

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022569Orig1s000

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

Lazanda (Fentanyl) Nasal Spray CII

Initial U.S. Approval: 1968

WARNINGS: POTENTIAL FOR ABUSE and IMPORTANCE OF PROPER PATIENT SELECTION

See full prescribing information for complete boxed warning.

- Contains fentanyl, a Schedule II controlled substance with abuse liability similar to other opioid analgesics. [9.1]
- **Contraindicated** in opioid non-tolerant patients. [1, 4]
- Life-threatening respiratory depression could occur at any dose in patients not taking chronic opiates. [5.1]
- **Contraindicated in management of acute or postoperative pain.** [4]
- Do not substitute Lazanda for any other fentanyl products. [5.2]
- Contains fentanyl in an amount that can be fatal to a child. Keep out of reach of children and dispose of unneeded bottles properly. [5.9]
- Use with strong and moderate CYP 3A4 inhibitors may cause potentially fatal respiratory depression. [7]
- Lazanda is available only through a restricted program called the Lazanda REMS program. Healthcare professionals who prescribe to outpatients, pharmacies, and distributors are required to enroll in the program (5.10)

INDICATIONS AND USAGE

Lazanda is an opioid analgesic indicated only for the management of breakthrough pain in cancer patients, 18 years of age and older, who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. [1]

DOSAGE AND ADMINISTRATION

- Initial dose of Lazanda for all patients is 100 mcg. [2.1]
- Individually titrate to an effective dose, from 100 mcg to 200 mcg to 400 mcg, and up to a maximum of 800 mcg, that provides adequate analgesia with tolerable side effects. [2.1]
- Dose is a single spray into one nostril or a single spray into each nostril (2 sprays). [2.1]
- Maximum dose is a single spray into one nostril or single spray into each nostril per episode; no more than four doses per 24 hours [2.1]
- Wait at least 2 hours before treating another episode of breakthrough pain with Lazanda. [2.1]
- During any episode, if adequate pain relief *is not achieved* within 30 minutes, the patient may use a rescue medication as directed by their healthcare provider.[2]

DOSAGE FORMS AND STRENGTHS

- Nasal spray; each spray delivers 100 mcL of solution containing either 100 mcg or 400 mcg fentanyl base. [3] Supplied in a 5 mL bottle containing 8 sprays.

CONTRAINDICATIONS

- Opioid–non-tolerant patients. [4]
- Management of acute or postoperative pain including headache/migraine, dental pain, or use in the emergency department. [4]
- Intolerance or hypersensitivity to fentanyl, Lazanda, or its components. [4]

WARNINGS AND PRECAUTIONS

- Do not convert patients to Lazanda from other fentanyl products on a mcg per mcg basis, or substitute a Lazanda prescription for another fentanyl product, such substitution may result in fatal overdose. [5.1]
- Clinically significant respiratory and CNS depression can occur. Monitor patients accordingly. [5.2]
- Lazanda bottles contain medicine that can be fatal to a child. Ensure proper storage and disposal. [5.9, 16.1, 16.2]
- Use with other CNS depressants and potent CYP450 3A4 inhibitors may increase depressant effects including hypoventilation, hypotension, and profound sedation. Consider dosage adjustments if warranted. [5.2, 5.4]
- Titrate Lazanda cautiously in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to hypoventilation. [5.2, 5.6]
- Administer Lazanda with extreme caution in patients susceptible to intracranial effects of CO₂ retention. [5.7]

ADVERSE REACTIONS

- Most common adverse events during titration (frequency ≥5%): nausea, vomiting, and dizziness. [6.1]
- Most common adverse events during maintenance phase (frequency ≥5%): vomiting, nausea, pyrexia, and constipation. [6.1]

To report SUSPECTED ADVERSE REACTIONS, contact Archimedes Pharma at 1-866-435-6775 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Monitor patients who begin therapy with, or increase the dose of, inhibitors of CYP3A4 for signs of opioid toxicity. [7.1, 12]
- Monitor patients who stop therapy with, or decrease the dose of, inducers of CYP3A4 for signs of opioid toxicity. [7.1, 12]
- Carefully monitor patients taking vasoconstrictive nasal agents to treat allergic rhinitis for compromise in efficacy of co-administered Lazanda. [7.2, 8.8, 12]

USE IN SPECIFIC POPULATIONS

- Safety and efficacy below 18 years of age have not been established. [8.4]
- Administer Lazanda with caution to patients with renal or hepatic impairment. [8.6]
- See 17 for *Patient Counseling Information and Medication Guide*.

Revised: [6/2011]

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FULL PRESCRIBING INFORMATION

WARNINGS: POTENTIAL FOR ABUSE and IMPORTANCE OF PROPER PATIENT SELECTION

Lazanda contains fentanyl, an opioid agonist and a Schedule II controlled substance, with an abuse liability similar to other opioid analgesics. Lazanda can be abused in a manner similar to other opioid agonists, legal or illicit. Consider the potential for abuse when prescribing or dispensing Lazanda in situations where the physician or pharmacist is concerned about an increased risk of misuse, abuse or diversion. Schedule II opioid substances which include morphine, oxycodone, hydromorphone, oxymorphone, and methadone have the highest potential for abuse and risk of fatal overdose due to respiratory depression. Serious adverse events, including deaths, in patients treated with other oral transmucosal fentanyl products have been reported. Deaths occurred as a result of improper patient selection (e.g., use in opioid non-tolerant patients) and/or improper dosing. The substitution of Lazanda for any other fentanyl product may result in fatal overdose.

Lazanda is indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain. Patients considered opioid tolerant are those who are taking at least 60 mg of oral morphine/day, 25 mcg of transdermal fentanyl/hour, 30 mg of oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for one week or longer.

Lazanda is contraindicated in opioid non-tolerant patients and is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room. Life-threatening respiratory depression could occur at any dose in opioid non-tolerant patients. Deaths have occurred in opioid non-tolerant patients treated with other fentanyl products. When prescribing, do not convert patients on a mcg per mcg basis from another fentanyl product to Lazanda. Patients beginning treatment with Lazanda must begin with titration from the 100 mcg dose. (see *Dosage and Administration* [2])

When dispensing, do not substitute a Lazanda prescription for any other fentanyl product. Substantial differences exist in the pharmacokinetics of Lazanda compared to other fentanyl products that could result in clinically important differences in the rate and extent of absorption of fentanyl and could result in fatal overdose.

Special care must be used when dosing with Lazanda. If the breakthrough pain episode is not relieved, patients must wait at least 2 hours before taking another dose of Lazanda. (see *Dosage and Administration* [2])

Lazanda is intended to be used only in the care of opioid tolerant patients with cancer and only by healthcare professionals who are knowledgeable of, and skilled in, the use of Schedule II opioids to treat cancer pain.

Patients and their caregivers must be instructed that Lazanda contains a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant. Lazanda must be kept out of the reach of children at all times. (see *Patient/Caregiver Instructions* [17.1])

The concomitant use of Lazanda with cytochrome P450 3A4 inhibitors may result in an increase in fentanyl plasma concentrations, and may cause potentially fatal respiratory depression.

Because of the risk for misuse, abuse, addiction, and overdose, Lazanda is available only through a restricted program, required by the Food and Drug Administration, called the Lazanda REMS (Risk Evaluation and Mitigation Strategy) program. Under the Lazanda REMS program, healthcare professionals who prescribe to outpatients, outpatients, pharmacies, and distributors must enroll in the program to prescribe, receive, dispense, and distribute Lazanda, respectively. [see *Warnings and Precautions* (5.10)]. Further information is available at www.LazandaREMS.com or by calling 1-855-841-4234.

1 INDICATIONS AND USAGE

Lazanda (fentanyl) nasal spray is indicated only for the management of breakthrough pain in cancer patients 18 years of age and older who **are already receiving and who are tolerant to opioid therapy for their underlying persistent cancer pain**. Patients considered opioid tolerant are those who are taking at least: 60 mg of oral morphine/day, 25 mcg of transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

Lazanda is contraindicated for patients who are not already tolerant to opioids because life-threatening respiratory depression and death could occur in patients not taking chronic opioids. For this reason, Lazanda is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency department. [4]

Lazanda is intended to be prescribed only by healthcare professionals who are knowledgeable of and skilled in the use of Schedule II opioids to treat cancer pain and is to be supplied only through the Lazanda REMS program [see *Warnings and Precautions* (5.10)].

