman may induce an acute opioid withdrawal syndrome (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome), which may precipitate preterm labor or fetal distress. Because of this risk and because animal reproduction studies are not always predictive of human response, naloxone should be used during pregnancy only if clearly needed (see **DOSAGE AND ADMINISTRATION**).

Nursing Women: It is not known whether naloxone is excreted in human milk. Studies in nursing mothers have shown that naloxone does not affect prolactin or oxytocin hormone levels.

Pediatrics: An accidental opioid exposure is possible in the pediatric population. Naloxone administration may cause an acute opioid withdrawal syndrome which may be life threatening in opioid dependent neonates if not recognized and properly treated (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome). Clinical data is limited and naloxone should be administered to a neonate only if clearly needed (see **DOSAGE AND ADMINISTRATION**). As for any use of naloxone, emergency medical assistance (*i.e.*, calling 911) should be requested immediately, before administering naloxone in a neonate.

Geriatrics (> 65 years of age): Geriatric patients have a greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy. Therefore, the systemic exposure of naloxone hydrochloride can be higher in these patients.

Clinical studies of naloxone hydrochloride 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.

ADVERSE REACTIONS

In clinical studies, nasal edema, nasal inflammation, nasal dryness, nasal congestion, muscle spasms, musculoskeletal pain, headache, dizziness, constipation, nausea, toothache, rhinalgia, xeroderma, and blood pressure increased were reported.

Abrupt reversal of opioid effects in persons physically dependent on opioids may result in body aches, pain, fever/pyrexia, sweating/hyperhidrosis, runny nose, sneezing, piloerection, yawning, weakness, asthenia, shivering, chills, tremor/trembling, convulsions/seizures, nervousness, restlessness, irritability, aggressive behavior, diarrhea, nausea, vomiting, abdominal cramps, increased blood pressure, and tachycardia. In the neonate, it may result in excessive crying and hyperactive reflexes as well (see **WARNINGS AND PRECAUTIONS**, Acute Opioid Withdrawal Syndrome).

Hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest have been associated with the use of naloxone post-operatively. Death, coma, and encephalopathy have been reported as sequelae of these events (see **WARNINGS AND PRECAUTIONS**, Cardiovascular, and Post-Operative Consideration). Excessive doses of naloxone hydrochloride in post-operative patients have resulted in significant reversal of analgesia, and have caused agitation.

Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

DRUG INTERACTIONS

Drug-Drug Interactions
Interactions with other drug products have not been established.

Drug-Food Interactions
Interactions with foods have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Emergency medical assistance (*i.e.* calling 911) should be requested immediately when an opioid overdose is suspected, before administering naloxone (see **WARNINGS AND PRECAUTIONS**, Rebound Opioid Toxicity). TEVA-NALOXONE NASAL SPRAY is not a substitute for emergency medical care.

Since the duration of action of most opioids exceeds that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary (see **WARNINGS AND PRECAUTIONS**, Rebound Opioid Toxicity).

Important Administration Instructions

TEVA-NALOXONE NASAL SPRAY is for intranasal use only.

No additional device assembly is required.

Because treatment of suspected opioid overdose must be performed by someone other than the patient, be sure to inform caregivers, family members, and other persons around the patient about the presence/location of TEVA-NALOXONE NASAL SPRAY in the home as well as the **PATIENT MEDICATION INFORMATION** and *Quick Start Guide*.

The pharmacist (or other health care professionals providing advice to patients) should instruct the patient or caregiver to read the **PATIENT MEDICATION INFORMATION** and the *Quick Start Guide* at the time they obtain TEVA-NALOXONE NASAL SPRAY and to become familiar with the administration procedures. As well, the pharmacist should emphasize the following instructions to the patient or caregiver:

- Always seek emergency medical assistance (*i.e.* call 911), or ask someone to call for you, in the event of a suspected opioid overdose. If you encounter problems on how to administer TEVA-NALOXONE NASAL SPRAY or any other problem, the 911 operator will guide you.

- As soon as the 911 call is made or while someone else is calling for you, administer the lowest available strength of naloxone hydrochloride nasal spray as quickly as possible because prolonged respiratory depression may result in damage to the central nervous system or death. Since the duration of action of most opioids exceeds that of naloxone hydrochloride and the suspected opioid overdose may occur outside of supervised medical settings, always keep the patient under continued surveillance until emergency personnel arrive.

- Additional doses of TEVA-NALOXONE NASAL SPRAY, using an additional TEVA-NALOXONE NASAL SPRAY device, may be required until emergency medical assistance becomes available:
    - If the patient responds to the first dose of TEVA-NALOXONE NASAL SPRAY but relapses back into respiratory depression before emergency assistance arrives, administer repeated doses of TEVA-NALOXONE NASAL SPRAY as necessary.
    - If the patient does not respond to the first dose of TEVA-NALOXONE NASAL SPRAY after 2-3 minutes, administer repeated doses of naloxone as necessary.

