Schedule II Naloxone Reference Manual for Ontario Community Pharmacies

This document lives at https://eDispensary.ca/naloxone

February 2017

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Dispensary Naloxone Program

A model program to manage dispensing of naloxone in Ontario community pharmacies

ELIGIBILITY

Naloxone is a Schedule II drug when indicated for use in an emergency opioid overdose situation outside of a hospital setting.

Pharmacists can dispense naloxone kits without a prescription to use to treat opioid overdose.

To receive a publicly funded naloxone kit, patients must be one of the following:

- “a person who is currently using opioids or is a past opioid user who is at risk of returning to opioid use,” or
- “a family member, friend or other person in a position to assist a person at risk of overdose from opioids”

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The Narcan nasal spray formulation of naloxone can be dispensed as a Schedule II drug. However, every publicly-funded naloxone kit must contain injectable naloxone. Injectable naloxone kits must include the following items:

- Two 1mL ampoules or vials of naloxone hydrochloride 0.4mg/mL injection, and
- Two safety engineered syringes with one inch 25G needles attached, and
- Two safe ampoule opening devices, if ampoules are given, and
- One pair of non-latex gloves, and
- One naloxone identifier card

BILLING

To ensure consistent recordkeeping, every naloxone kit should be recorded in the pharmacy software, whether it is publicly-funded or not. Always create a separate prescription for the dispensing of the exact drug under its DIN and for the professional services provided.

<table>
<thead>
<tr>
<th>PIN</th>
<th>DESCRIPTION</th>
<th>COST</th>
<th>FEE</th>
<th>TOTAL COST</th>
</tr>
</thead>
<tbody>
<tr>
<td>93877251</td>
<td>Initial training and provision of 1 kit</td>
<td>$35</td>
<td>$35</td>
<td>$70</td>
</tr>
<tr>
<td>93877252</td>
<td>Replacement of 1 kit</td>
<td>$35</td>
<td>$10</td>
<td>$45</td>
</tr>
</tbody>
</table>

Follow the same procedures as you use for billing MedsChecks and other professional services: the pharmacist should be entered as the prescriber and the PS & ML intervention codes used as necessary for non-ODB eligible patients.
PROCESSING
To ensure consistency, use a special recordkeeping workflow for dispensing naloxone. When recording a naloxone prescription in the pharmacy software for billing purposes, imagine a generic "prescription".

The patient should always be the person to whom the kit is supplied, not the opioid user upon whom they expect to use the kit.

The prescriber should always be the dispensing pharmacist. That is, the pharmacist who actually provides the kit, training and counselling to the person receiving the kit.

Dispense under the actual DIN of the naloxone product and bill your training separately under the relevant pseudo-DIN. There must be a label with the actual drug and DIN to go on the vials containing the naloxone. You don’t want to confuse end-users in an emergency.

The first fill at your pharmacy should always include pharmacist training, even if the patient self-declares that they have already been trained in use of a naloxone kit. Training should be recorded under the 93877251 PIN (Initial Training) for every patient who has not been trained in use of a naloxone kit, even for non-publicly funded kits. Subsequent fills (for example, to replace a used or expired kit) should record training under 93877252.

The sig should be a concise summary of the instructions for emergency use of naloxone. The label will be on the vial containing the ampoules of naloxone and could be referred to in an emergency. For example:

FOR OPIOID OVERDOSE: CALL 911, THEN INJECT ONE AMPOULE (1ML) INTO UPPER ARM OR LEG MUSCLE, THEN PROVIDE CPR. REPEAT IN 3-5 MINUTES IF NO IMPROVEMENT.

Create an internal sig code/shortcut in your pharmacy software, such as *NALOXONE

<table>
<thead>
<tr>
<th>Model Prescription for processing Naloxone as a Schedule II drug in Ontario</th>
<th>2 RXs: 1 WITH THE DIN, 1 WITH THE PIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>ALWAYS CREATE ONE NEW RX FOR DISPENSING AND ONE NEW RX FOR TRAINING</td>
</tr>
<tr>
<td>Prescriber</td>
<td>THE 93877251 PIN DENOTES THAT THE PHARMACIST PROVIDED INITIAL TRAINING IN THE USE OF THE KIT.</td>
</tr>
<tr>
<td>Drug</td>
<td>THE 93877252 PIN DENOTES THAT THIS IS A REPLACEMENT KIT OR THE PATIENT DECLINES TRAINING</td>
</tr>
<tr>
<td>Sig</td>
<td></td>
</tr>
<tr>
<td>Quantity</td>
<td></td>
</tr>
<tr>
<td>Refills</td>
<td></td>
</tr>
</tbody>
</table>

Only one publicly funded naloxone kit can be provided to a person at a time (two vials/ampoules of naloxone). If a kit has been used or expired, another one can be billed under the 93877252 pseudo-DIN. The quantity of cash naloxone kits is at the discretion of the dispensing pharmacist.

Do not add refills to the prescription or set it to "unlimited refills". Use new "prescriptions" every time.
**Recordkeeping**
The pharmacy team should have a common standard when dispensing naloxone. Having a single standard policy and documentation template file on hand keeps everyone on the same page and gives staff a clear workflow. It promotes consistent, and well-documented evidence-based patient care.

**Record training and dispensing under separate prescriptions.** We always want to keep an exact record of what drug was dispensed and an exact record of the professional services provided. Dispensing under the naloxone DIN and recording services under the ONPP pseudo-DIN means that we can take advantage of automatic inventory management and drug interaction analysis.

There is more to document when providing training for emergency use of injectable naloxone than can reasonably be made to fit on a single prescription hardcopy.

**Reporting**
The Designated Manager must make a quarterly report to the Ministry of Health and Long-Term Care regarding publicly-funded naloxone kits that you have dispensed. In order to complete these reports, you track essential statistics about how the kits that you dispensed are used and the rationale for their use. The form should be emailed or faxed in quarterly. Using a standard form that captures the information that you need for these reports makes your quarterly reporting a breeze. Consider filing them separately to ensure they’re easily accessible for producing your quarterly reports, quality assurance, and for audit purposes.

**Training Materials**
The POINT “5 Steps to Save a Life” are a good patient aid for illicit drug users, covering overdose prevention and response. The University of Waterloo’s naloxone infographic is a good patient aid for chronic pain patients. The pharmacist should record which aids were actually provided. Avoid giving more than a couple of pages of patient aids: the kit will be opened in an emergency and it’s important that there be very straightforward and clear instructions.
<table>
<thead>
<tr>
<th>Rationale for Dispensing (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>person is currently using opioids or is a past opioid user who is at risk of returning to opioid use</td>
</tr>
<tr>
<td>person is prescribed chronic long-term opioid therapy</td>
</tr>
<tr>
<td>person is a family member, friend or other person in a position to assist a person at risk of overdose from opioids</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Billing (circle one)</th>
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</thead>
<tbody>
<tr>
<td>ONPP/ODB OR CASH</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Rationale for Professional Services (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>93877251 OR 93877252</td>
</tr>
<tr>
<td>This person is receiving a naloxone kit and first-time training by a pharmacist OR This person is receiving a replacement naloxone kit and has already received first-time training</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacist Verification of Kit Contents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two 1mL ampoules or vials of naloxone hydrochloride 0.4mg/mL injection</td>
</tr>
<tr>
<td>Naloxone is packed in cotton inside two easy-open vials with naloxone label, including the store custom sig</td>
</tr>
<tr>
<td>Two safe ampoule opening devices, if ampoules are given</td>
</tr>
<tr>
<td>Completed naloxone identifier card with training label on back</td>
</tr>
<tr>
<td>Two safety engineered syringes with one inch 25G needles attached</td>
</tr>
<tr>
<td>One pair of non-latex gloves</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacist Verification of Allergies (circle one)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Does the person the naloxone is intended for have any known allergies to naloxone, or concomitant ingredients in specific formulations of naloxone (methylparaben or propylparaben)?</td>
</tr>
<tr>
<td>YES</td>
</tr>
<tr>
<td>NO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacist’s Professional Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common Counselling Points (tick which ones)</td>
</tr>
<tr>
<td>Prevention of opioid overdose</td>
</tr>
<tr>
<td>Signs of and response to opioid overdose</td>
</tr>
<tr>
<td>Administration of naloxone and aftercare</td>
</tr>
<tr>
<td>Notifying pharmacy when kit is used</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pharmacist Signature and License Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>eDispensary.ca</td>
</tr>
<tr>
<td>patient retention • workflow automation</td>
</tr>
</tbody>
</table>
5 STEPS TO SAVE A LIFE

1. SHAKE & SHOUT at shoulders their name

2. CALL 911 if unresponsive

3. INJECT NALOXONE 1 ampoule (1mL) into arm or leg muscle

4. CHEST COMPRESSIONS or full CPR and/or rescue breathing as trained

5. IS IT WORKING? If no improvement in 3-5 minutes repeat steps 3 & 4

STAY! Stick around until EMS arrives in case they still need help
OVERDOSE PREVENTION

- Avoid mixing drugs or using with alcohol. Try to use one at a time and use drugs before alcohol.
- Know your tolerance, if you haven’t used for a while, (3 days or more) your body can’t handle the same amount as before. Start as if you have never used before.
- Do a tester and ask around with a new supply or dealer. Taste it, smoke it, use a little and see what others are saying.
- Use with a friend but avoid injecting at the same time in case one of you needs help.
- Have a plan, talk about overdose before it happens and with people you trust.