2 DOSAGE AND ADMINISTRATION

As with all opioids, the safety of patients using such products is dependent on healthcare professionals prescribing them in strict conformity with their approved labeling with respect to patient selection, dosing, and proper conditions for use. Healthcare professionals who prescribe Lazanda for outpatient use must enroll in the Lazanda REMS program [see *Warnings and Precautions* (5.10)].

Open the child-resistant container just prior to product use and **always replace the bottle in the child-resistant container between doses.**

2.1 Dose Titration

The goal of dose titration is to find the individual patient's effective and tolerable dose. The dose of Lazanda is not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and **MUST** be determined by dose titration.

Starting Dose: Individually titrate Lazanda to a dose that provides adequate analgesia with tolerable side effects. Begin treatment of **all** patients (including those switching from another fentanyl product) using ONE 100 mcg spray of Lazanda (1 spray in one nostril). Due to differences in pharmacokinetic properties and individual variability, do not switch patients on a mcg per mcg basis from any other fentanyl product to Lazanda as Lazanda is not equivalent with any other fentanyl product, nor is Lazanda a generic version of any other fentanyl product.

If adequate analgesia is obtained within 30 minutes of administration of the 100 mcg single spray, treat subsequent episodes of breakthrough pain with this dose.

Titration steps: If adequate analgesia *is not achieved* with the first 100 mcg, dose, dose escalate in a step-wise manner over consecutive episodes of breakthrough pain until adequate analgesia with tolerable side effects is achieved.

Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with Lazanda.

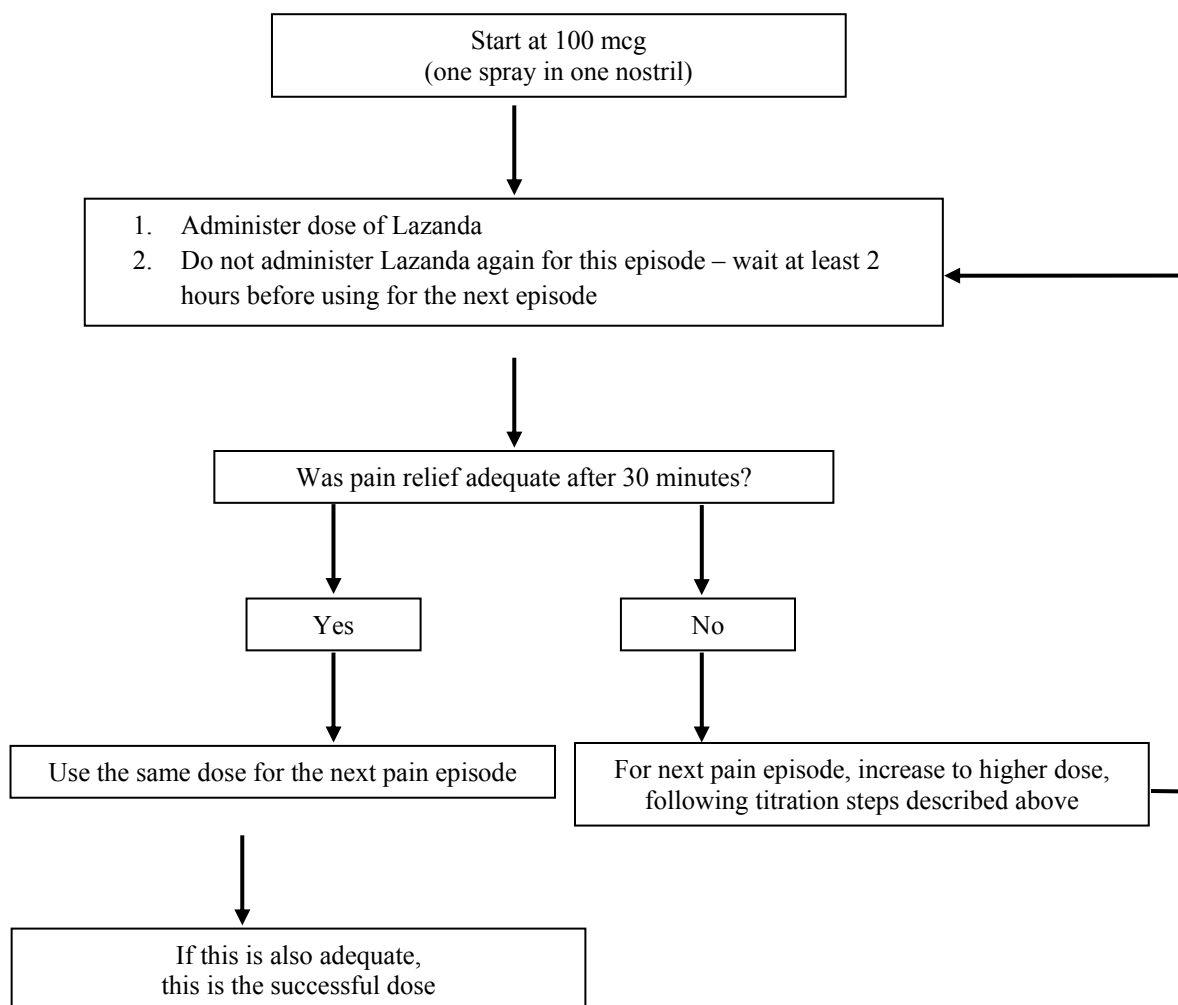
The titration steps should be:

- Lazanda Dose	- Using
- 100 mcg	- 1 x 100mcg spray
- 200 mcg	- 2 x 100 mcg spray (1 in each nostril)
- 400 mcg	- 1 x 400 mcg
- 800 mcg	- 2 x 400mcg (1 in each nostril)

Patients should confirm the dose of Lazanda that works for them with a second episode of breakthrough pain and review their experience with their physicians to determine if that dose is appropriate, or whether a further adjustment is warranted

The safety and efficacy of doses higher than 800 mcg have not been evaluated in clinical studies. There are no clinical data to support the use of a combination of dose strengths to treat an episode.

Lazanda TITRATION PROCESS



In order to minimize the risk of Lazanda-related adverse reactions and to identify the appropriate dose, it is imperative that patients be supervised closely by health professionals during the titration process.

2.2 Maintenance Treatment

Once an appropriate dose has been established, instruct patients to use that dose for each subsequent breakthrough cancer pain episode. Limit Lazanda use to four or fewer doses per day.

Patients MUST wait at least 2 hours before treating another episode of breakthrough cancer pain with Lazanda.

During any episode of breakthrough cancer pain, if there is inadequate pain relief after 30 minutes following Lazanda dosing or if a separate episode of breakthrough cancer pain occurs before the next dose of Lazanda is permitted (i.e. within 2 hours), the patients may use a rescue medication as directed by their healthcare provider.

2.3 Dose Re-Adjustment

If the response (analgesia or adverse reactions) to the titrated Lazanda dose markedly changes, an adjustment of dose may be necessary to ensure that an appropriate dose is maintained.

If more than four episodes of breakthrough pain are experienced per day, re-evaluate the dose of the long-acting opioid used for persistent underlying cancer pain. If the long-acting opioid or dose of long-acting opioid is changed, re-evaluate and re-titrate the Lazanda dose as necessary to ensure the patient is on an appropriate dose.

Limit the use of Lazanda to treat four or fewer episodes of breakthrough pain per day.

It is imperative that any dose re-titration is monitored carefully by a healthcare professional.

2.4 Administration of Lazanda

Instruct patients on the proper use of Lazanda.

1. Prime the device before use by spraying into the pouch (4 sprays in total) following the instructions for use in the *Medication Guide* [17.3]).
2. Insert the nozzle of the Lazanda bottle a short distance (about ½ inch or 1 cm) into the nose and point towards the bridge of the nose, tilting the bottle slightly.
3. Press down firmly on the finger grips until they hear a “click” and the number in the counting window advances by one.

Advise patients that the fine mist spray is not always felt on the nasal mucosal membrane and to rely on the audible click and the advancement of the dose counter to confirm a spray has been administered.

2.5 Discontinuation of Therapy

For patients no longer requiring opioid therapy, consider discontinuing Lazanda along with a gradual downward titration of other opioids to minimize possible withdrawal effects.