- **Do not reuse TEVA-NALOXONE NASAL SPRAY**. Each TEVA-NALOXONE NASAL SPRAY device contains a single dose of naloxone and cannot be reused.

- Administer TEVA-NALOXONE NASAL SPRAY in alternate nostrils with each dose.

- Administer TEVA-NALOXONE NASAL SPRAY according to the printed instructions in the **PATIENT MEDICATION INFORMATION** or *Quick Start Guide*.

- Place the patient on their back. Prior to administration, be sure the device nozzle is inserted in either nostril of the patient, and provide support to the back of the neck to allow the head to tilt back. In young children, the nozzle may not fit in the nostril. In this case, make sure the nozzle seals the nostril before administration.

- Do not prime or test the device.

- To administer the dose press firmly on the device plunger.

- Remove the device nozzle from the nostril after use.

- Turn patient on their side as shown in the **PATIENT MEDICATION INFORMATION** or *Quick Start Guide*.

Dosage forms TEVA-NALOXONE NASAL SPRAY is supplied in:

- One carton containing 2 sprayer devices each providing a single 4 mg dose of naloxone hydrochloride in a 0.1 mL intranasal spray.

Recommended Initial Dosing
In all cases, the lowest available strength of naloxone hydrochloride nasal spray should be used as the initial dose.

Dosing in Neonate Patients and pediatrics below 2 years of age
If TEVA-NALOXONE NASAL SPRAY is procured with the intention of use in this population, the pharmacist may suggest alternate formulations of naloxone (*e.g.* for intramuscular administration) which allow for smaller doses of naloxone.

Naloxone could trigger an acute opioid withdrawal syndrome in the dependent neonate which may be life-threatening if not recognized and properly treated. **Naloxone should be administered to neonates only if clearly needed (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).**

Dosing in Pregnant Women
Naloxone could trigger an acute opioid withdrawal syndrome in the opioid-dependent pregnant woman, which may precipitate preterm labor or fetal distress (see **WARNINGS AND PRECAUTIONS**, Special Populations, Pregnant Women). To reduce the risk an acute opioid withdrawal syndrome in the opioid-dependent pregnant woman, the lowest available strength of naloxone hydrochloride nasal spray should be used as the initial dose.

Repeat Dosing

- The requirement for repeat doses of TEVA-NALOXONE NASAL SPRAY depends upon the amount, type, and route of administration of the opioid being antagonized;

- If the patient does not respond within 2-3 minutes to the first dose of TEVA-NALOXONE NASAL SPRAY, administer an additional dose of naloxone every 2-3 minutes (if additional doses are available), using a new TEVA-NALOXONE NASAL SPRAY device for each dose, until the desired response is obtained. If no response is obtained after 5 doses of TEVA-NALOXONE NASAL SPRAY, an opioid overdose is unlikely to be the cause of the symptoms. In these cases, additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance;

- Once a desired response is obtained, continue surveillance of the patient while awaiting for emergency medical assistance and administer subsequent doses as necessary if the patient relapses back into respiratory depression;

Administer TEVA-NALOXONE NASAL SPRAY in alternate nostrils with each dose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

While the mechanism of action of naloxone hydrochloride is not fully understood, the preponderance of evidence suggests that naloxone antagonizes the opioid effects by competing for the same receptor sites.

Pharmacodynamics

TEVA-NALOXONE NASAL SPRAY prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. It can also reverse the psychosomimetic and dysphoric effects of agonist-antagonists such as pentazocine. TEVA-NALOXONE NASAL SPRAY is an essentially pure opioid antagonist, *i.e.*, it does not possess the agonistic or morphine-like properties characteristic of other opioid antagonists; naloxone does not produce respiratory depression, psychosomimetic effects or pupillary constriction.

Naloxone has not been shown to produce tolerance or to cause physical or psychological dependence.

Pharmacokinetics

Following administration, naloxone hydrochloride is rapidly distributed in the body. Naloxone hydrochloride is metabolized in the liver, primarily by glucuronide conjugation, and is excreted in urine.

The study "Naloxone-Ph1a-002" was conducted to determine the PK of 4 different approaches to administer 3 different intranasal (IN) doses [2 mg (2 mg spray in one nostril), 4 mg (2 mg spray in each nostril), 4 mg (4 mg spray in one nostril), and 8 mg (4 mg spray in each nostril)] of naloxone compared to a 0.4 mg dose of naloxone administrated IM.

<u>Study Demographics and Trial Design</u>

Table 1: Summary of Patient Demographics

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
Ph1a-002	Inpatient, Open-Label, Randomized, 5-Period, 5-Treatment, 5-Sequence, Crossover Study	Treatment A 2 mg – One Spray 20 mg/mL IN Treatment B 4 mg – Two Sprays (1 per nostril) 20 mg/mL IN	n = 30	35.9 years (22-55 years)	Female = 12 Male = 18

Study #	Trial Design	Dosage, route of administration and duration	Study subjects (n=number)	Mean age (Range)	Gender
		Treatment C 4 mg – One Spray 40 mg/mL IN Treatment D 8 mg – Two Sprays (1 per nostril) 40 mg/mL IN Treatment E 0.4 mg IM			

Subjects in study Naloxone-Ph1a-002 were more frequently male (60.0%), and more frequently African American or Black (76.7%). Two subjects were of Hispanic ethnicity. Subjects had an average height of 173.3 cm, weight of 80.1 kg, and a mean (range) body mass index (BMI) of 26.5 (19.6 to 29.8) kg/m^2.