SIGNS OF OPIOID OVERDOSE

- Can’t wake the person up
- Breathing is very slow, erratic or has stopped
- Deep snoring or gurgling sounds
- Fingernails or lips are blue or purple
- Body is very limp
- Pupils are very small

RECOVERY POSITION

Put person in recovery position if:

- Unconscious and breathing
- You have to leave the person unattended

- Head should be tilted back slightly to open airway
- Place their hand under their head for support
- Bend knee forward to prevent body from rolling onto stomach

The Works 277 Victoria St. Toronto, Ontario 416-392-0520

Call 311 toronto.ca/health | Toronto Public Health
Naloxone is an antidote for opioids which can include:

- Codeine
- Demerol
- Hydromorphone
- Heroin
- Oxycodone
- Dilaudid
- Morphine
- Buprenorphine
- Fentanyl
- Methadone

1. **Signs of an Overdose**
   - Soft/no breath or snoring
   - Pinpoint pupils
   - Blue lips, nails, or skin
   - Cold, clammy skin
   - Limp body
   - Doesn’t respond to shouting

2. **Call 911**

3. **Give Naloxone**
   - Break drug ampoule
   - Pull into needle slowly
   - Inject into large muscle

4. **Check The Person’s Breathing**
   - Breathing
     - Hand supports head
     - Knee stops body from rolling onto stomach
   - Not Breathing
     - Push hard and fast in center of chest to the beat of Stayin’ Alive
     - Give compressions until help arrives

5. **Stay Calm**
   - Don’t put them in a bathtub/shower
   - Wait for help to arrive
   - Don’t inject stimulants (ie. meth)
   - Don’t stand them up

More info:
3. [http://www.albertahealthservices.ca/info/page12491.aspx](http://www.albertahealthservices.ca/info/page12491.aspx)
4. [http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm](http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6423a2.htm)
On June 24, 2016, the National Association of Pharmacy Regulatory Authorities (NAPRA) finalized the scheduling change for naloxone hydrochloride injection ("naloxone"). Naloxone, when indicated for emergency use for opioid overdose outside hospital settings, is now classified as a Schedule II drug in the NAPRA’s National Drug Schedule (NDS).

As a result, effective June 24, 2016, naloxone no longer requires a prescription to be sold in Ontario pharmacies if indicated for emergency use for opioid overdose outside hospital settings.

Effective June 24, 2016, all pharmacies may receive reimbursement for providing naloxone emergency kits by submitting claims through the Health Network System (HNS).

If you have any questions, please contact the ministry by email at PublicDrugPrgrms.moh@ontario.ca or the Ontario Drug Benefit (ODB) Help Desk at 1-800-668-6641.

**Background**

On June 3, 2016, the Ministry of Health and Long-Term Care’s (ministry) new Ontario Naloxone Program for Pharmacies (ONPP) made publicly-funded naloxone available in pharmacies that dispense opioid agonist maintenance therapy (methadone/Suboxone) under a prescription order from the Chief Medical Officer of Health (CMOH) for Ontario. The CMOH’s prescription order required this prior to NAPRA’s decision has expired, effective June 24, 2016.

In addition, completion of the “2016 Naloxone Training Module” respecting the preparation and administration of emergency naloxone kits is no longer required. Completion of a signed Attestation for Participation in the Ontario Naloxone Pharmacy Program (ONPP) is also no longer required.
Pharmacy Compliance

This notice and the accompanying Frequently Asked Questions (FAQs) constitute a ministry policy that pharmacy operators must comply with when submitting claims through the HNS for providing naloxone kits. Compliance with the ministry policy is required under section 3.2 of the HNS Subscription Agreement for Pharmacy Operators.

Eligibility

As of June 24, 2016, all pharmacies are eligible to provide naloxone emergency kits at no cost to eligible persons, if certain terms and conditions are met. Criteria for an “eligible person” includes:

- a person who is either currently using opioids or is a past opioid user who is at risk of returning to opioid use, or
- a family member, friend or other person in a position to assist a person at risk of overdose from opioids.

Procedures for Providing and Billing

Pharmacists must be trained prior to providing naloxone kits. The Ontario Pharmacists Association (OPA) has developed an online education module available on their website. There may be other resources available to pharmacists. The OCP has developed a guidance document for the providing or selling of naloxone available on their website.

The trained pharmacist who provides the publicly funded naloxone emergency kit must be identified in the pharmacist field on the claim submitted for payment through the HNS using the proper PIN that was provided.

For eligible persons, who are first time users and do not have training with the naloxone kit, the Initial Naloxone Emergency Kit (which includes a professional training component) will be provided by the pharmacist. For eligible persons, who do have training with the naloxone kit, the Replacement Naloxone Emergency Kit (excludes the professional training) can be provided by the pharmacist.

Pharmacists must ensure that the eligible person’s name, date of birth, and Ontario health card number are entered accurately as part of the HNS claims submission.

Pharmacists, where possible, must ensure that the quarterly report-back form (available at: www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/eo_communiq.aspx) relating to outcomes for individuals who were provided a naloxone emergency kit, be completed.
Pharmacies will procure naloxone and the required supplies to assemble the naloxone kit through usual suppliers (i.e., pharmacy-assembled naloxone kits). The emergency kit shall be assembled by a pharmacist, or a person under the supervision of a pharmacist and contain the follow:

- Two 1 ml ampoules or vials of naloxone hydrochloride 0.4 mg/ml injection;
- Two safety engineered syringes with 25 g one inch needles attached;
- Two safe ampoules opening devices (also known as “breakers”, “snappers”, or “openers”) as applicable;
- One pair of non-latex gloves;
- One rescue breathing barrier; and
- One naloxone identifier card.

The ministry is aware that some of supplies (e.g., ampoule openers/snappers/breakers, rescue breathing barriers) listed can be ordered from Canadian based suppliers such as Pharmasystem, Canadian Safety Supplies, and Kohl and Frisch. The Ontario Pharmacists Association has also compiled a list of the required kit components as well as some suppliers for these items, in the event that pharmacists are unable to procure some or all of the elements through their usual suppliers. This list can be found at [www.opatoday.com/professional/naloxone_kit_tools](http://www.opatoday.com/professional/naloxone_kit_tools). Types of containers that have been reportedly used to contain all the components include sunglasses cases, eyeglass cases, pencil cases, or a variation of a compact, portable container resembling a case or box. Pharmacies are encouraged to seek out these and/or other local suppliers for obtaining components required for pharmacy-assembled naloxone kits.

**Pharmacy Eligibility**

All pharmacies that comply with the requirements of this ministry policy are able to provide emergency naloxone kits, and bill the cost of those kits to the ministry through the HNS.

Prior to providing naloxone kits to eligible persons, pharmacies must ensure that their pharmacists are trained to provide the necessary training to eligible persons who are to receive the naloxone kits.
Pharmacy Record Requirements

Standard record keeping requirements under current standards of practice apply. Pharmacies must keep a record when the naloxone kit (see table below) is provided to the eligible person.

For billing purposes, pharmacy records must be maintained in a readily available format for the purpose of a ministry audit of billing for a minimum of 2 years.

Pharmacists shall keep records consistent with their obligations under the Pharmacy Act, 1991, the Drug and Pharmacies Regulation Act and any instructions provided by the Ontario College of Pharmacists or the ministry. These records must include, at a minimum:

- Full instructions for use of drug; and

- The drug’s material risks, including material side-effects, contradictions or precautions were discussed with the eligible person to ensure that they provide appropriate training to individuals receiving naloxone emergency kits.

Pharmacy billing procedure

Naloxone emergency kits will be reimbursed by the Ontario Government, effective June 24, 2016, in accordance with this ministry policy. The PINs listed in Table 1 below are to be used whenever an emergency naloxone kit is supplied to an eligible person, regardless of the person’s eligibility under the Ontario Drug Benefit (ODB) Program.

Table 1: PINs to support reimbursement of Naloxone emergency kits

<table>
<thead>
<tr>
<th>PIN</th>
<th>Description</th>
<th>Total Amount Reimbursed</th>
</tr>
</thead>
<tbody>
<tr>
<td>93877251</td>
<td>Initial Naloxone Emergency Kit (reimbursed amount includes naloxone kit at $35, plus professional fee at $10, plus professional training at $25)</td>
<td>$70.00</td>
</tr>
<tr>
<td>93877252</td>
<td>Replacement Naloxone Emergency Kit (reimbursed amount includes naloxone kit at $35 plus professional fee at $10)</td>
<td>$45.00</td>
</tr>
</tbody>
</table>

Claims must be submitted using the ministry-assigned PIN associated with the naloxone...
emergency kit and service provided. Do not use the Drug Identification Number (DIN) of the naloxone that is contained in the naloxone kit.