In patients who continue to take their chronic opioid therapy for persistent pain but no longer require treatment for breakthrough pain, Lazanda therapy can usually be discontinued immediately.

3 DOSAGE FORMS AND STRENGTHS

Nasal Spray, Lazanda is formulated to deliver a spray of 100 mcL of solution containing 100 mcg or 400 mcg fentanyl base.

4 CONTRAINDICATIONS

Lazanda is contraindicated in the management of pain in opioid non-tolerant patients, because life-threatening hypoventilation could occur at any dose in patients not already taking around-the-clock opioid therapy.

Patients considered opioid tolerant are those who are taking at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid for a week or longer.

Lazanda is contraindicated in the management of acute or postoperative pain, including headache/migraine, dental pain, or use in the emergency room.

Lazanda is contraindicated in patients with known intolerance or hypersensitivity to any of its components or the drug fentanyl. Anaphylaxis and hypersensitivity have been reported in association with the use of other oral transmucosal fentanyl products.

5 WARNINGS AND PRECAUTIONS

5.1 Lazanda and other Fentanyl Products

Lazanda is NOT equivalent to other fentanyl products used to treat breakthrough pain on a mcg per mcg basis. There are differences in the pharmacokinetics of Lazanda relative to other fentanyl products which could potentially result in clinically important differences in the amount of fentanyl absorbed and could result in a fatal overdose.

When prescribing Lazanda to a patient, DO NOT convert from other fentanyl products. Directions for safely converting patients to Lazanda from other fentanyl products are not currently available. (Note: This includes oral, transdermal, or parenteral formulations of fentanyl). Therefore, for opioid-tolerant patients starting treatment for breakthrough pain, the initial dose of Lazanda is 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects. [See *Dosage and Administration* (2.1)]

When dispensing Lazanda to a patient, DO NOT substitute it for any other fentanyl product prescription.

5.2 Respiratory Depression

Serious or fatal respiratory depression can occur even at recommended doses in patients using Lazanda. Respiratory depression is more likely to occur in patients with underlying respiratory disorders and elderly or debilitated patients, in opioid non-tolerant patients, or when opioids are given in conjunction with other drugs that depress respiration.

Respiratory depression from opioids is manifested by a reduced urge to breathe and a decreased rate of respiration, often associated with a “sighing” pattern of breathing (deep breaths separated by abnormally long pauses). Carbon dioxide retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids. This makes overdoses involving drugs with sedative properties and opioids especially dangerous.

5.3 Information for Patients and Their Caregivers

Patients and their caregivers must be instructed that Lazanda contains medicine in an amount that could be fatal to a child.

Patients and their caregivers must be instructed to keep both used and unused bottles in their child-resistant container and out of the reach of children at all times. Partially used bottles represent a special risk to children. As soon as they are no longer required, all used, unopened or partially used bottles must be completely emptied of accessible fentanyl solution by spraying the remaining contents into the carbon-lined pouch. The sealed pouch and the empty bottle should be put into the child-resistant container before discarding in the trash. Hands must be washed with soap and water immediately after handling the pouch. (see *Storage and Handling* [16.2], *Disposal of Lazanda* [16.3], and *Patient/Caregiver Instructions* [17.1])

Physicians and dispensing pharmacists must question patients and caregivers specifically about the presence of children in the home on a full-time or visiting basis and counsel accordingly regarding the dangers to children of inadvertent exposure to Lazanda.

Lazanda could be fatal to individuals for whom it is not prescribed and for those who are not opioid tolerant.

5.4 Additive CNS Depressant Effects

The concomitant use of Lazanda with other CNS depressants, including other opioids, sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, skeletal muscle relaxants, sedating antihistamines, and alcoholic beverages may produce increased depressant effects (e.g., hypoventilation, hypotension, and profound sedation). Concomitant use with potent inhibitors of cytochrome P450 3A4 isoform (e.g., erythromycin, ketoconazole, and certain protease inhibitors) may increase fentanyl levels, resulting in increased depressant effects [see *Drug Interactions* [7.1]].

Patients on concomitant CNS depressants must be monitored for a change in opioid effects and may require adjustment of the dose of Lazanda.

5.5 Effects on Ability to Drive and Use Machines

Opioid analgesics impair the mental and/or physical ability required for the performance of potentially dangerous tasks (e.g., driving a car or operating machinery). Warn patients taking Lazanda of these dangers and counsel them accordingly.

5.6 Chronic Pulmonary Disease

Because potent opioids can cause respiratory depression, cautiously adjust the dose of Lazanda in patients with chronic obstructive pulmonary disease or preexisting medical conditions predisposing them to respiratory depression. In such patients, even normal therapeutic doses of Lazanda may further decrease respiratory drive to the point of respiratory failure.

5.7 Head Injuries and Increased Intracranial Pressure

Administer Lazanda with extreme caution in patients who may be particularly susceptible to the intracranial effects of CO₂ retention, such as those with evidence of increased intracranial pressure or impaired consciousness. Opioids may obscure the clinical course of a patient with a head injury; only use opioids if clinically warranted.

5.8 Cardiac Disease

Intravenous fentanyl may produce bradycardia. Use Lazanda with caution in patients with bradyarrhythmias.

5.9 MAO Inhibitors

Lazanda is not recommended for use in patients who have received MAO inhibitors within 14 days, because severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. (see *Drug Interactions* [7.2]).

5.10 Lazanda REMS (Risk Evaluation and Mitigation Strategy) Program

Because of the risk for misuse, abuse, addiction, and overdose, Lazanda is available only through a restricted program called the Lazanda REMS program. Healthcare professionals who prescribe to outpatients, pharmacies and distributors must be enrolled in and comply with the Lazanda REMS program to prescribe, receive, dispense, and distribute Lazanda, respectively.

An overview of the requirements for prescribers, pharmacies, patients and distributors is included below.

- Healthcare professionals who prescribe Lazanda for outpatient use must review the prescriber educational materials, enroll in the Program, and commit to comply with the REMS requirements.
- To receive Lazanda, outpatients must understand the risks and benefits of the drug and sign a Patient-Prescriber Agreement with their healthcare provider; outpatients will be enrolled by the pharmacy at the time their first prescription is filled.
- Outpatient pharmacies that dispense Lazanda for outpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements.
- Inpatient pharmacies that dispense Lazanda for inpatient use must enroll in the Program, train their pharmacy staff on the REMS requirements, and agree to comply with the REMS requirements.
- Wholesalers and distributors that distribute Lazanda must enroll in the Program and commit to distributing only to authorized enrolled pharmacies.

To learn more about the specific REMS requirements and to enroll in the Lazanda REMS program call 1-855-841-4234 or visit www.LazandaREMS.com.

6 ADVERSE REACTIONS

The following serious adverse reactions described elsewhere in the labeling include:

Respiratory Depression [see Warnings and Precautions (5.2, 5.6)]

CNS Depression [see Warnings and Precautions (5.4)]

Increased Intracranial Pressure [see Warnings and Precautions (5.7)]

Bradycardia [see Warnings and Precautions (5.8)]

6.1 Clinical Studies Experience

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

The safety of Lazanda has been evaluated in a total of 523 opioid-tolerant patients with breakthrough cancer pain. The average duration of therapy in patients in the long-term study was 73 days, with 153 patients being treated for over 3 months. Patients continuing into the open-label extension period of the safety study have been treated for up to 26 months.

The most commonly observed adverse events seen with Lazanda are typical of opioid side effects, such as nausea, constipation, somnolence, and headache. Expect opioid side effects and manage them accordingly.

The clinical trials of Lazanda were designed to evaluate safety and efficacy in treating breakthrough cancer pain; all patients were also taking concomitant opioids, such as sustained-release morphine, sustained-release oxycodone, or transdermal fentanyl, for their persistent cancer pain. The adverse reaction data presented in Table 1 reflect the actual percentage of patients experiencing each adverse effect among patients who received Lazanda for breakthrough cancer pain along with a concomitant opioid for persistent cancer pain. There has been no attempt to correct for concomitant use of other opioids, duration of Lazanda therapy, or cancer-related symptoms. Adverse events are included regardless of causality or severity. Table 1 lists adverse reactions with an overall frequency of 5% or greater within the total population that occurred during titration by maximum dose received. The ability to assign Lazanda a dose-response relationship to these adverse events is limited by the titration schemes used in these studies.