Participants were assigned to one of 5 sequences (Table 1), with 6 participants planned in each sequence. On the day after clinic admission, participants were administered study drug in randomized order with a 4-day washout period between doses until all 5 treatments had been administered. Blood was collected for PK analysis prior to administration and up to 12 hours after each dose; ECG, vital signs, and other AE assessments were performed.

Thirty participants were randomized, and received at least one dose of naloxone; 28 (93%) completed the study. One male participant was discontinued on Day 5 prior to receiving the second treatment due to a predose systolic blood pressure (BP) reading greater than 140 mmHg.

Study Results

Table 2: Geometric Mean Pharmacokinetic Parameters (CV%) of Naloxone Following Intranasal Administration and Intramuscular Injection of Naloxone to Healthy Subjects

Parameter	Treatment A 2 mg – One Spray 20 mg/mL IN (N = 29)	Treatment B 4 mg – Two Sprays 20 mg/mL IN (N = 29)	Treatment C 4 mg – One Spray 40 mg/mL IN (N = 29)	Treatment D 8 mg – Two Sprays 40 mg/mL IN (N = 29)	Treatment E 0.4 mg IM (N = 29)
λz (1/h)	0.382 (34.9)	0.310 (34.5)	0.334 (29.5)	0.330 (32.4)	0.557 (25.9)
t½ (h)	1.81 (34.9)	2.23 (34.5)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
t_{max} (h)[a]	0.33 (0.25, 1.00)	0.33 (0.17,0.57)	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
C_{max} (ng/mL)	2.92 (34.3)	6.20 (31.9)	4.83 (43.1)	9.70 (36.0)	0.877 (30.5)
C_{max}/Dose (ng/mL/mg)	1.46 (34.3)	1.55 (31.9)	1.21 (43.1)	1.21 (36.0)	2.19 (30.5)

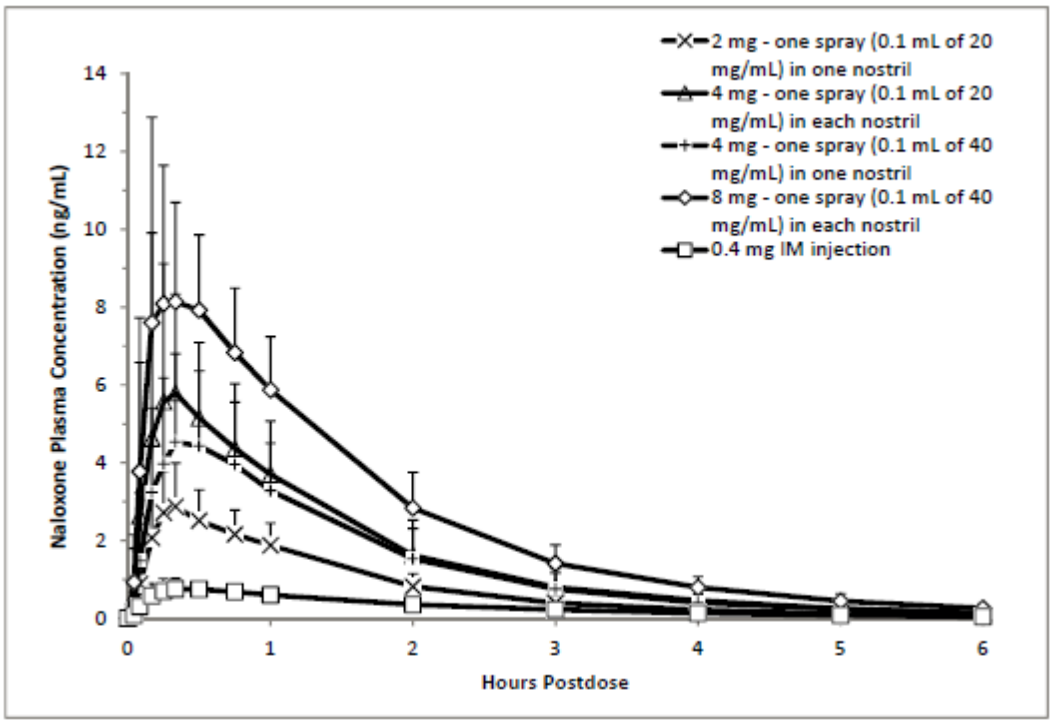
Parameter	Treatment A 2 mg – One Spray 20 mg/mL IN (N = 29)	Treatment B 4 mg – Two Sprays 20 mg/mL IN (N = 29)	Treatment C 4 mg – One Spray 40 mg/mL IN (N = 29)	Treatment D 8 mg – Two Sprays 40 mg/mL IN (N = 29)	Treatment E 0.4 mg IM (N = 29)
AUC_{0-t} (h*ng/mL)	4.51 (27.2)	9.32 (24.0)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
AUC_{0-t}/Dose (h*ng/mL/mg)	2.25 (27.2)	2.33 (24.0)	1.97 (37.4)	1.91 (23.0)	4.29 (22.9)
AUC_{0-inf} (h*ng/mL)	4.56 (26.9)	9.43 (24.0)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
AUC_{0-inf}/Dose (h*ng/mL/mg)	2.28 (26.9)	2.36 (24.0)	1.99 (37.3)	1.93 (22.7)	4.40 (22.6)
AUC% Extrapolated (%)	1.06 (56.5)	0.935 (60.1)	0.965 (53.5)	0.963 (69.3)	2.18 (57.5)
CL/F (L/h)	438 (26.9)	424 (24.0)	503 (37.3)	518 (22.7)	227 (22.6)
Dose Normalized Relative BA (%) vs. IM	51.9 (21.7)	53.6 (22.5)	46.7 (31.4)[b]	43.9 (23.8)	100
C_{max}/Dose Ratio (IN vs. IM) (%)	66.6 (41.4)	70.7 (37.7)	56.6 (47.5)[b]	55.3 (41.4)	100