For ODB-eligible recipients:

The claim submission follows the normal process for submitting claims on the HNS with the following additional information:

- Intervention code ‘PS’: (Professional Care Services)
- Product Identification Number (PIN): see table above for list of PINs
- Valid Pharmacist ID
- Professional Fee: see table above for “Maximum Reimbursed Amount” for each kit

For Non-ODB eligible recipients:

When submitting a claim for an eligible person who does not have ODB coverage, pharmacists must submit the following information:

- Person’s Gender: ‘F’ = female; ‘M’ = male
- Person’s Date of Birth: Valid YYYYMMDD
- Person’s Ontario Health Card number
- Intervention codes:
  - PS: Professional Care Services
  - ML: Established eligibility coverage (i.e., 1 day of the Plan ‘S’ coverage)
- Carrier ID: ‘S’
- Product Identification Number (PIN): see table above for list of PINs
- Valid Pharmacist ID
- Professional Fee: see table above for “Maximum Reimbursed Amount” for each kit

Restrictions:

A maximum of one (1) naloxone kit may be provided to an eligible person at one time.
Ontario Naloxone Program for Pharmacies (ONPP) 
Frequently Asked Questions for Pharmacy 
Dispensers: Providing Publicly Funded Naloxone Kits 
and Claims Submission Using the Health Network 
System 

Updated August 17, 2016 

1. When are dispensers able to provide publicly funded naloxone emergency 
kits for Ontarians? 

All pharmacies that have a billing account under the Ontario Public Drugs Program 
(OPDP) are eligible to provide naloxone emergency kits free-of-charge, effective June 
24, 2016, subject to their compliance with the Ministry of Health and Long-Term Care’s 
(ministry) policy. 

2. What are the publicly available kits that dispensers can bill Health Network 
System (HNS) for reimbursement? 

Table 1: PINs to support reimbursement of Naloxone emergency kits 

<table>
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<td>$45.00</td>
</tr>
</tbody>
</table>

The “Initial Naloxone Emergency Kit” PIN would be entered when a pharmacist provides 
a naloxone emergency kit for the first time to a person, and provides the required 
training. The “Replacement naloxone emergency kit” PIN would be entered when an 
individual who has already received an initial naloxone emergency kit and the required
training, is being provided a subsequent naloxone emergency kit.

3. What are the contents of the Naloxone Emergency Kits?

Pharmacies will purchase naloxone and the required supplies to assemble the naloxone kit through usual suppliers (i.e., pharmacy-assembled naloxone kits). The emergency kit must be assembled by a pharmacist or a person under the supervision of a pharmacist, and contain the following:

a. Two 1 mL ampoules or vials of naloxone hydrochloride 0.4 mg/ml injection;

b. Two safety engineered syringes with 25 g one inch needles attached;

c. Two safe ampoules opening devices (also known as “breakers”, “snappers”, or “openers”) as applicable;

d. One pair of non-latex gloves;

e. One rescue breathing barrier; and

f. One naloxone identifier card.

The ministry is aware that some of supplies (e.g., ampoule openers/snappers/breakers, rescue breathing barriers) listed can be ordered from Canadian based suppliers such as Pharmasystem, Canadian Safety Supplies, and Kohl and Frisch. The Ontario Pharmacists Association has also compiled a list of the required kit components as well as some suppliers for these items, in the event that pharmacists are unable to procure some or all of the elements through their usual suppliers. This list can be found at www.opatoday.com/professional/naloxone_kit_to... Types of containers that have been reportedly used to contain all the components include sunglasses cases, eyeglass cases, pencil cases, or a variation of a compact, portable container resembling a case or box. Pharmacies are encouraged to seek out these and/or other local suppliers for obtaining components required for pharmacy-assembled naloxone kits.

4. Are dispensers authorized to provide non-publicly funded naloxone kits?

Yes, naloxone may be provided to people who do not meet the eligibility criteria for the Ontario Naloxone Program for Pharmacies (ONPP).

Eligibility

5. Are all Ontarians eligible to receive publicly funded naloxone kits?

Eligible people include a person who is either:
• Currently using opioids;
• Is a past opioid user who is at risk of returning to opioid use; or
• A family member, friend or other person in a position to assist a person at risk of overdose from opioids.

The individual must also indicate their understanding that the person for whom the naloxone is intended has no known contraindications to the use of naloxone.

Pharmacy Eligibility

6. What do I have to do before providing naloxone emergency kits and billing the ministry through the HNS for the kits?

Only pharmacies that comply with the requirements of the ministry policy set out in the Executive Officer’s Notice, dated August 17, 2016, will be able to provide naloxone emergency kits, and bill the cost of those kits to the ministry through the HNS.

The ministry strongly encourages that pharmacists complete appropriate training prior to providing naloxone emergency kits. The ministry is aware of naloxone online webinar training (recorded) and additional resources available on the Ontario Pharmacists Association website. There may be other resources available to pharmacists.

Please refer to your professional college and/or association for guidance and/or resources for training required for providing naloxone kits.

Ministry Payment

7. How is payment made by the ministry?

The payment is paid through the ministry’s Health Network System (HNS) to the eligible pharmacy that has a billing account with OPDP.

8. Can I submit manual (paper) claims for naloxone emergency kits?

No. All claims for naloxone emergency kits must be submitted electronically through the HNS.
Pharmacy Participation

9. What training are pharmacists required to complete prior to providing naloxone emergency kits?

The ministry strongly encourages pharmacists complete appropriate training prior to providing the naloxone emergency kits. Please refer to your professional college and/or association for guidance and/or resources for training required for the providing of naloxone kits.

Documentation and Record Keeping

10. What is the pharmacist required to document when providing a naloxone kit to eligible Ontarians?

Standard record keeping requirements under current standards of practice apply. Pharmacists must keep a record when the naloxone kit is provided to an eligible person (see question 5).

Pharmacists must keep records consistent with their obligations under the Pharmacy Act, 1991, the Drug and Pharmacies Regulation Act and any instructions provided by the Ontario College of Pharmacists or the ministry. These records must include, at a minimum:

- The name, address and phone number of the eligible person.
- Full instructions for use of drug.
- The drug’s material risks, including side-effects, contradictions or precautions were discussed with the Eligible Person.

Please refer to your professional college and/or association for guidance relating to documentation within scope of practice.

11. How long should the record be kept for billing purposes?

For billing purposes, pharmacy documentation must be maintained in a readily available format for the purpose of ministry audit for a minimum of 2 years.

12. Are pharmacists required to track outcomes of the individuals who were provided a naloxone kit?

Pharmacists, where possible, must ensure that a quarterly report (available at: http://www.health.gov.on.ca/en/pro/programs/drugs/opdp_eo/eo_communiq.aspx),
relating to outcomes for individuals who were provided a naloxone emergency kit, be completed and returned to the ministry. The reporting schedule is as follows:

Table 2: Quarterly Reporting Requirements for Providing Naloxone

<table>
<thead>
<tr>
<th>Quarter</th>
<th>Report due date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1 (April – June)</td>
<td>June 30</td>
</tr>
<tr>
<td>Q2 (July – September)</td>
<td>October 30</td>
</tr>
<tr>
<td>Q3 (October – December)</td>
<td>January 30</td>
</tr>
<tr>
<td>Q4 (January – March)</td>
<td>April 30</td>
</tr>
</tbody>
</table>

Claim for Payment through the HNS

13. When does the pharmacist submit the claim for the payment?
Pharmacists should submit the claim for payment through the HNS after providing of the naloxone emergency kits to the eligible person the same day the naloxone kit was provided.

14. How are claims for naloxone emergency kits submitted through the HNS?
Claims must be submitted for a publicly funded naloxone emergency kit using the appropriate PIN of the kit (i.e., Initial Naloxone Emergency Kit, Replacement Naloxone Emergency Kit).
Pharmacists must ensure that the individual's name, date of birth, and Ontario health card number are entered accurately as part of the HNS claims submission. Failure to do so may impact the ability to submit future claims for these individuals.

15. What is the procedure to submit the claim to the HNS for a publicly funded naloxone kit for an ODB eligible recipient?
The claim submission follows the normal process for submitting claims on the HNS with the following additional information:
- Intervention code ‘PS’: (Professional Care Services)
- Product Identification Number (PIN): see table above for a list of PINs
• Valid Pharmacist ID
• Professional Fee: see table above for the “Maximum Reimbursed Amount” for each naloxone emergency kit

16. What is the procedure to submit the claim to the HNS for a publicly funded naloxone kit for an eligible person who does not have ODB coverage?

When submitting a claim for a person who does not have ODB coverage, pharmacists must submit the following information:

• Person’s Gender: ‘F’ = female; ‘M’ = male
• Person’s Date of Birth: Valid YYYYMMDD
• Person’s Ontario Health Card number
• Intervention codes:
  o PS: Professional Care Services
  o ML: Established eligibility coverage (i.e., 1 day of the Plan ‘S’ coverage)
• Carrier ID: ‘S’
• Product Identification Number (PIN): see table above for a list of PINs
• Valid Pharmacist ID
• Professional Fee: see table above for the “Maximum Reimbursed Amount” for each kit

17. I have questions about providing naloxone kits?

Please refer to your professional college and/or association regarding questions about guidance and/or resources for naloxone kits, including contents preparation and providing of the naloxone kit.