Table 1: Adverse Reactions That Occurred During Titration at a Frequency of $\geq 5\%$

System Organ Class MedRA preferred term, n (%)	100 mcg (N=483)	200 mcg (N=380)	400 mcg (N=301)	800 mcg (N=161)	Total (N=516)
Gastrointestinal disorders					
Nausea	19 (4)	6 (2)	6 (2)	5 (3)	35 (7)
Vomiting	14 (3)	10 (3)	9 (3)	1 (1)	33 (6)
Nervous system disorders					
Dizziness	14 (3)	11 (3)	6 (2)	4 (2)	31 (6)

Table 2 lists, by dose, adverse reactions with an overall frequency of $\geq 5\%$ within the total population that occurred after a final titrated dose had been determined.

Table 2: Adverse Reactions That Occurred During Maintenance Treatment at a Frequency of $\geq 5\%$

System Organ Class MedDRA preferred term, n (%)	100 mcg (N=61)	200 mcg (N=68)	400 mcg (N=109)	800 mcg (N=108)	Total (N=346)
Gastrointestinal disorders					
Vomiting	8 (13)	5 (7)	9 (8)	12 (11)	34 (10)
Nausea	4 (7)	6 (9)	4 (4)	9 (8)	23 (7)
Constipation	6(10)	1(1)	8(7)	5(5)	20(6)
General disorders and administration site conditions					
Pyrexia	3 (5)	5 (7)	8 (7)	6 (6)	22 (6)

The adverse reactions listed below represent those that occurred in $\geq 1\%$ of patients from clinical trials while receiving Lazanda. Events are classified by system organ class.

Adverse Events ($\geq 1\%$)

Eye disorders: dry eye, swelling, ptosis, strabismus

Blood and Lymphatic System Disorders: anemia, neutropenia

Cardiac Disorders: cardiorespiratory arrest

Gastrointestinal Disorders: vomiting, nausea, constipation, diarrhea, abdominal pain, gastritis, ascites, dry mouth, dyspepsia, mouth ulcer, proctalgia

General Disorders and Administration Site Conditions: pyrexia, fatigue, edema peripheral, asthenia, edema

Hepatobiliary Disorders: jaundice

Immune System Disorders: hypersensitivity

Infections and Infestations: urinary tract infection, pneumonia, nasopharyngitis, infection, rhinitis, upper respiratory tract infection, bronchitis

Injury, Poisoning and Procedural Complications: fall

Investigations: weight decreased, blood alkaline phosphatase increased

Metabolism and Nutrition Disorders: dehydration, decreased appetite, hyperglycemia, anorexia

Musculoskeletal and Connective Tissue Disorders: back pain, pain in extremity, arthralgia

Nervous System Disorders: dizziness, somnolence, headache, dysgeusia

Psychiatric Disorders: anxiety, insomnia, depression, confusional state, disorientation, agitation

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, cough, pharyngolaryngeal pain, nasal discomfort, rhinorrhea, nasal congestion, postnasal drip, pulmonary embolism

Skin and Subcutaneous Tissue Disorders: pruritus, hyperhidrosis, decubitus ulcer, mouth ulceration

Vascular Disorders: hypertension, deep vein thrombosis,

7 DRUG INTERACTIONS

7.1 Metabolic Drug Interactions

Fentanyl is metabolized mainly via the human cytochrome P450 3A4 isoenzyme system (CYP3A4); therefore potential interactions may occur when Lazanda is given concurrently with agents that affect CYP3A4 activity.

CYP3A4 inhibitors

The concomitant use of Lazanda with CYP3A4 inhibitors (e.g., indinavir, nelfinavir, ritonavir, clarithromycin, itraconazole, ketoconazole, nefazodone, saquinavir, telithromycin, aprepitant, diltiazem, erythromycin, fluconazole, grapefruit juice, verapamil, or cimetidine) may result in a potentially dangerous increase in fentanyl plasma concentrations, which could increase or prolong adverse drug effects and may cause potentially fatal respiratory depression. Patients receiving Lazanda who begin therapy with, or increase the dose of, CYP3A4 inhibitors are to be carefully monitored for signs of opioid toxicity over an extended period of time. Increase dose conservatively [see *Warnings and Precautions* (5.4)].

CYP3A4 inducers

The concomitant use of Lazanda with CYP3A4 inducers (e.g., barbiturates, carbamazepine, efavirenz, glucocorticoids, modafinil, nevirapine, oxcarbazepine, phenobarbital, phenytoin, pioglitazone, rifabutin, rifampin, St. John's wort, or troglitazone) may result in a decrease in fentanyl plasma concentrations, which could decrease the efficacy of Lazanda. Patients receiving Lazanda who stop therapy with, or decrease the dose of, CYP3A4 inducers may experience sudden increase in fentanyl plasma concentrations and are to be monitored for signs of increased Lazanda activity. Adjust the dose of Lazanda accordingly.

7.2 Non-metabolic Drug Interactions

Agents used to treat Allergic Rhinitis

The presence of allergic rhinitis is not expected to affect Lazanda absorption. However, co-administration of a vasoconstrictive nasal decongestant such as oxymetazoline to treat allergic rhinitis leads to lower peak plasma concentrations and a delayed Tmax of fentanyl that may cause Lazanda to be less effective in patients with allergic rhinitis who use such decongestants, thus potentially impairing pain management. Additionally, in view of the possibility that the titration of a patient while they are experiencing an acute episode of rhinitis could lead to incorrect dose identification (particularly if they are using a vasoconstrictive decongestant), titration under these circumstances must be avoided (see *Clinical Pharmacology* [12.3])

MAO inhibitor

Concomitant use of Lazanda with an MAO inhibitor, or within 14 days of discontinuing an MAO inhibitor, is not recommended.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy – Category C

There are no adequate and well-controlled studies in pregnant women.

Use Lazanda during pregnancy only if the potential benefit justifies the potential risk to the fetus. No epidemiological studies of congenital anomalies in infants born to women treated with fentanyl during pregnancy have been reported.

Chronic maternal treatment with fentanyl during pregnancy has been associated with transient respiratory depression, behavioral changes, or seizures in newborn infants characteristic of neonatal abstinence syndrome.

In women treated acutely with intravenous or epidural fentanyl during labor, symptoms of neonatal respiratory or neurological depression were no more frequent than would be expected in infants of untreated mothers.

Transient neonatal muscular rigidity has been observed in infants whose mothers were treated with intravenous fentanyl.

Fentanyl is embryocidal in rats as evidenced by increased resorptions in pregnant rats at doses of 30 mcg/kg IV or 160 mcg/kg SC. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for Lazanda.

Fentanyl citrate was not teratogenic when administered to pregnant animals. Published studies demonstrated that administration of fentanyl (10, 100, or 500 mcg/kg/day) to pregnant rats from day 7 to 21 of their 21 day gestation, via implanted microosmotic minipumps was not teratogenic. The high dose was approximately 3-times the human dose of 800 mcg per pain episode on a mg/m² basis. Intravenous administration of fentanyl (10 or 30 mcg/kg) to pregnant female rats from gestation days 6 to 18 was embryo or fetal toxic and caused a slightly increased mean delivery time in the 30 mcg/kg/day group, but it was not teratogenic.

8.2 Labor and Delivery

Fentanyl readily passes across the placenta. Therefore do not use Lazanda during labor and delivery (including caesarean section) since it may cause respiratory depression in the fetus or in the newborn infant.

8.3 Nursing Mothers

Fentanyl is excreted in human milk; therefore, do not use Lazanda in women who are nursing because of the risk of sedation and/or respiratory depression in their infants. Symptoms of opioid withdrawal may occur in infants upon cessation of nursing by women using Lazanda.

8.4 Pediatric Use

The safety and efficacy of Lazanda have not been established in patients below the age of 18 years.

8.5 Geriatric Use

Of the 523 opioid tolerant cancer patients with breakthrough cancer pain in clinical studies of Lazanda, 148 (28%) were aged 60 years and over. No clinically meaningful difference was noted in the safety profile of the group aged over 60 years versus that of younger patients in Lazanda clinical trials.

Elderly patients have been shown to be more sensitive to the effects of fentanyl when administered intravenously compared with the younger population. Therefore, exercise caution when individually titrating Lazanda in elderly patients.