a: Median (minimum, maximum)

b: N=28 for Relative Bioavailability (BA) and C_{max}/Dose ratio of Treatment C

Figure 1: Mean ± SD Plasma Concentration of Naloxone, (a) 0-6 h and (b) 0-1 h Following Intranasal Administration and Intramuscular Injection

(a)



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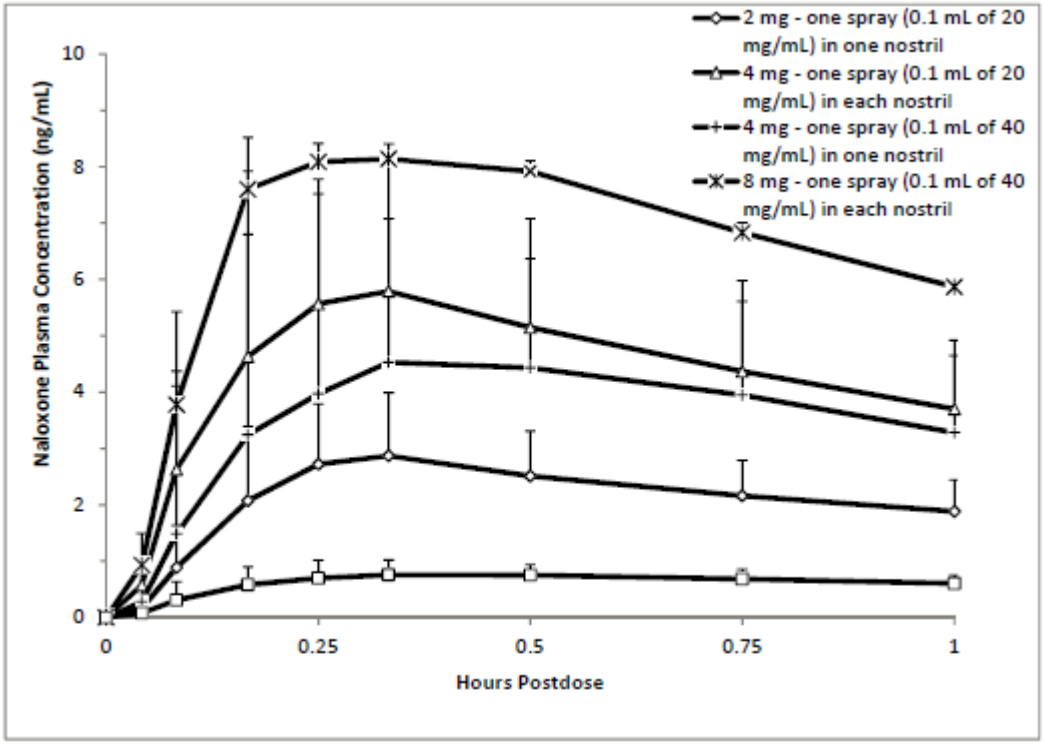


Naloxone plasma concentrations were at measurable concentrations 2.5 minutes after IN administration, the first collection time point, in all but 2 samples. The median t_{max} values after IN and IM dosing ranged from 20 to 30 minutes, indicating that naloxone was absorbed quickly following either route of administration.

Dose proportionality for the 4 IN doses of naloxone was assessed using the ratio of the dose-normalized geometric mean values (R_{dnm}) of C_{max} and $AUC_{0\text{-}inf}$. The R_{dnm} value (90% confidence interval (CI)) value for C_{max} was 0.831 (0.744-0.927); for AUC0-inf, the R_{dnm} value was 0.847 (0.786-0.912). Both C_{max} and $AUC_{0\text{-}inf}$ increased slightly less dose proportionally, as indicated by R_{dnm} values less than 1 and confidence intervals that were outside the range of 0.80-1.25.