If pharmacies have any questions or concerns related to this policy or billing issues, please contact the Ontario Drug Benefit (ODB) Help Desk 1-800-668-6641.

18. Do I need to submit these PINs to the Narcotics Monitoring System (NMS)?

No. Naloxone emergency kits are not included on the Monitored Drugs List, therefore submission to the NMS is not required.
Restrictions

19. What are the restrictions for naloxone kits?

A maximum of one (1) naloxone kit may be provided to an eligible person at one time.

Additional Questions

20. Can I process a claim via the HNS for a publicly-funded naloxone kit if the eligible person does not want to provide their Ontario health care number (OHIP) number to the pharmacy?

No. An eligible person must submit their OHIP number for a claim to be processed through HNS for a publicly-funded naloxone kit at the pharmacy.

21. I am having trouble putting the claim through. Who should I contact?

If pharmacies have any questions or concerns related to this policy or billing issues, please contact the Ontario Drug Benefit (ODB) Help Desk 1-800-668-6641.
Ontario Public Drug Programs, Ministry of Health and Long-Term Care

Ontario Naloxone Program for Pharmacies (ONPP) Quarterly Reporting Form

<table>
<thead>
<tr>
<th>Pharmacy Name:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Date:</td>
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<tr>
<td>Contact:</td>
<td></td>
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<tr>
<td>Email:</td>
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<tr>
<td>Telephone:</td>
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Key Outcomes for the Quarter*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Initial Naloxone Emergency kits dispensed to persons</td>
<td></td>
</tr>
<tr>
<td>a) Number of persons at-risk of opioid overdose trained to administer naloxone</td>
<td></td>
</tr>
<tr>
<td>b) Number of family and/or friends of persons trained to administer naloxone</td>
<td></td>
</tr>
<tr>
<td>Number of persons who administered naloxone that they received from a pharmacy, including how many doses were given per overdose</td>
<td></td>
</tr>
<tr>
<td>Number of persons who reported receiving an injection of naloxone that was acquired from a pharmacy, including how many doses were received per person</td>
<td></td>
</tr>
<tr>
<td>Number of times that 911 was called when naloxone was administered or received</td>
<td></td>
</tr>
<tr>
<td>Number of Replacement Naloxone Emergency kits dispensed</td>
<td></td>
</tr>
</tbody>
</table>

Feedback

Please provide any information you feel is important to report regarding successes or challenges in regards to your naloxone distribution program:

Your reporting form may be submitted electronically (preferred) to: PublicDrugPrgrms.moh@ontario.ca
Should you not be able to submit electronically, you may submit via fax to: 416-325-6647.

* Due 30 days after the end of each quarter in a fiscal year. The first report back will be due on October 30, 2016. Please refer to the FAQs for details on the reporting schedule.
Notice from the Executive Officer: Reminder – the Ontario Naloxone Program for Pharmacies

August 17, 2016

This notice is a reminder that since June 24, 2016:

- Naloxone hydrochloride for injection is now Schedule II and no longer requires a prescription to be dispensed in pharmacies if indicated for emergency use for opioid overdose outside hospital settings.

- All pharmacies will be reimbursed for providing naloxone emergency kits to eligible Ontario residents and in accordance with the Ontario Naloxone Program for Pharmacies (ONPP) through the Health Network System (HNS).

For further information on naloxone and the ONPP, please refer to the EO Notice and FAQs on naloxone posted on the ministry’s website:


If you have any questions or concerns, please call the ODB Help Desk at 1-800-668-6641.

Naloxone Nasal Spray

The nasal spray formulation of naloxone hydrochloride (NARCAN® Nasal Spray, ADAPT Pharma) is now permitted for sale in Canada, without a prescription. For more information, please refer to Health Canada’s website:


Further updates on the availability and ONPP reimbursement of the nasal spray format of naloxone will follow shortly.

Pharmacist Training and Naloxone Guidance

As is required when delivering any service, it is the pharmacist’s professional responsibility to ensure that he or she has undergone the appropriate training and has the required skills and resources to ensure that the service is provided in a safe and effective manner. The Ontario Pharmacists Association (OPA) has been working very closely with the ministry on the ONPP
and has developed an online education program which can be accessed, free of charge, through the OPA website at [www.opatoday.com/224122](http://www.opatoday.com/224122).

Pharmacies should continue to refer to the requirements outlined in the *Ontario College of Pharmacists Guidance – Dispensing or Selling Naloxone* with regards to providing naloxone.

**Procurement of Naloxone kits**

In advance of the June 2016 roll-out of the ONPP, the ministry arranged for a small, one-time-only auto-shipment of preassembled naloxone kits (i.e., “one-time bridge”) to be made to select methadone and/or Suboxone-dispensing pharmacies across the province. The ministry recognizes that access to pre-assembled kits and/or some of the individual components may be difficult at this time as they are not yet available to all pharmaceutical distributors. We have been working closely with OPA to identify the various suppliers of kits or their components. Please check the OPA website at [www.opatoday.com/professional/naloxone_kit_tools](http://www.opatoday.com/professional/naloxone_kit_tools) for additional resources related to kit/component procurement.

Thank you for your support and contribution to the reduction of opioid overdose deaths in Ontario.
DISPENSING OR SELLING NALOXONE

Guidance for pharmacy professionals when dispensing or selling naloxone as a Schedule II drug.
Purpose
The intent of this document is to provide guidance for pharmacists and pharmacy technicians regarding their respective responsibilities when dispensing or selling naloxone as a Schedule II drug.

Introduction
In response to the influx of opioid related overdoses across Canada, naloxone has been made available for emergency use for opioid overdose outside hospital settings. Accidental overdoses can occur in both individuals who use opioids as prescribed by their physician, and those using opioids for non-medical reasons. The goal of providing naloxone in community pharmacies is to increase public access to this life-saving medication.

Naloxone is a non-addictive opioid antagonist that temporarily reverses the effects of opiates including, respiratory depression, sedation and hypotension. Naloxone is a safe and effective therapy: with proper administration naloxone is a drug that can save lives in opioid overdose situations when a person appropriately identifies the overdose and takes the required action. In the absence of an opioid, naloxone exhibits no effects and the only contraindication to the use of naloxone is in patients known to be hypersensitive to it. Naloxone does not increase the likelihood of risk-taking behaviours, and cannot be abused.

Naloxone Availability in Community Pharmacies
As of June 24, 2016 naloxone, when indicated for emergency use for opioid overdose outside hospital settings, is available as a Schedule II drug. Any patient or patient’s agent (agent) are now permitted to obtain Schedule II naloxone directly from any community pharmacist without a prescription.

Pharmacists are authorized to dispense naloxone kits obtained through the Ministry of Health and Long-Term Care Ontario Naloxone Program for Pharmacies or privately procured naloxone and kit

Update as of December 23, 2016
As of December 22, 2016 naloxone hydrochloride nasal spray, when indicated for emergency use for opioid overdose outside hospital setting, is available as a Schedule II drug.

The College notes that pharmacists are authorized to dispense any formulation of naloxone available for sale and distribution in Canada.

When dispensing any formulation of naloxone, pharmacists are expected to practice in accordance with all of the requirements outlined in the College’s Guidance for pharmacy professionals when dispensing or selling naloxone.
supplies. The Ministry of Health and Long-Term Care will provide funding for naloxone for patients according to criteria defined by the Ministry.

Pharmacists should always dispense two ampoules or vials (or units of any formulation) of naloxone to the patient or agent to ensure that a second dose of naloxone is available for administration if needed.

When dispensing naloxone the pharmacist is strongly encouraged to also ensure that the patient or agent receives the following supplies to aid in the administration of naloxone, including:

- Two Safety syringes with 25G one inch needles attached if dispensing injectable formulation – they reduce the risk of needle stick injury, can be disposed of in the trash, prevent re-use as there is no way to push the needle back out, and are unlikely to be used for any other purpose (unlike insulin syringes);
- One rescue breathing barrier – a plastic barrier that is used when administering cardiopulmonary resuscitation (CPR);
- Two safe ampoule opening devices – small plastic snappers which prevent people from cutting their hands on broken glass when snapping an ampoule; these are not needed if vials or any other formulation are being provided; and
- One pair of non-latex gloves and alcohol swabs — optional supplies to reduce the risk of infection given that an injection can be provided through clothing.
- One naloxone identifier card – a card that can be filled out with the name of the person who has been trained in responding to opioid overdoses, the date the naloxone supplies were issued, and the expiry date of the naloxone.

**Responsibilities of the Pharmacist when Dispensing Naloxone**

The pharmacists’ responsibilities include ensuring the following requirements are met when dispensing naloxone:

**Standards of Practice**

Schedule II drugs, when dispensed or sold in a pharmacy, must be stored and provided to patients from the dispensary where patient self-selection is restricted. Each transaction must occur under the direct supervision of a pharmacist and pharmacists are expected to counsel each patient or agent
when dispensing naloxone in order to enable the patient to receive the intended benefit of the drug therapy.