8.6 Patients with Renal or Hepatic Impairment

Insufficient information exists to make recommendations regarding the use of Lazanda in patients with impaired renal or hepatic function. Fentanyl is metabolized primarily via the human CYP3A4 isoenzyme system and the inactive metabolite is mostly

eliminated in urine. If the drug is used in these patients, it is to be used with caution because of the hepatic metabolism and renal excretion of fentanyl.

It is recommended that Lazanda be titrated to clinical effect for all patients with special care taken in patients with severe renal or hepatic disease.

8.7 Gender

Both male and female opioid-tolerant cancer patients were studied for the treatment of breakthrough cancer pain. No clinically relevant gender differences were observed in adverse events.

8.8 Patients with Allergic (Seasonal) Rhinitis

The pharmacokinetic and safety profiles of Lazanda in individuals with known allergic (seasonal) rhinitis showed no clinically meaningful differences in rate or extent of exposure to fentanyl, or in local tolerability of Lazanda when compared to Asymptomatic (Unchallenged) state. However, when treated for their rhinitis with oxymetazoline, Lazanda absorption was compromised (see *Pharmacokinetics* [12.3]).

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Lazanda contains fentanyl, which is a Schedule II controlled substance. Schedule II substances such as fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone have a high potential for abuse and addiction. Lazanda may be subject to misuse and criminal diversion.

9.2 Abuse and Addiction

Manage the handling of Lazanda to minimize the risk of abuse, including restriction of access and accounting procedures as appropriate to the clinical setting and as required by law [*see How Supplied/Storage and Handling (16.1, 16.2)*].

Concerns about abuse and addiction should not prevent the proper management of pain. However, all patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over drug use, compulsive use, continued use despite harm, and craving. Drug addiction is a treatable disease, utilizing a multidisciplinary approach, but relapse is common. “Drug-seeking” behavior is very common in addicts and drug abusers.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of addiction and is characterized by misuse for nonmedical purposes, often in combination with other psychoactive substances. Since Lazanda may be abused or diverted for nonmedical use, careful record keeping of prescribing information, including quantity, frequency, and renewal requests, is strongly advised.

Proper assessment of patients, proper prescribing practices, periodic reevaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Contact your State Professional Licensing Board or State Controlled Substances Authority for information on how to prevent and detect abuse or diversion of this product.

9.3 Dependence

Physical dependence is not ordinarily a concern when treating a patient with cancer and chronic pain, and fear of tolerance and physical dependence should not deter using doses that adequately relieve the pain.

Opioid analgesics may cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity, e.g., naloxone, nalmefene, or mixed agonist/antagonist analgesics (e.g., pentazocine, butorphanol, buprenorphine, nalbuphine).

Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued opioid usage. Tolerance, in which increasingly larger doses are required in order to produce the same degree of analgesia, initially manifests as a shortened duration of analgesic effect, and subsequently as decreases in the intensity of analgesia.

10 OVERDOSAGE

10.1 Clinical Presentation

The manifestations of overdose with Lazanda are expected to be similar to those for intravenous fentanyl and other opioids, and are an extension of its pharmacological actions, with the most serious significant adverse effect being hypoventilation. (see *Clinical Pharmacology* (12))

10.2 Immediate Management

Immediate management of opioid overdose includes removal of the Lazanda pectin gel, if still in the nostril, ensuring a patent airway, physical and verbal stimulation of the patient, and assessment of level of consciousness, ventilatory status, and circulatory status.

10.3 Treatment of Overdosage (Accidental Ingestion) in Opioid Non-Tolerant Patients

Provide ventilatory support, obtain intravenous access, and administer naloxone or other opioid antagonists as clinically indicated. The duration of respiratory depression following overdose may be longer than the effects of the opioid antagonist's action (e.g., the half-life of naloxone ranges from 30 to 81 minutes) and repeated administration may be necessary. Consult the package insert of the individual opioid antagonist for details about such use.

10.4 Treatment of Overdose in Opioid-Tolerant Patients

Provide ventilatory support and obtain intravenous access as clinically indicated. Judicious use of naloxone or another opioid antagonist may be warranted in some instances, but it is associated with the risk of precipitating an acute withdrawal syndrome.

10.5 General Considerations for Overdose

Management of severe Lazanda overdose includes: securing a patent airway, assisting or controlling ventilation, and establishing intravenous access. In the presence of hypoventilation or apnea, assist or control ventilation, and administer oxygen as indicated.

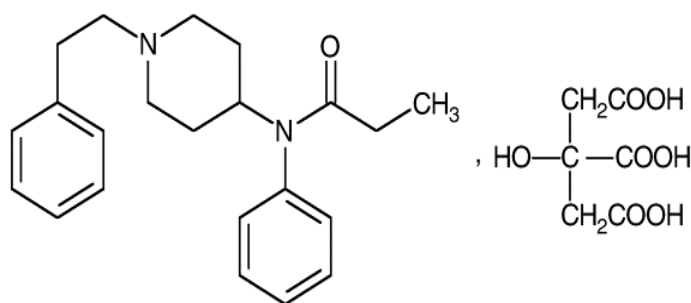
Carefully observe and appropriately manage overdosed patients until their clinical condition is well controlled.

Although muscle rigidity interfering with respiration has not been observed following the use of Lazanda, this is possible with fentanyl and other opioids. If it occurs, manage by the use of assisted or controlled ventilation, by administration of an opioid antagonist, and, as a final alternative, by the administration of a neuromuscular blocking agent.

11 DESCRIPTION

Lazanda (fentanyl) nasal spray is a liquid formulation of fentanyl citrate intended for intranasal transmucosal administration. The product consists of a practically clear to clear, colorless, aqueous solution of fentanyl citrate in a glass multidose container to which is attached a metered-dose nasal spray pump with a visual and audible spray counter. Each actuation is designed to deliver a spray of 100 mcL of solution containing 100 mcg or 400 mcg fentanyl base, respectively. This enables doses of 100 mcg or 400 mcg to be administered using a single spray into one nostril (1 spray) and 200 mcg or 800 mcg to be administered using a single spray into both nostrils (2 sprays).

Active ingredient: Fentanyl citrate, USP is N-(1-phenethyl-4-piperidyl) propionanilide citrate (1:1). Fentanyl is a highly lipophilic compound (octanol-water partition coefficient at pH 7.4 is 816:1). Fentanyl citrate is sparingly soluble in water (1:40). The molecular weight of the free base and citrate salt are 336.5 and 528.6, respectively. The pKa is 8.4. The compound has the following structural formula:



Lazanda is available in 2 strengths of nasal spray: 100 mcg fentanyl (yellow label) and 400 mcg fentanyl (violet label). The strength is expressed as the amount of fentanyl free base per spray, e.g., the 100 mcg strength provides 100 mcg of fentanyl free base per 100 mL spray.

Inactive ingredients: mannitol, pectin, phenylethyl alcohol, propylparaben, sucrose, water. Sodium hydroxide and/or hydrochloric acid are added if required for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Fentanyl is a pure opioid agonist whose principal therapeutic action is analgesia. Other members of the class known as opioid agonists include substances such as morphine, oxycodone, hydromorphone, codeine, and hydrocodone.

12.2 Pharmacodynamics

Pharmacological effects of opioid agonists include anxiolysis, euphoria, feelings of relaxation, respiratory depression, constipation, miosis, cough suppression, and analgesia. Like all pure opioid agonist analgesics, with increasing doses there is increasing analgesia, unlike with mixed agonist/antagonists or non-opioid analgesics, where there is a limit to the analgesic effect with increasing doses. With pure opioid agonist analgesics, there is no defined maximum dose; the ceiling to analgesic effectiveness is imposed only by side effects, the more serious of which may include somnolence, respiratory depression and death.

Analgesia: In general, the effective concentration and the concentration at which toxicity occurs increase with increasing tolerance to any and all opioids.

The rate of development of tolerance varies widely among individuals. As a result, individually titrate the dose of Lazanda to achieve the desired effect. (see *Dosage and Administration* [2])

Central Nervous System: The precise mechanism of the analgesic action is unknown although fentanyl is known to be a *mu*-opioid receptor agonist. Specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Fentanyl produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem to increases in carbon dioxide and to electrical stimulation.

Fentanyl causes miosis even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origin may produce similar findings).