Evaluations were also done to compare the geometric mean ratios (GMR) of the dose-normalized PK parameters for one spray versus 2 sprays of the 20 mg/mL formulation; similar comparisons were done for the 40 mg/mL formulation. The GMRs for the PK parameters were between 94% and 97% when one spray (2 mg) and 2 sprays (4 mg) were delivered using the 20 mg/mL formulation. The values of the 90% CI for both $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were within 80-125% for the GMR while the values for C_{max} were 78.7 to113%. For the 40 mg/mL formulation, the GMRs and 90% CIs for all 3 PK parameters were within the 80-125% range when results using one spray (4 mg) and two sprays (8 mg) were compared.

The conclusions of the PK study were that the naloxone nasal formulation can deliver a dose of naloxone intranasally with approximately 50% the bioavailability of IM administrations. As such, a 2 mg and 4 mg intranasal dose will provide a dose similar to intramuscular doses of 1 mg and 2 mg, respectively. The t_{max} is approximately the same as injectable naloxone indicating that time to onset of action will be similar.

STORAGE AND STABILITY

Store TEVA-NALOXONE NASAL SPRAY in the blister and cartons provided.
Store between 15°C to 30°C. Excursions permitted up to 40°C. Do not freeze or expose to excessive heat above 40°C. Protect from light.

TEVA-NALOXONE NASAL SPRAY freezes at temperatures below -15°C. If this happens, the device will not spray. If TEVA-NALOXONE NASAL SPRAY is frozen and is needed in an emergency, do NOT wait for TEVA-NALOXONE NASAL SPRAY to thaw. Get emergency medical help right away.

However, TEVA-NALOXONE NASAL SPRAY may be thawed by allowing it to sit at room temperature for 15 minutes, and it may still be used if it has been thawed after being previously frozen.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-NALOXONE NASAL SPRAY 4 mg/0.1 mL:
Each sprayer containing 0.1 mL of aqueous solution for intranasal administration contains: 4 mg naloxone hydrochloride, benzalkonium chloride (preservative), edetate disodium (stabilizer), sodium chloride, hydrochloric acid and sodium hydroxide to adjust pH, and purified water.

TEVA-NALOXONE NASAL SPRAY is available as:

- 4 mg/0.1 mL single-dose sprayer, carton of 2 devices.

Latex-Free: TEVA-NALOXONE NASAL SPRAY is not made with dry natural rubber.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

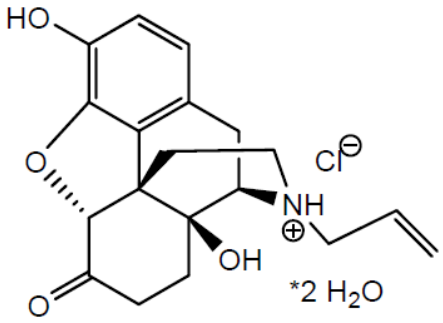
Proper name: Naloxone Hydrochloride

Chemical name: (5*R*,9*R*,13*S*,14*S*)-17-Allyl-3,14-dihydroxy-4,5-epoxymorphinan-6-on hydrochloride dihydrate

Molecular formula: $C_{19}H_{21}NO_4$ HCl · $2H_20$

Molecular mass: 399.87 g/mol

Structural formula:



Physicochemical properties: Naloxone hydrochloride, an opioid antagonist, is a synthetic congener of oxymorphone. In structure, it differs from oxymorphone in that the methyl group on the nitrogen atom is replaced by an allyl group.

General properties of naloxone hydrochloride are outlined below:

Appearance (colour, physical form)	White to almost white powder
Solubility	Freely soluble in water, soluble in ethanol (96%) and practically insoluble in toluene.
Melting range	200 - 201°C
Solution pH	Approx. 5.5 (1% solution in water / 20°C)

CLINICAL TRIALS

Comparative Bioavailability Study

An open label, randomized, single dose, two treatment, two period, crossover bioequivalence study of TEVA-NALOXONE NASAL SPRAY, 4 mg/0.1 mL (Teva Canada Limited) and Narcan® (naloxone) Nasal Spray, 4 mg/0.1 mL (Adapt Pharma, USA), administered as a single 4 mg dose, was conducted in healthy, adult human male subjects (N=60) under fasting conditions. The results from the 56 subjects who completed the study are summarized in the table below:

Naloxone (1 x 4 mg) Geometric Mean Arithmetic Mean (CV %)				
Parameter	**Test[1]**	**Reference[2]**	**% Ratio of Geometric Means**	**90% Confidence Interval**
AUC_T (h*ng/mL)	13.80 15.21 (40.36)	13.50 14.61 (39.08)	102.2	94.1 to 111.1
AUC_I (h*ng/mL)	14.35 15.68 (39.05)	14.00 15.06 (38.04)	102.5	94.8 to 110.8
C_{max} (ng/mL)	7.29 7.89 (37.80)	7.39 7.98 (40.31)	98.6	89.6 to 108.6
T_{max}[3] (h)	0.42 (0.17- 1.33)	0.50 (0.25 - 1.83)		
$T_{½}$[4] (h)	1.32 (47.57)	1.33 (22.84)		