Pharmacists and pharmacy technicians are expected to practice in accordance with the NAPRA Supplemental Standards of Practice for Schedule II and III Drugs, which set out the minimum acceptable standards of practice, including standards regarding the distribution or sale of Schedule II drugs.

**Patient Assessment**

When dispensing naloxone the pharmacist must determine the following:

- If the person who naloxone is intended for has any known allergies to naloxone, or concomitant ingredients in specific formulations of naloxone (methylparaben or propylparaben). Allergies are very rare and the benefits of naloxone are likely to outweigh the risks of an allergic reaction.

- Where the intended person has a known allergy to naloxone or concomitant ingredients the pharmacist should encourage the person to seek medical attention from a physician.

- Naloxone should not be dispensed where the intended person has a known allergy to naloxone unless the pharmacist confirms with a physician that the emergency kit should be dispensed.

**Pharmacist Training**

It is the professional responsibility of a pharmacist to ensure that he or she has sufficient knowledge, skills and abilities to competently deliver any pharmacy service. As is required when delivering any new service, a pharmacist must ensure he or she has undergone the appropriate training and has the required resources to ensure that the service is provided in a safe and effective manner. There are a number of training programs and resources available to pharmacists (see links on College website).

**Providing Patient and/or Agent Education**

It is critical that the pharmacist is properly trained on the essential information required to effectively educate the patient or agent and prepare him or her for dealing with an opioid overdose, prior to providing naloxone. Patients and/or agents must be educated on more than just naloxone...
therapy and how to administer it. Pharmacists should ensure patients and/or agents purchasing naloxone are also educated on such topics as:

- Harm reduction strategies when using opioids;
- How to identify an opioid overdose;
- Importance of immediately calling 9-1-1;
- Importance of cardiopulmonary resuscitation (CPR) and how and when to give breaths;
- When and how to administer naloxone;
- Aftercare and the importance of staying with the person until emergency first responders arrive;
- Withdrawal symptoms occur following naloxone administration and reversal of the effects of the opioid overdose. Doses of naloxone administered via one or two vials or ampoules will, in most cases, only produce mild withdrawal symptoms and the benefits outweigh the risks associated with withdrawal;
- Naloxone may have variable efficacy in reversing the clinical effects of an overdose due to preparations containing buprenorphine;
- Naloxone is not effective against respiratory depression due to non-opioid drugs;
- Risk of secondary overdose if opioids used when patient regains consciousness; and
- Any other information the pharmacist deems relevant.

Pharmacists must also provide educational information and the steps for dealing with an opioid overdose in writing to the patient and/or agent. Written resources are not a replacement for pharmacist interaction with the patient or agent, and are to be used as a supplemental resource only.

**Documentation Requirements**

The record keeping requirements for naloxone are the same as for any other Schedule II product as outlined in the College’s Documentation Guidelines and the NAPRA Supplemental Standards of Practice for Schedule II and III Drugs. There are no additional documentation requirements.

Pharmacists may be required to report additional information in accordance with requirements set out by the Ontario Naloxone Program for Pharmacies.
NALOXONE: 5 Things Pharmacists Need to Know

Maria Zhang, RPh, BScPhm, PharmD, MSc and Beth Sproule, RPh, BScPhm, PharmD
Centre for Addiction and Mental Health (CAMH)
Leslie Dan Faculty of Pharmacy, University of Toronto

1. NALOXONE IS NOW A SCHEDULE II DRUG

On March 22, 2016, Health Canada delisted naloxone as a prescription drug. The National Association of Pharmacy Regulatory Authorities (NAPRA) then reclassified naloxone as a Schedule II medication when used in an emergency opioid overdose situation outside of hospital settings.

While most take-home naloxone kits currently contain intramuscular formulations of naloxone, there is an Interim Order, issued by the Minister of Health that allows the importation and sale of NARCAN® nasal spray for the emergency treatment of known or suspected opioid overdoses. Like the parenteral formulations, intranasal naloxone is also available without a prescription.

2. ONTARIANS WITH A HEALTH CARD ARE ELIGIBLE FOR A FREE TAKE-HOME NALOXONE KIT THROUGH THE ONTARIO NALOXONE PHARMACY PROGRAM

Pharmacies are provided up to $70.00 for each naloxone kit they dispense and provide training. Eligibility criteria for the program include anyone who is:

- Currently using opioids,
- A past opioid user who is at risk of returning to opioid use, or
- A family member, friend, or other person in a position to assist a person at risk of opioid overdose.

Essentially, any Ontarian with a health card should be provided with a naloxone kit and training, upon request. Pharmacists’ main role in this program is to provide education to naloxone kit recipients and minimize barriers to access. Those who do not have health cards can be directed to local public health units. Intranasal naloxone is available for free for recently released at-risk inmates.

3. PATIENTS ON CHRONIC OPIOID THERAPY SHOULD BE OFFERED A TAKE-HOME NALOXONE KIT

While there are known factors that increase the risk of opioid overdose, including concurrent use of other sedating agents (e.g., alcohol, benzodiazepines) and concomitant medical conditions such as chronic obstructive pulmonary disease (COPD), it is clear that there is a link between daily doses and overdose death. The risk of opioid-related mortality is increased even at doses of 50 mg of morphine equivalents per day. Therefore, take-home naloxone kits should be proactively offered to anyone on chronic opioid therapy, regardless of dose.
Given the profound stigma around people living with substance use disorders, pharmacists may encounter patients on opioids who do not wish to receive a naloxone kit. Pharmacists can highlight that having a naloxone kit around the house is a way to protect the person using opioids, and anyone who may inadvertently consume them, and describe it as similar to having a first-aid kit.

4. PRE-ASSEMBLED TAKE-HOME NALOXONE KITS ARE AVAILABLE
Pharmacies no longer have to self-assemble take-home naloxone kits as pre-assembled ones are available for ordering. Pharmacies are encouraged to check with their usual pharmaceutical distribution channels.

5. RESOURCES EXIST TO SUPPORT PHARMACISTS IN PROVIDING NALOXONE KIT TRAINING

**Centre for Addiction and Mental Health:**
- Pharmacists' Checklist (vial or ampoule)
- "5 Steps to Save a Life" kit insert for naloxone kit recipients
- Poster for dispensing area
- Portico clinical tools for opioid misuse and addiction, including specific naloxone resources

**University of Waterloo**
- Naloxone at pharmacies: what you need to know to combat the opioid crisis
- Video: How to administer naloxone (ampoule)
  *Note: do not need to open (or use) an alcohol wipe to open an ampoule

**Ontario College of Pharmacists**
- Guidance for Pharmacists on Dispensing or Selling Naloxone

**Ontario Pharmacists Association**
- Take home naloxone in community pharmacies: online module.

REFERENCES:


PrNALOXONE HYDROCHLORIDE INJECTION SDZ
Preservative Free
Naloxone Hydrochloride Dihydrate

0.4 mg/mL

Therapeutic Classification
Opioid Antagonist
Naloxone Hydrochloride Injection SDZ
Preservative Free
0.4 mg/mL

THERAPEUTIC CLASSIFICATION

Opioid Antagonist

CLINICAL PHARMACOLOGY

Naloxone hydrochloride prevents or reverses the effects of opioids, including respiratory depression, sedation, and hypotension. Also, it can reverse the psychosomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone hydrochloride 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. In the absence of opioids or agonistic effects of other opioid antagonists it exhibits essentially no pharmacologic activity. Naloxone has not been shown to produce tolerance or to cause physical or psychological dependence. In the presence of physical dependence on opioids naloxone will produce withdrawal symptoms.

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

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

INDICATIONS AND CLINICAL USE

Naloxone is indicated for the complete or partial reversal of opioid depression, including respiratory depression induced by opioids, including natural and synthetic opioids, propoxyphene, methadone and the agonist-antagonist analgesics nalbuphine, pentazocine and butorphanol. Naloxone is also indicated for the diagnosis of suspected acute opioid overdose.

Naloxone is not effective in counteracting depression due to barbiturates, tranquilizers or other non-opioid anesthetics or sedatives. It has been safely administered to patients who received both opioid and non-opioid drugs.
CONTRAINDICATION

Naloxone is contraindicated in patients known to be hypersensitive to it.

WARNINGS

Naloxone should be administered cautiously to persons, including newborns of dependent mothers, who are known or suspected to be physically dependent on opioids. In such cases an abrupt and complete reversal of opioid effects may precipitate an acute abstinence syndrome. The severity of such a syndrome will depend on the degree of physical dependence and the dose of antagonist administered. In the presence of serious respiratory depression in a physically dependent individual, the antagonist, when indicated, should be administered with extreme care, under close monitoring, by using appropriate titration with smaller doses than usual.

The patient who has satisfactorily responded to naloxone should be kept under continued surveillance and repeated doses of naloxone should be administered as necessary since the duration of action of some opioids may exceed that of naloxone.

Naloxone is not effective against respiratory depression due to non-opioid drugs (see INDICATIONS AND CLINICAL USE). It has been safely administered to patients who received both opioid and non-opioid drugs. Reversal of buprenorphine-induced respiratory depression may be incomplete. If an incomplete response occurs, respiration should be mechanically assisted.