Gastrointestinal System: Fentanyl causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and in the duodenum. Digestion of food is delayed in the small intestine and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of the sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System: Fentanyl may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System: Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species (e.g., rats and dogs). Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Respiratory System: All opioid *mu*-receptor agonists, including fentanyl, produce dose-dependent respiratory depression. The risk of respiratory depression is less in patients receiving chronic opioid therapy who develop tolerance to respiratory depression and other opioid effects.

Serious or fatal respiratory depression can occur even at recommended doses. Fentanyl depresses the cough reflex as a result of its CNS activity. Although not observed with Lazanda, in clinical trials, fentanyl given rapidly by intravenous injection in large doses has interfered with respiration by causing rigidity in the muscles of respiration. Physicians and other healthcare providers should be aware of this potential complication. (see *Boxed Warning*, *Contraindications* [4], *Warnings and Precautions* [5], *Adverse Reactions* [6], and *Overdosage* [10] for additional information on hypoventilation)

12.3 Pharmacokinetics

Absorption: In a study that compared the relative bioavailability of Lazanda and an oral transmucosal fentanyl citrate product, the bioavailability of fentanyl from Lazanda was approximately 20% higher. Fentanyl is absorbed from the nasal mucosa following

intranasal administration of Lazanda, with median T_{max} values ranging from 15-21 min after administration of a single dose. C_{max} and AUC values for fentanyl following administration of Lazanda increase linearly over the 100- to 800-mcg dose range.

Mean plasma concentration versus time profiles are presented in Figure 1. Mean pharmacokinetic parameters are presented in Table 3.

Figure 1.
Mean Plasma Fentanyl Concentration (pg/mL) in Normal Subjects Receiving 100, 200, 400 and 800 mcg Lazanda or 200 mcg OTFC

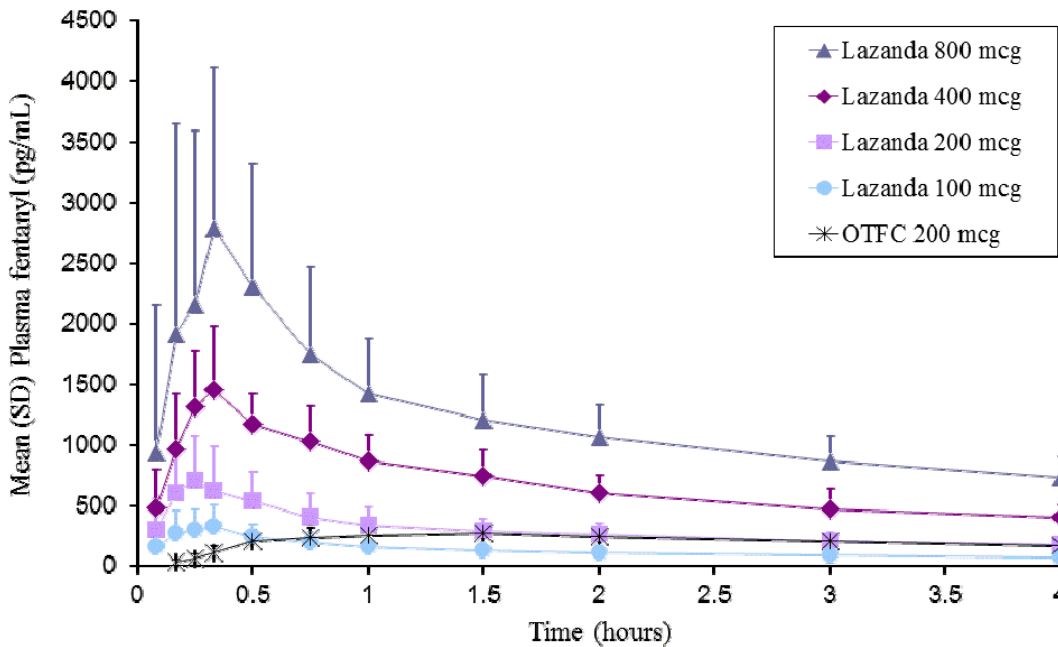


Table 3.

Pharmacokinetic Parameters in Normal Subjects Receiving 100, 200, 400, and 800 mcg of Lazanda or 200 mcg OTFC

PHARMACOKINETIC PARAMETERS	Lazanda				OTFC
	100 mcg	200 mcg	400 mcg	800 mcg	200 mcg
T_{max} , hours median (range)	0.33 (0.08–1.50)	0.25 (0.17–1.60)	0.35 (0.25–0.75)	0.34 (0.17–3.00)	1.50 (0.50–8.00)
C_{max} , pg/mL Mean (%CV)	351.5 (51.3)	780.8 (48.4)	1552.1 (26.2)	2844.0 (56.0)	317.4 (29.9)
AUC_{inf} , pg.hour/mL Mean (%CV)	2460.5 (17.9)	4359.9 (29.8)	7513.4 (26.7)	17272 (48.9)	3735.0 (32.8)
$t_{1/2}$, hour Mean (%CV)	21.9 (13.6)	24.9 (51.3)	15.0 (24.7)	24.9 (92.5)	18.6 (31.4)

In a pharmacokinetic study that evaluated multiple-dose pharmacokinetics of Lazanda when two doses of Lazanda are administered in the same nostril and are separated by a 1, 2 or 4 h time lapse, C_{max2} (C_{max} after second administration) was greater than C_{max1} (C_{max} after first administration), by 30% when Lazanda was administered 1 h apart, by 25% when Lazanda was administered 2 h apart and by 10% when Lazanda was administered 4 h apart. Based on these results and based on T_{max} range of Lazanda observed across pharmacokinetic studies, and frequency of breakthrough pain episodes in a cancer population, a waiting period of 2 h between two consecutive doses of Lazanda is recommended (see *Dosage and Administration* [2]).

In a pharmacokinetic study to evaluate differences in Lazanda absorption in individuals with induced allergic (seasonal) rhinitis, no clinically meaningful differences were observed in rate or extent of exposure to fentanyl, when compared to the Asymptomatic (Unchallenged) state, indicating that presence of allergic rhinitis does not affect Lazanda absorption. This study also assessed

differences in Lazanda absorption, if any, when co-administered with oxymetazoline, a nasal decongestant in subjects undergoing treatment for seasonal allergic rhinitis. Mean C_{\max} values for Treated arm (Rhinitis treated with oxymetazoline) were about 32% and 40% lower and mean AUC_t values were about 10% and 17% lower for Ragweed and Tree pollen induced cohorts respectively as compared to the Asymptomatic arm in each cohort. In addition, mean T_{\max} of Lazanda in the Treated arm was 0.75 h (range 0.08-3 h) for the Ragweed pollen induced cohort and 1.25 h (range 0.08-3 h) for Tree pollen induced cohort as compared to 0.25 h (0.17-1 h) and 0.33 h (0.17-2 h) for the Asymptomatic arm in each cohort respectively. These results indicate that co-administration with oxymetazoline leads to lower peak plasma concentrations and delayed T_{\max} of Lazanda (see *Drug Interactions* [7.2]).

Distribution: Fentanyl is highly lipophilic. The plasma protein binding of fentanyl is 80% to 85%. The main binding protein is alpha-1-acid glycoprotein, but both albumin and lipoproteins contribute to some extent. The mean volume of distribution at steady state (V_{ss}) was 4 L/kg.

Metabolism: The metabolic pathways following intranasal administration of Lazanda have not been characterized in clinical studies. The progressive decline of fentanyl plasma concentrations results from the uptake of fentanyl in the tissues and biotransformation in the liver. Fentanyl is metabolized in the liver and in the intestinal mucosa to norfentanyl by cytochrome P450 3A4 isoform. In animal studies, norfentanyl was not found to be pharmacologically active.

Elimination: The disposition of fentanyl following intranasal administration of Lazanda has not been characterized in a mass balance study. Fentanyl is primarily (more than 90%) eliminated by biotransformation to N-dealkylated and hydroxylated inactive metabolites. Less than 7% of the administered dose is excreted unchanged in the urine, and only about 1% is excreted unchanged in the feces. The metabolites are mainly excreted in the urine, while fecal excretion is less important.

The total plasma clearance of fentanyl following intravenous administration is approximately 42 L/h.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate the carcinogenic potential of fentanyl.

Fentanyl citrate was not mutagenic in the *in vitro* Ames reverse mutation assay in *S. typhimurium* or *E. coli*, or the mouse lymphoma mutagenesis assay, and was not clastogenic in the *in vivo* mouse micronucleus assay.