[1] TEVA-NALOXONE NASAL SPRAY [naloxone (as naloxone hydrochloride)], 4 mg/spray (Teva Canada Limited)

[2] NARCAN® [naloxone (as naloxone hydrochloride)] Nasal Spray, 4 mg/spray (Adapt Pharma, USA)

[3] Expressed as the median (range) only

[4] Expressed as the arithmetic mean (CV%) only

DETAILED PHARMACOLOGY

On the basis of animal experiments, naloxone is a relatively specific narcotic antagonist that interacts preferentially with the mu-receptor subtypes. Naloxone is devoid of opioid agonist effects and consequently it has no abuse potential.

Very low doses of narcotic antagonists, such as naloxone, are known to elicit aversive effects in morphine-dependent animals. When the dose of naloxone is increased, a similar aversive quality is manifested in animals, which are not dependent upon opioids. Examination of the basis for the production of aversive behavior in opioid-free animals suggests that the effects of naloxone are stereospecific and may possibly involve antagonism of endogenous opioid peptides.

In addition to antagonizing the effects of opioid drugs, naloxone has been reported to influence pharmacological responses to a variety of non-opioid drugs by antagonizing the secondary effects of these agents. Some of the effects of naloxone may be unrelated to the direct occupation of opioid receptors. For example, at very high doses naloxone appears to be a gamma aminobutyric acid (GABA) antagonist and this has been implicated in the convulsant properties associated with high doses of naloxone in rats.

Further, naloxone hydrochloride reverses the effects of opioids, including respiratory depression, sedation, and hypotension. In addition, it can reverse the psychotomimetic and dysphoric effects of agonist-antagonists, such as pentazocine and does not produce respiratory depression, psychotomimetic effects, or pupillary constriction. In the absence of narcotics or agonistic effects of other narcotic antagonists it exhibits essentially no pharmacologic activity.

TOXICOLOGY

Acute and Sub-acute Toxicity

Single-dose studies have been performed in mice, rats, guinea pigs, rabbits, cats, dogs, and monkeys using various routes of administration. The compound has an LD_{50} value ranging from 52 mg/kg IV in rabbits to over 500 mg/kg when given SC to adult rats. Newborn rats were more sensitive than adult animals with an LD_{50} of 260 mg/kg. In mice, the IV LD_{50} was 150 ± 5 mg/kg and in rats 109 ± 4 mg/kg.

Sub-acute studies (up to 30 days of treatment) have been performed in rats, monkeys, and dogs. Rats were given SC doses of naloxone in doses up to 200 mg/kg five days per week for four weeks, with convulsions at the highest dose being the only major reaction. Monkeys exhibited convulsions at 60 mg/kg given SC for 30 days. After 4 mg/kg IV for 14 days, dogs experienced hind limb weakness as the major effect.

Mutagenesis and Carcinogenesis

Naloxone was weakly positive in the Ames mutagenicity and in the in vitro human lymphocyte chromosome aberration test, but was negative in the in vitro Chinese hamster V79 cell HGPRT mutagenicity assay and in the in vivo rat bone marrow chromosome aberration study.
Long-term animal studies to evaluate the carcinogenic potential of naloxone have not been completed.

Reproductive and Development Toxicology

Naloxone hydrochloride was administered during organogenesis to mice and rats at subcutaneous doses up to 10 mg/kg/day (equivalent to 6-times and 12-times, respectively, a human dose of 8 mg (two naloxone hydrochloride nasal spray devices)) (based on body surface area comparison). These studies demonstrated no embryo toxic or teratogenic effects due to naloxone hydrochloride.

Pregnant female rats were administered 2 or 10 mg/kg naloxone subcutaneously from Gestation Day 15 to Postnatal day 21. There were no adverse effects on the offspring (up to 12-times a

human dose of 8 mg/day (two naloxone hydrochloride nasal spray devices) based on body surface area comparison).

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10. NARCAN® NASAL SPRAY (naloxone hydrochloride) Product Monograph, Adapt Pharma Canada Ltd. Submission Control No: 234832, Date of Revision: September 9 2020.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

TEVA-NALOXONE NASAL SPRAY
naloxone hydrochloride nasal spray

4 mg

Read this carefully before administering TEVA-NALOXONE NASAL SPRAY and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about TEVA-NALOXONE NASAL SPRAY.