Use in Pregnancy
Reproduction studies performed in mice and rats at doses up to 1,000 times the human dose revealed no evidence of impaired fertility or harm to the fetus due to naloxone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, naloxone should be used during pregnancy only if clearly needed.

Nursing Mothers
It is not known whether naloxone is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when naloxone is administered to a nursing woman.

PRECAUTIONS

In addition to naloxone other resuscitative measures such as maintenance of a free airway, artificial ventilation, cardiac massage, and vasopressor agents should be available and employed when necessary to counteract acute opioid poisoning.
Several instances of hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been reported. These have occurred in postoperative patients in whom pre-existing cardiovascular disorders or other drugs may have contributed to the adverse cardiovascular effects.

Although a direct cause-and-effect relationship has not been established, naloxone should be used with caution in patients with preexisting cardiac disease or patients who have received potentially cardiotoxic drugs. The clinical course should be monitored by ECG.

**ADVERSE REACTIONS**

Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, and tremulousness. In postoperative patients, larger than necessary dosages of naloxone may result in significant reversal of analgesia and in excitement. Hypotension, hypertension, ventricular tachycardia and fibrillation, and pulmonary edema have been associated with the use of naloxone postoperatively (see PRECAUTIONS and USAGE IN ADULTS, Postoperative Opioid Depression). Seizures have been reported to occur infrequently after the administration of naloxone; however, a causal relationship has not been established.

**SYMPTOMS AND TREATMENT OF OVERDOSAGE**

There is no clinical experience with naloxone overdosage in humans.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

**DOSAGE AND ADMINISTRATION**

Naloxone hydrochloride may be administered intravenously (IV), intramuscularly (IM), or subcutaneously (SC). The most rapid onset of action is achieved by intravenous administration, and it is recommended in emergency situations.

Since the duration of action of some opioids may exceed that of naloxone, the patient should be kept under continued surveillance and repeated doses of naloxone should be administered, as necessary.

**Intravenous Infusion**

Infusion may be useful in cases of overdose with long-acting drugs such as methadone and propoxyphene. The infusion rate for adults is approximately 100 mL/hour.
Infusion rate and concentration should be individually adjusted to obtain the desired antagonist effect without fluid overload or production of withdrawal.

**Dilution for Intravenous Use**

Naloxone may be diluted for intravenous infusion in Sodium Chloride Injection 0.9% or Dextrose Injection 5%. The addition of 2 mg of Naloxone Hydrochloride Injection in 500 mL of diluent provides a concentration of 4 mcg (0.004 mg)/mL. Mixtures should be used within 24 hours. After 24 hours, the remaining unused solution must be discarded. The rate of administration should be titrated in accordance with the patient’s response.

Parenteral drug products should be inspected visually for particulate matter and discolouration prior to administration whenever solution and container permit. Naloxone should not be mixed with preparations containing bisulphite, metabisulphite, long-chain or high-molecular-weight anions, or any solution having an alkaline pH. No drug or chemical agent should be added to naloxone unless its effect on the chemical and physical stability of the solution has first been established.

**USAGE IN ADULTS**

**Opioid Overdose – Known or Suspected**

An initial dose of 0.4 mg to 2 mg of naloxone may be administered intravenously. If the desired degree of counteraction and improvement in respiratory functions is not obtained, it may be repeated at two- to three-minute intervals. If no response is observed after 10 mg of naloxone has been administered, the diagnosis of opioid-induced or partial opioid-induced toxicity should be questioned. Intramuscular or subcutaneous administration may be necessary if the intravenous route is not available.

**Postoperative Opioid Depression**

For the partial reversal of opioid depression following the use of opioids during surgery, smaller doses of naloxone are usually sufficient. The dose of naloxone should be titrated according to the patient’s response. Naloxone should be injected in increments of 0.1 to 0.2 mg intravenously at two- to three-minute intervals to the desired degree of reversal – i.e. adequate ventilation and alertness without significant pain or discomfort. Larger than necessary dosage of naloxone may result in significant reversal of analgesia and increase in blood pressure. Similarly, too rapid reversal may induce nausea, vomiting, sweating, or circulatory stress.

Repeat doses of naloxone may be required within one- to two-hour intervals depending upon the amount, type (i.e. short- or long-acting) and time interval since last administration of opioid. Supplemental intramuscular doses have been shown to produce a longer-lasting effect.

**USAGE IN CHILDREN**

**Opioid Overdose – Known or Suspected**

The usual initial dose in children is 0.01 mg/kg body weight given IV. If this dose does
not result in the desired degree of clinical improvement, a subsequent dose of 0.1 mg/kg body weight may be administered. If an IV route of administration is not available, naloxone may be administered IM or SC in divided doses. If necessary, naloxone can be diluted with sterile water for injection.

**Postoperative Opioid Depression**
Follow the recommendations and cautions under Adult Postoperative Opioid Depression. For the initial reversal of respiratory depression naloxone should be injected in increments of 0.005 mg to 0.01 mg intravenously at two- to three-minute intervals to the desired degree of reversal.

**Usage in Neonates**

**Opioid-Induced Depression**
The usual dose is 10 mcg (0.01 mg)/kg body weight administered IV, IM or SC routes. This dose may be repeated in accordance with adult administration guidelines.

<table>
<thead>
<tr>
<th>Summary of Dosages</th>
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<tbody>
<tr>
<td>Adults</td>
</tr>
<tr>
<td><strong>Opioid Overdose</strong></td>
</tr>
<tr>
<td>0.4 to 2 mg IV repeated if necessary at 2- to 3-minute intervals.</td>
</tr>
</tbody>
</table>

**Postoperative Opioid Depression**
0.1 to 0.2 mg IV repeated if necessary at 2- to 3-minute intervals.

IV, IM or SC.

<table>
<thead>
<tr>
<th>Children</th>
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</thead>
<tbody>
<tr>
<td><strong>Opioid Overdose</strong></td>
</tr>
<tr>
<td>0.01 mg/kg IV. If desired degree of improvement is not obtained, 0.1 mg/kg IV may be administered. Naloxone may be diluted with sterile water for injection.</td>
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</tbody>
</table>

**Postoperative Opioid Depression**
0.005 to 0.01 mg IV repeated if necessary at 2- to 3-minute intervals.

<table>
<thead>
<tr>
<th>Neonates</th>
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</thead>
<tbody>
<tr>
<td><strong>Opioid-Induced Depression</strong></td>
</tr>
<tr>
<td>0.01 mg/kg IV, IM or SC repeated if necessary at 2- to 3-minute intervals. Naloxone may be diluted with sterile water for injection.</td>
</tr>
</tbody>
</table>
PHARMACEUTICAL INFORMATION

DRUG SUBSTANCE

Common Name: Naloxone hydrochloride dihydrate

Chemical Name: 17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphine hydrochloride dihydrate

Structural Formula:

\[
\text{O} \quad \text{O} \quad \text{H} \\
\text{H} \quad \text{N} \quad \text{CH}_2 \\
\text{HO} \quad \text{HO} \quad \text{O} \quad \text{H} \\
, \text{HCl, 2 H}_2\text{O}
\]

Molecular Formula: \( \text{C}_{19}\text{H}_{21}\text{NO}_4, \text{HCl, 2H}_2\text{O} \)

Molecular Weight: 399.9 g/mol

Description: 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.

Naloxone hydrochloride occurs as a white to slightly off-white powder, and is soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol; practically insoluble in ether and in chloroform. It melts at about 200-205°C. The pH of aqueous solutions is acidic.
COMPOSITION

Naloxone Hydrochloride Injection SDZ Preservative Free (0.4 mg/mL): Each mL of aqueous injectable solution contains: naloxone hydrochloride 400 mcg, sodium chloride 9.0 mg, hydrochloric acid to adjust pH and water for injection.

STABILITY AND STORAGE RECOMMENDATIONS

Naloxone Hydrochloride Injection SDZ Preservative Free should be stored between 15 and 25°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Naloxone Hydrochloride Injection SDZ Preservative Free is available in 0.4 mg/mL, 1 mL ampoules, boxes of 10. Single use. Discard unused portion.

PHARMACOLOGY

Single subcutaneous doses of naloxone as high as 24 mg/70 kg (0.343 mg/kg) and multiple doses of 90 mg daily, for two weeks, administered to normal volunteers produced no behavioural or physiological changes, yet its antagonistic activity to subsequent morphine challenge persisted.

Naloxone hydrochloride at doses of 0.7 to 10 mg administered intravenously to heroin addicts abolished the effects of 10 to 20 mg of heroin whether administered before or after the heroin. The effects of the heroin began to recur three hours after naloxone administration, indicating naloxone has a shorter duration of action than heroin.