Fentanyl has been shown to impair fertility in rats at doses of 30 mcg/kg subcutaneously. Conversion to human equivalent doses indicates this is within the range of the human recommended dosing for Lazanda.

14 CLINICAL STUDIES

The efficacy of Lazanda was evaluated in one clinical trial in opioid tolerant adult patients experiencing breakthrough cancer pain. Breakthrough cancer pain was defined as a transient flare of moderate-to-severe pain occurring in patients experiencing persistent cancer pain otherwise controlled with maintenance doses of opioid medications including at least 60 mg of oral morphine/day or an equianalgesic dose of another opioid (which could be fentanyl) for a week or longer. All patients were on stable doses of either long-acting oral opioids or transdermal fentanyl for their persistent cancer pain.

The clinical trial included an open-label titration phase where a dose was identified that provided adequate analgesia with tolerable side effects, within the range of 100 to 800 mcg. In the double-blind, placebo-controlled portion of the study, patients who were titrated to an adequate dose were randomized to a blinded sequence of 10 treatments with 7 being the identified dose of Lazanda and 3 being placebo.

Of the patients who enrolled in the study, 73% achieved an adequate dose during the titration phase, 6% withdrew for lack of effective pain relief, and 5% withdrew due to adverse events.

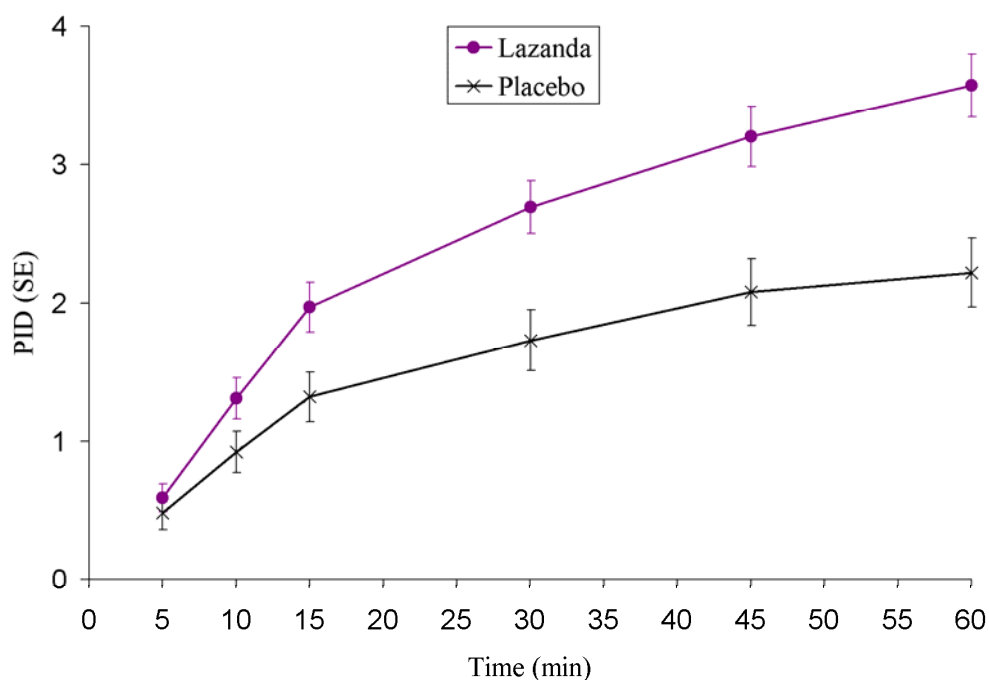
The distribution of final titrated doses is shown in Table 4. The final titrated dose of Lazanda for breakthrough pain was not predicted from the daily maintenance dose of opioid used to manage the persistent cancer pain and, therefore, the dose was determined by titration starting at 100 mcg.

Table 4. Dose of Lazanda Following Initial Titration (ITT population)

Lazanda Dose	(N=83) n (%)
100 mcg	12 (14)
200 mcg	7 (8)
400 mcg	27 (33)
800 mcg	37 (45)

The primary outcome measure, the mean sum of the pain intensity difference at 30 minutes (SPID30), was statistically significantly higher for Lazanda than for placebo (see Figure 2).

Figure 2. Pain Intensity Differences (PID) following Lazanda or Placebo in Adult Patients with Breakthrough Cancer Pain



16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 Lazanda REMS Program

Lazanda can only be dispensed from a pharmacy that is enrolled in the Lazanda REMS program. For a list of pharmacies that are enrolled in the Lazanda REMS program, and information on how a pharmacy can enroll, visit www.LazandaREMS.com or telephone 1-888-508-8084.

There are no refills for this Schedule II product. Dispensing Lazanda after the initial prescription requires a new valid prescription that has been verified in the Lazanda REMS program.

Ensure that a Lazanda Medication Guide is provided to the patient each time Lazanda is dispensed, as required by law.

16.2 Storage and Handling of Lazanda

Lazanda is supplied in glass bottles, containing 8 sprays of 100 mcL containing 100 mcg/100 mcL or 400 mcg/100 mcL concentration solution. Each bottle is supplied in a child-resistant container.

Store at up to 25°C. Do not freeze.

Return the bottle to the child-resistant container after each use. Put the bottle in its child-resistant container and the pouch in the cardboard carton and store securely out of the reach of children and protect from light

Note: Carton and bottle label colors are a secondary aid in product identification. Confirm the printed dosage before dispensing.

16.3 Disposal of Lazanda

Patients and caregivers must be instructed to properly dispose of all unused, partially used and used Lazanda bottles. The remaining liquid in all bottles must be sprayed into the pouch, provided in the pack, for safe disposal as soon as possible.

The patient should be instructed how to do this correctly. If there are any unwanted therapeutic sprays remaining in the bottle, instruct the patient to spray these into the pouch until the number “8” appears in the counting window and there are no more full therapeutic sprays obtainable from the bottle. After the counter has advanced to “8”, the patient should continue to push down on the finger grips a total of four times in order to expel any residual medicine from the bottle. After the 8 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond “8”; further sprays emitted will not be full sprays and should always be trapped in the pouch, **not** used therapeutically.

The patient and caregiver must be instructed to seal the pouch and place both it and the empty bottle into the child-resistant storage container. Hands must be washed with soap and water immediately after handling the pouch. The patient must discard the child-resistant container containing the pouch and the bottle in the trash.

The patient or caregiver must continue to store the Lazanda bottle in the specially provided child-resistant container and the pouch out of the reach of children until proper disposal, as described above, is possible.

Instruct the patient to dispose of the Lazanda bottle and start a new one if:

- it has been 5 days or more since they last used the bottle of Lazanda
- it has been 14 days or more since they primed the bottle.

In the event that caregivers or patients require additional assistance with the disposal of Lazanda bottles, call the Archimedes Pharma toll-free number (1-866-435-6775).

16.4 How Supplied

Lazanda is supplied in a 5.3 ml capacity clear glass bottle with an attached metered-dose nasal spray pump incorporating a visual and audible spray counter, and a protective dust cover. Each bottle contains a net fill weight of 1.57 grams and, after priming, delivers 8 sprays. The pump will remain primed for up to 5 days after priming or use. The nasal spray delivers 8 full sprays. There are 2 product strengths and each 100 mcL spray contains either 100 mcg or 400 mcg of fentanyl. Each bottle is supplied in a child-resistant container.

Bottles in their child-resistant containers are supplied in cartons containing 1 or 4 bottles with instructions for use.

Each carton contains one carbon-lined pouch per bottle for disposal of priming sprays unwanted doses and residual fentanyl solution.