Serious Warnings and Precautions

- Before administering TEVA-NALOXONE NASAL SPRAY, call 911 for emergency medical help. Do this immediately if you suspect or are aware of an opioid overdose.
- Make sure to watch the person who received TEVA-NALOXONE NASAL SPRAY. You may need to give additional doses of TEVA-NALOXONE NASAL SPRAY until emergency medical help arrives.
- You may need to help the person who received TEVA-NALOXONE NASAL SPRAY. The patient may have a reaction such as becoming aggressive, shaking and/or vomiting. You will need to pay special attention when giving TEVA-NALOXONE NASAL SPRAY to a newborn who is less than four weeks old or a pregnant woman. Some of these reactions can be life-threatening for a newborn or fetus.

What is TEVA-NALOXONE NASAL SPRAY used for?
TEVA-NALOXONE NASAL SPRAY is used to treat someone who has overdosed on opioids. TEVA-NALOXONE NASAL SPRAY can be used by anyone to reverse the effects of the overdose until medical help arrives. Signs of an opioid overdose include:

- trouble breathing or not breathing
- extreme drowsiness
- pale and clammy skin
- slow or no heartbeat
- passing out
- unable to be woken up by touch, shaking of shoulders or shouting
- very small pupils, like a pinpoint.

How does TEVA-NALOXONE NASAL SPRAY work?
Opioid drugs work by acting on specific receptors found in the brain and in the nervous system. When these drugs attach to those receptors, they reduce the amount of pain felt. Taking too many

opioids can lead to an overdose and that can stop someone from breathing. The person may also experience other symptoms. TEVA-NALOXONE NASAL SPRAY stops the opioids from being attached to the receptors and this reverses the effects and symptoms of the overdose.

What are the ingredients in TEVA-NALOXONE NASAL SPRAY?
Medicinal ingredient: naloxone hydrochloride

Non-medicinal ingredients: benzalkonium chloride, edetate disodium, sodium chloride, hydrochloric acid, sodium hydroxide and purified water.

TEVA-NALOXONE NASAL SPRAY comes in the following dosage forms:
Each TEVA-NALOXONE NASAL SPRAY device contains 4 mg of naloxone hydrochloride in 0.1 mL of solution.

Do not use TEVA-NALOXONE NASAL SPRAY if:

- you are sure that the patient is allergic to naloxone hydrochloride or to any of the ingredients in TEVA-NALOXONE NASAL SPRAY.

Warnings you should know about:

Non-opioid overdoses: TEVA-NALOXONE NASAL SPRAY does not reduce the effects of an overdose caused by other drugs such as:

- barbiturates
- benzodiazepines
- psychostimulants (for example: cocaine, amphetamines or methylphenidate)
- alcohol
- anesthetics
- sedatives.

Giving TEVA-NALOXONE NASAL SPRAY to a person because of a non-opioid overdose is unlikely to cause more harm.

Return of Opioid Overdose Symptoms: It may be possible that the signs of an opioid overdose return after a dose of TEVA-NALOXONE NASAL SPRAY has been given. For example, a patient who responded to the first dose may experience a return of the signs of an overdose.

You should:

- monitor the patient.
- give repeated doses of TEVA-NALOXONE NASAL SPRAY to the patient if needed and available.
- lie the patient on their side to help them have a clear airway.
- perform artificial respiration or cardiac massage, only if needed and if you know how.
- wait for emergency medical help to arrive.

Acute Opioid Withdrawal Syndrome:

- TEVA-NALOXONE NASAL SPRAY should be given with caution to a patient who may be or who is addicted to opioids.
- After receiving TEVA-NALOXONE NASAL SPRAY, the patient may go into Acute Opioid Withdrawal Syndrome. Symptoms include:
    - shaking or having seizures
        - move away any sharp and dangerous objects to prevent injury.
        - do not try to hold the patient down.
    - vomiting
        - place the patient on their side to prevent choking if they vomit.
    - pain
    - fever
    - restlessness
    - irritability
    - aggressive behavior
    - sweating
    - yawning
    - weakness
    - shivering
    - trembling
    - increased blood pressure

- Acute Opioid Withdrawal Syndrome can be life-threatening for a newborn. Symptoms in newborns also include:
    - excessive crying
    - twitching and hyperactive reflexes.

Heart problems:

Naloxone is the active ingredient in TEVA-NALOXONE NASAL SPRAY. After using naloxone some patients had:

- a heart attack
- an increased heart rate
- an irregular heartbeat.

These side effects were rare. It is not known if the reactions were caused by naloxone or by the overdose.

Patients who have had surgery: The following occurred when some patients who had a recent surgery received naloxone:

- high and low blood pressure
- increased heart rate
- rapid irregular heartbeat
- a build-up of fluid in the lungs
- in rare cases, cardiac arrest

These side effects were rare. It is not known if the reactions were caused by naloxone or by the overdose.

Patients with nasal problems: It is not known if having any nasal problems will impact how TEVA-NALOXONE NASAL SPRAY works. Examples of nasal problems include a blocked or runny nose or nasal polyps. If TEVA-NALOXONE NASAL SPRAY is the only medication available to treat an opioid overdose, it should always be used.

Pregnant Women: TEVA-NALOXONE NASAL SPRAY should only be used in pregnant women when clearly needed.