Naloxone was able to reverse the respiratory depression induced by various anesthetics: morphine, fentanyl, cyclopropane, pentazocine, meperidine, alphaprodine, oxymorphone, nalorphine and levallorphan in patients, whether administered IV, IM or SC at 0.4 to 2 mg/mL. Naloxone caused no respiratory depression, psychotomimetic effects, clinically significant circulatory effects, nor analgesia when administered alone. Subjects did not develop tolerance to naloxone. Temporary nausea and vomiting were reported in two studies, but as other anesthetics/analgesics were being administered concurrently, these effects could not be causally related to naloxone.

When naloxone is administered intravenously the onset of action is generally apparent within two minutes; the onset of action is only slightly less rapid when it is administered subcutaneously or intramuscularly. The duration of action is dependent upon the dose and route of administration. Intramuscular administration produces a more prolonged effect than
intravenous administration. The requirement for repeat doses will also be dependent upon the amount, type, and route of administration of the opioid being antagonized.

Following parenteral administration naloxone is rapidly distributed in the body. It is metabolized in the liver, primarily by glucuronide conjugation, and excreted in urine. In one study the mean serum half-life in adults was 4.7 minutes for the distribution phase and 64 minutes for the elimination phase. In a neonatal study the mean plasma half-life was observed to be 3.1 ± 0.5 hours.

In a nine-week study of nine males (22 to 47 years of age) who were addicted to opioids, naloxone was administered in single daily oral doses in increments of 50 mg (3 subjects), 100 mg (4 subjects) and 300 mg (2 subjects). Up to 3,000 mg of naloxone hydrochloride daily was administered (1 subject). No significant toxic symptoms occurred over nine weeks of naloxone administration. Sporadic abnormal laboratory findings including elevated white blood cell counts occurred, but are common in cases of opioid addiction. One patient receiving 1,500 mg of naloxone daily reported psychic depression, apathy and decreased appetite, which were relieved when the dosage was decreased.

**TOXICOLOGY**

**Acute Toxicity**
The maximum nontoxic subcutaneous dose in rats was 50 mg/kg.

In acute SC toxicity studies in newborn rats, the LD<sub>50</sub> is 260 mg/kg. Naloxone was only twice as toxic in newborn as in six week old rats. At toxic doses naloxone produced excitation, hyperactivity, salivation, tremors, and tonic-clonic convulsions. Respiration was slightly stimulated in rabbits as shown by the minute-volume measurements.

**Subacute Toxicity**
Subacute SC toxicity experiments in rats and monkeys and a subacute IV toxicity experiment in dogs demonstrated very little cumulative toxicity and no organic pathological changes.

**Reproduction and Teratology**
Reproduction studies in mice and rats using naloxone hydrochloride dosages up to 1,000 times the usual human dosage have not revealed evidence of impaired fertility or harm to the fetus.

**Mutagenicity and Carcinogenicity**
Mutagenicity and carcinogenicity studies have not been conducted using naloxone.
REFERENCES


PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

NALOXONE HYDROCHLORIDE NASAL SPRAY

2 mg/0.1 mL and 4 mg/0.1 mL

Opioid Antagonist

Adapt Pharma Operations Limited
45 Fitzwilliam Square
Dublin 2
Ireland

Date of Preparation:
October 3, 2016

Submission Control No: 193199
NALOXONE HYDROCHLORIDE NASAL SPRAY

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Dosage Form / Strength</th>
<th>Nonmedicinal Ingredients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intranasal</td>
<td>Solution for intranasal administration, 2 mg/0.1 mL (20 mg/mL) and 4 mg/0.1 mL (40 mg/mL)</td>
<td>Benzalkonium chloride, disodium ethylenediaminetetraacetate, sodium chloride, hydrochloric acid to adjust pH and purified water.</td>
</tr>
</tbody>
</table>

INDICATIONS AND CLINICAL USE

Naloxone Hydrochloride Nasal Spray is a pure opioid antagonist indicated for emergency use outside of a hospital to reverse known or suspected opioid overdose, as manifested by respiratory and/or severe central nervous system depression.

Naloxone Hydrochloride 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 the 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 Naloxone Hydrochloride 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 manoeuvres. Moreover, vasopressor agents should be employed (if available) whenever necessary if a health care professional is present.

Acute Opioid Withdrawal Syndrome
Naloxone Hydrochloride 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 Consideration
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). Naloxone Hydrochloride 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

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

- **Do not reuse Naloxone Hydrochloride Nasal Spray.** Each Naloxone Hydrochloride Nasal Spray device contains a single dose of naloxone and cannot be reused.

- Administer Naloxone Hydrochloride Nasal Spray in alternate nostrils with each dose.

- Administer Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray is supplied in:

- One carton containing 2 sprayer devices each providing a single 2 mg dose of naloxone hydrochloride in a 0.1 mL intranasal spray or;
- 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 Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray, administer an additional dose of naloxone every 2-3 minutes (if additional doses are available), using a new Naloxone Hydrochloride Nasal Spray device for each dose, until the desired response is obtained. If no response is obtained after 5 doses of the 4 mg Naloxone Hydrochloride Nasal Spray or 10 doses of the 2 mg Naloxone Hydrochloride 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 Naloxone Hydrochloride 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
Naloxone hydrochloride 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. Naloxone hydrochloride 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.

**Study Demographics and Trial Design**

<table>
<thead>
<tr>
<th>Study #</th>
<th>Trial design</th>
<th>Dosage, route of administration and duration</th>
<th>Study subjects (n = number)</th>
<th>Mean age (Range)</th>
<th>Gender</th>
</tr>
</thead>
</table>
| 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  
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 | n = 30                      | 35.9 years (22 - 55 years) | Female = 12  
Male = 18 |

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/m².

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.**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment A 2 mg - One Spray 20 mg/mL IN (N = 29)</th>
<th>Treatment B 4 mg - Two Sprays 20 mg/mL IN (N = 29)</th>
<th>Treatment C 4 mg - One Spray 40 mg/mL IN (N = 29)</th>
<th>Treatment D 8 mg - Two Sprays 40 mg/mL IN (N = 29)</th>
<th>Treatment E 0.4 mg IM (N = 29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\lambda_z$ (1/h)</td>
<td>0.382 (34.9)</td>
<td>0.310 (34.5)</td>
<td>0.334 (29.5)</td>
<td>0.330 (32.4)</td>
<td>0.557 (25.9)</td>
</tr>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>1.81 (34.9)</td>
<td>2.23 (34.5)</td>
<td>2.08 (29.5)</td>
<td>2.10 (32.4)</td>
<td>1.24 (25.9)</td>
</tr>
<tr>
<td>$t_{max}$ (h) $^a$</td>
<td>0.33 (0.25, 1.00)</td>
<td>0.33 (0.17, 0.57)</td>
<td>0.50 (0.17, 1.00)</td>
<td>0.33 (0.17, 1.00)</td>
<td>0.38 (0.08, 2.05)</td>
</tr>
<tr>
<td>$C_{max}$ (ng/mL)</td>
<td>2.92 (34.3)</td>
<td>6.20 (31.9)</td>
<td>4.83 (43.1)</td>
<td>9.70 (36.0)</td>
<td>0.877 (30.5)</td>
</tr>
<tr>
<td>$C_{max}$/Dose (ng/mL/mg)</td>
<td>1.46 (34.3)</td>
<td>1.55 (31.9)</td>
<td>1.21 (43.1)</td>
<td>1.21 (36.0)</td>
<td>2.19 (30.5)</td>
</tr>
<tr>
<td>$AUC_{0-t}$ (h*ng/mL)</td>
<td>4.51 (27.2)</td>
<td>9.32 (24.0)</td>
<td>7.87 (37.4)</td>
<td>15.3 (23.0)</td>
<td>1.72 (22.9)</td>
</tr>
<tr>
<td>$AUC_{0-t}$/Dose (h*ng/mL/mg)</td>
<td>2.25 (27.2)</td>
<td>2.33 (24.0)</td>
<td>1.97 (37.4)</td>
<td>1.91 (23.0)</td>
<td>4.29 (22.9)</td>
</tr>
<tr>
<td>$AUC_{0-inf}$ (h*ng/mL)</td>
<td>4.56 (26.9)</td>
<td>9.43 (24.0)</td>
<td>7.95 (37.3)</td>
<td>15.5 (22.7)</td>
<td>1.76 (22.6)</td>
</tr>
<tr>
<td>$AUC_{0-inf}$/Dose (h*ng/mL/mg)</td>
<td>2.28 (26.9)</td>
<td>2.36 (24.0)</td>
<td>1.99 (37.3)</td>
<td>1.93 (22.7)</td>
<td>4.40 (22.6)</td>
</tr>
<tr>
<td>AUC% Extrapolated (%)</td>
<td>1.06 (56.5)</td>
<td>0.935 (60.1)</td>
<td>0.965 (53.5)</td>
<td>0.963 (69.3)</td>
<td>2.18 (57.5)</td>
</tr>
<tr>
<td>CL/F (L/h)</td>
<td>438 (26.9)</td>
<td>424 (24.0)</td>
<td>503 (37.3)</td>
<td>518 (22.7)</td>
<td>227 (22.6)</td>
</tr>
<tr>
<td>Dose Normalized Relative BA (%) vs. IM</td>
<td>51.9 (21.7)</td>
<td>53.6 (22.5)</td>
<td>46.7 (31.4)$^b$</td>
<td>43.9 (23.8)</td>
<td>100</td>
</tr>
<tr>
<td>$C_{max}$/Dose Ratio (IN vs. IM) (%)</td>
<td>66.6 (41.4)</td>
<td>70.7 (37.7)</td>
<td>56.6 (47.5)$^b$</td>
<td>55.3 (41.4)</td>
<td>100</td>
</tr>
</tbody>
</table>

---

$a$: 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) 0-1h Following Intranasal Administration and Intramuscular Injection

(a)

(b)
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 $t_{\text{max}}$ 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 ($R_{\text{dnm}}$) of $C_{\text{max}}$ and AUC$_{0-\text{inf}}$. The $R_{\text{dnm}}$ value (90% confidence interval (CI)) value for $C_{\text{max}}$ was 0.831 (0.744-0.927); for AUC$_{0-\text{inf}}$, the $R_{\text{dnm}}$ value was 0.847 (0.786-0.912). Both $C_{\text{max}}$ and AUC$_{0-\text{inf}}$ increased slightly less dose proportionally, as indicated by $R_{\text{dnm}}$ 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$_{0-t}$ and AUC$_{0-\text{inf}}$ were within 80-125% for the GMR while the values for $C_{\text{max}}$ were 78.7 to 113%. 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 $t_{\text{max}}$ is approximately the same as injectable naloxone indicating that time to onset of action will be similar.

**STORAGE AND STABILITY**

Naloxone Hydrochloride Nasal Spray should be stored between 15°C to 25°C (excursions permitted up to 40°C), protected from light and in the blister and cartons provided. Do not freeze or leave Naloxone Hydrochloride Nasal Spray in a car during winter. As well, Naloxone Hydrochloride Nasal Spray should not be left in a car during hot summer days as the temperature can reach levels that will impair the integrity of naloxone.

If those situations occur, Naloxone Hydrochloride Nasal Spray may lose its effectiveness and should be replaced. The potentially impaired units of Naloxone Hydrochloride Nasal Spray device should only be discarded once a new blister of Naloxone Hydrochloride Nasal Spray devices is available. If Naloxone Hydrochloride Nasal Spray is needed and the potentially impaired unit of Naloxone Hydrochloride Nasal Spray was not replaced it should be used.
DOSAGE FORMS, COMPOSITION, AND PACKAGING

Naloxone Hydrochloride Nasal Spray 2 mg/0.1 mL:

Each sprayer containing 0.1 mL of aqueous solution for intranasal administration contains: 2 mg naloxone hydrochloride, benzalkonium chloride (preservative), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water.

Naloxone Hydrochloride 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), disodium ethylenediaminetetraacetate (stabilizer), sodium chloride, hydrochloric acid to adjust pH, and purified water.

Naloxone Hydrochloride Nasal Spray is available as:

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

Latex-Free: Naloxone Hydrochloride Nasal Spray is not made with dry natural rubber.
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Naloxone hydrochloride

Chemical name: Morphinan-6-one, 4,5-epoxy-3,14-dihydroxy-17-(2-propenyl)-, hydrochloride, (5 )-, dihydrate 17-Allyl-4,5 -epoxy-3,14- dihydroxymorphinan-6-one hydrochloride dihydrate

Molecular formula and molecular mass: \( C_{19}H_{21}NO_4\text{HCl,2H}_2O \), 399.87

Structural formula:

\[
\text{Naloxone Hydrochloride Nasal Spray Page 17 of 28}
\]

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:

<table>
<thead>
<tr>
<th>Appearance (color, physical form)</th>
<th>Naloxone hydrochloride is a white or off white powder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solubility</td>
<td>Soluble in water, in dilute acids, and in strong alkali; slightly soluble in alcohol, practically insoluble in ether and in chloroform.</td>
</tr>
</tbody>
</table>
| Melting range                     | 177°C to 180°C Naloxone  
|                                  | 200°C to 205°C Naloxone |
| Solution pH                       | The pH of an aqueous solution is in the range 2.5 to 3.5 |
| Specific Rotation                 | -170° to -181° |
CLINICAL TRIALS

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 LD50 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 LD50 of 260 mg/kg. In mice, the IV LD50 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 Sprays)) (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 Sprays) based on body surface area comparison).
REFERENCES


PART III: PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

Naloxone Hydrochloride Nasal Spray
2 mg and 4 mg

Read this carefully before administering Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray.

Serious Warnings and Precautions

- Before administering Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray. You may need to give additional doses of Naloxone Hydrochloride Nasal Spray until emergency medical help arrives.
- You may need to help the person who received Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 a fetus.

What is Naloxone Hydrochloride Nasal Spray used for?
Naloxone Hydrochloride Nasal Spray is used to treat someone who has overdosed on opioids. Naloxone Hydrochloride 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 Naloxone Hydrochloride 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. Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray?
Medicinal ingredient: naloxone hydrochloride

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

Naloxone Hydrochloride Nasal Spray comes in the following dosage forms:
Each Naloxone Hydrochloride Nasal Spray device contains either 2 mg or 4 mg in 0.1mL of solution.

Do not use Naloxone Hydrochloride Nasal Spray if:
- you are sure that the patient is allergic to naloxone hydrochloride or to any of the ingredients in Naloxone Hydrochloride Nasal Spray.

Warnings you should know about:

Non-opioid overdoses: Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 Naloxone Hydrochloride 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:

- Naloxone Hydrochloride Nasal Spray should be given with caution to a patient who may be or who is addicted to opioids.
- After receiving Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 Naloxone Hydrochloride Nasal Spray works. Examples of nasal problems include a blocked or runny nose or nasal polyps. If Naloxone Hydrochloride Nasal Spray is the only medication available to treat an opioid overdose, it should always be used.

Pregnant Women: Naloxone Hydrochloride Nasal Spray should only be used in pregnant women when clearly needed.

How to Administer Naloxone Hydrochloride Nasal Spray:

Important Points:

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

Dose:

- Naloxone Hydrochloride Nasal Spray is available as a 2 mg or 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 if opioid overdose and call for emergency medical help

- Check for signs of an opioid overdose:
  - person DOES NOT wake up after you shake their shoulders, shout their name or firmly rub the middle of their chest.
  - their breathing is very slow, irregular or has stopped.
  - the center part of their eye is very small, like a pinpoint.

- If an opioid overdose is known or suspected:
  - call 911 or ask someone to call for you
  - go to Step 2.

Step 2: Give Naloxone Hydrochloride Nasal Spray

- Remove Naloxone Hydrochloride Nasal Spray from the blister packaging.

- Lay the person on their back.
- Tilt their head back.
- Provide support under the neck with your hand.

- Hold Naloxone Hydrochloride Nasal Spray with your thumb on the bottom of the plunger and your first and middle fingers on either side of the nozzle.

- Gently insert the tip of the nozzle into one nostril. Make sure your fingers are right up against the nose.
  - If giving Naloxone Hydrochloride Nasal Spray to a child, make sure the nozzle seals the nostril

- Press the plunger firmly with your thumb to give the dose.
- Remove Naloxone Hydrochloride Nasal Spray from the nostril after giving the dose.
Step 3: Evaluate need for second dose and provide support

- Move the person on their side (recovery position).
- Watch the person closely.
- After 2-3 minutes, give another dose in the **other nostril** if the person DOES NOT:
  - wake up.
  - respond to touch or voice.
  - have normal breathing.
- If more Naloxone Hydrochloride Nasal Spray is available, give additional doses every 2-3 minutes until the person responds. Keep alternating nostrils after each dose. If you know how and if needed, perform artificial respiration or cardiac massage.

What are possible side effects from using Naloxone Hydrochloride Nasal Spray?

- Swelling in the nose
- Dryness in the nose
- Congested nose
- Runny nose
- Yawning
- Nervousness
- Pain
- Aggressive behaviors, 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 Naloxone Hydrochloride 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 help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**

- Online at [MedEffect](http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9
    Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect.

**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:

- Keep Naloxone Hydrochloride Nasal Spray in its box until ready to use.
- Store between 15°C to 25°C.
  - Naloxone Hydrochloride Nasal Spray may be stored for short periods up to 40°C.
  - Do not store Naloxone Hydrochloride Nasal Spray in the car on hot summer days.
  - Do not freeze or leave Naloxone Hydrochloride Nasal Spray in a car during the winter.
  - Naloxone Hydrochloride Nasal Spray may not be as effective if it is not stored properly. If Naloxone Hydrochloride Nasal Spray gets frozen or is stored at 40°C for long periods of time, you should replace it. Only discard the Naloxone Hydrochloride Nasal Spray once you have a replacement for it. If you don’t replace Naloxone Hydrochloride Nasal Spray before it is needed, it is better to use it, even if it hasn’t been stored properly.
- Store in a dark place and protect from light.
- Replace Naloxone Hydrochloride Nasal Spray before the expiration date on the box.
  - If only expired Naloxone Hydrochloride 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 Naloxone Hydrochloride 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer’s website www.adaptpharma.com or by calling 1-844-462-7226.

This leaflet was prepared by Adapt Pharma Operations Limited.

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