How to Administer TEVA-NALOXONE NASAL SPRAY:

Important Points:

- TEVA-NALOXONE NASAL SPRAY is for use in the nose only.
- Do not test the TEVA-NALOXONE NASAL SPRAY device. Keep TEVA-NALOXONE NASAL SPRAY in the package until it is needed.
- Each TEVA-NALOXONE NASAL SPRAY device contains only 1 dose and cannot be reused.
- TEVA-NALOXONE NASAL SPRAY is not a substitute for emergency medical care. Always call 911 before administering TEVA-NALOXONE NASAL SPRAY.

Dose:

- TEVA-NALOXONE NASAL SPRAY is available as a 4 mg nasal spray device.
- The lowest available strength should be used as the initial dose.
- The pharmacist may recommend using an alternate form of naloxone in newborns or children under two years old. This is because smaller doses can be given with the injectable form of naloxone.

Step 1: Identify Opioid Overdose & Call for Emergency Medical Help

Check for signs of an opioid overdose:

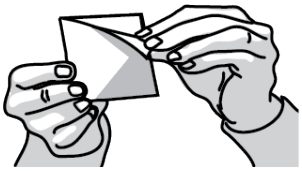
- Person DOES NOT wake up after you shout, shake their shoulders, or firmly rub the middle of their chest
- Breathing is very slow, irregular or has stopped
- Centre part of their eye is very small, like a pinpoint.

Call 911 or ask someone to call for you.

Lay the person on their back.

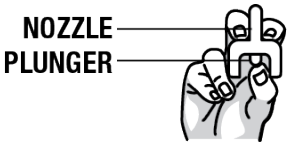
Step 2: Give TEVA-NALOXONE NASAL SPRAY

Remove device from packaging. **Do not test the device.** There is only one dose per device.



Tilt the person's head back and provide support under their neck with your hand.

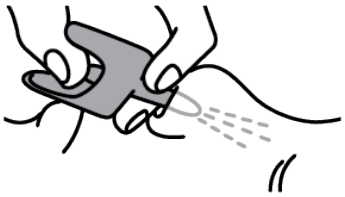
Hold the device with your thumb on the bottom of the plunger. Put your first and middle fingers on either side of the nozzle.



Gently insert the tip of the nozzle into one nostril. Your fingers should be right up against the nose. If giving to a child, make sure the nozzle seals the nostril.

Press the plunger firmly with your thumb to give the dose.

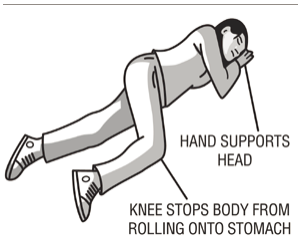
Remove the device from the nostril.



Step 3: Evaluate and Support

Move the person on their side (recovery position).
Watch them closely.

Give a second dose after 2 to 3 minutes if the person has not woken up or their breathing is not improved. **Alternate nostrils with each dose.**



You can give a dose every 2 to 3 minutes, if more are available and are needed.

Perform artificial respiration or cardiac massage until emergency medical help arrives, if know how and if it is needed.

What are possible side effects from using TEVA-NALOXONE NASAL SPRAY?

- Swelling in the nose
- Dryness in the nose
- Congested nose
- Runny nose

- Yawning
- Nervousness
- Pain
- Aggressive behaviours, irritability, restlessness, agitation
- Blood pressure increased
- Increased heart rate
- Nausea, vomiting
- Diarrhea, abdominal cramps
- Shivering, chills, tremors, trembling
- Fever
- Sweating
- Weakness
- Seizures
- Shaking
- Muscle spasms
- Dizziness
- Headache

911 should be called before administering TEVA-NALOXONE NASAL SPRAY. This will ensure the patient gets the help needed to deal with any overdose symptoms and any side effects.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store TEVA-NALOXONE NASAL SPRAY in the blister and cartons provided.
- Store between 15°C to 30°C. Can be stored up to 40°C only for short periods of time. Do not freeze or expose to excessive heat above 40°C.
- TEVA-NALOXONE NASAL SPRAY freezes at temperatures below -15°C. If this happens, the device will not spray. If TEVA-NALOXONE NASAL SPRAY is frozen and is needed in an emergency, do NOT wait for TEVA-NALOXONE NASAL SPRAY to thaw. Get emergency medical help right away.
- You can thaw TEVA-NALOXONE NASAL SPRAY by allowing it to sit at room temperature for 15 minutes. You can still use it if it has been thawed after being previously

frozen.

- Replace TEVA-NALOXONE NASAL SPRAY before the expiration date on the box.
    - If only expired TEVA-NALOXONE NASAL SPRAY is available, it should be used in an overdose situation.
- Keep out of reach and sight of children.

If you want more information about TEVA-NALOXONE NASAL SPRAY:

- Talk to your healthcare professional
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website http://www.tevacanada.com; or by calling 1-800-268-4127 ext. 3; or email druginfo@tevacanada.com.

This leaflet was prepared by Teva Canada Limited, Toronto, Ontario M1B 2K9

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