Lazanda Dosage Strength (fentanyl base)	Number of Bottles per Carton	NDC Number
100 mcg	1	51772-311-01
100 mcg	4	51772-311-04
400 mcg	1	51772-314-01
400 mcg	4	51772-314-04

17 PATIENT COUNSELING INFORMATION

17.1 Patient/Caregiver Instructions

- Physicians must enroll patients in the Lazanda REMS Program before they can receive Lazanda.
- Allow patients the opportunity to ask questions and discuss any concerns regarding Lazanda or the Lazanda REMS program.
- Instruct patients and their caregivers that the amount of fentanyl contained in a bottle can be fatal to a child. Patients and their caregivers must be instructed to keep Lazanda in its child-resistant container at all times and to store it and the pouch securely and out of the reach of children.
- Instruct patients how to safely dispose of the priming sprays and any remaining fentanyl solution in the pouch provided before disposing of both the empty bottle and the pouch inside the child-resistant container in the trash.
- Provide patients and their caregivers with a *Medication Guide* each time Lazanda is dispensed because new information may be available.
- Instruct patients not to take Lazanda for acute pain, postoperative pain, pain from injuries, headache, migraine, or any other short-term pain, even if they have taken other opioid analgesics for these conditions.
- Instruct patients on the meaning of opioid tolerance and Lazanda is only to be used as a supplemental pain medication for patients with pain requiring regular opioids, who have developed tolerance to the opioid medication and who need additional opioid treatment of breakthrough pain episodes.
- Instruct that if they are not taking an opioid medication on a regular around-the-clock basis, they must not take Lazanda.
- Instruct patients that they **MUST** wait at least 2 hours before treating another episode of breakthrough pain with Lazanda.
- Instruct patients **NOT** to share Lazanda and that sharing Lazanda with anyone else could result in the other individual's death due to overdose.
- Advise patients that Lazanda contains fentanyl, which is a pain medication similar to hydromorphone, methadone, morphine, oxycodone, and oxymorphone.
- Advise patients that the active ingredient in Lazanda, fentanyl, is a drug that some people abuse. Lazanda is to be taken only by the patient for whom it was prescribed, and protected from theft or misuse in the work or home environments.
- Instruct patients to talk to their doctor if breakthrough pain is not alleviated or worsens after taking Lazanda.
- Instruct patients to use Lazanda exactly as prescribed by their doctor and not to take Lazanda more often than prescribed.
- Caution patients that Lazanda can affect a person's ability to perform activities that require a high level of attention (such as driving or using heavy machinery). Warn patients taking Lazanda of these dangers and counsel accordingly.
- Warn patients not to combine Lazanda with alcohol, sleep aids, or tranquilizers except by order of the prescribing physician, because dangerous additive effects may occur resulting in serious injury or death.
- Inform female patients that if they become pregnant or plan to become pregnant during treatment with Lazanda to ask their doctor about the effects that Lazanda (or any medicine) may have on them and their unborn child.
- **Instruct the patient to dispose of the Lazanda bottle and start a new one if:**
 - it has been 5 days or more since they last used the bottle of Lazanda
 - it has been 14 days or more since they primed the bottle.
- **Patients must sign the Patient-Prescriber Agreement Form to confirm that they understand the risks, appropriate use, and storage of Lazanda.** Patients will be enrolled in the Lazanda REMS Program by the pharmacy at the time their first prescription is filled.
- Advise patients that Lazanda is only available through pharmacies that are enrolled in the Lazanda REMS program. To help patients identify enrolled pharmacies, call 1-855-841-4234 or visit www.LazandaREMS.com.
- Advise patients that they may be requested to participate in a survey to evaluate the effectiveness of the Lazanda REMS program.

17.2 Disposal of Used Lazanda Bottles

Instruct patients and caregivers to properly dispose of all unused, partially used and used Lazanda bottles as soon as no longer needed.

Instruct patients that, to dispose of Lazanda properly, the remaining liquid in all bottles must be sprayed into the pouch provided in the pack for safe disposal as soon as possible. This includes any unwanted therapeutic sprays remaining in the bottle. After the counter has advanced to "8", the patient should continue to push down on the finger grips a total of four times in order to expel any

residual medicine from the bottle. After the 8 therapeutic sprays have been emitted, the patient will not hear a click and the counter will not advance beyond “8”; further sprays emitted will not be full sprays and should always be trapped in the pouch, **not** used therapeutically.

Instruct the patient and caregiver to seal the pouch and to place both the empty bottle and the sealed pouch into the child-resistant storage container and discard in the trash. Lazanda must be stored in the specially provided child-resistant container out of the reach of children until proper disposal is possible.

Instruct the patient and caregiver to wash their hands with soap and water immediately after handling the pouch.

If the pouch is lost, instruct the patient and caregiver to use a pouch from another Lazanda pack to prime and dispose of unused medicine from the current bottle as well as from the next bottle. If they do not have an empty pouch available, the patient or caregiver can order one by calling 1-866-435-6775. They will receive the replacement pouch in the mail.

Rx Only.

Distributed by Archimedes Pharma US Inc.

One Crossroads Drive

Bedminster NJ 07921

For information about this product call:

1- 866-435-6775

U.S. Patent No. 6432440

Lazanda is a registered trademark of Archimedes Development Ltd.

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PIUS-300



See enclosed Medication Guide

Lazanda™
fentanyl/nasal spray

100 mcg per spray



For nasal administration only
Each bottle delivers 8 full sprays. Each spray delivers 100 microliters of solution.

Each 100 microliter spray contains fentanyl citrate equivalent to 100 mcg fentanyl base.

Usual dosage: see enclosed prescribing information

Inactive ingredients: water, mannitol, pectin, sucrose, phenylethyl alcohol, propylparaben, hydrochloric acid and/or sodium hydroxide for pH adjustment
Store at up to 77°F (25°C).
Do not freeze.

Distributed by Archimedes Pharma

One Crossroads Drive, Bedminster NJ 07921

For information about this product call: 1-866-435-6775

U.S. Patent No. 6432440

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Item # 111649

Printed in USA

Lot #

Exp Date



Place Pharmacy label here

To the Pharmacist:

- **PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY DO NOT SUBSTITUTE LAZANDA FOR OTHER FENTANYL PRODUCTS**
- Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode
- Instruct patients to read the enclosed Lazanda Medication Guide

Rx Only

NDC 51772-311-04

100 mcg per spray

Lazanda™
fentanyl/nasal spray

For nasal administration only

Dispense the enclosed Medication Guide to each patient

4 bottles, containing 8 sprays each, and 4 disposal pouches

WARNING: Keep out of the reach of children

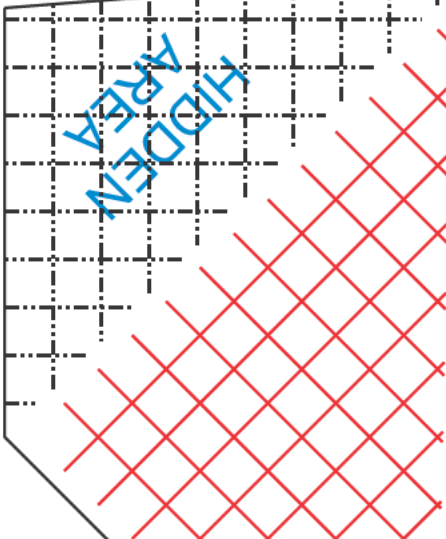
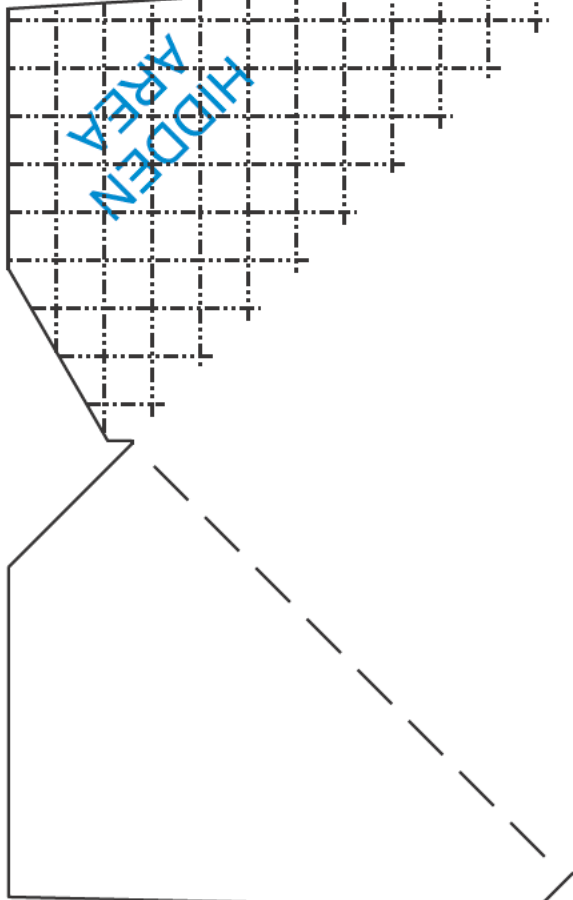
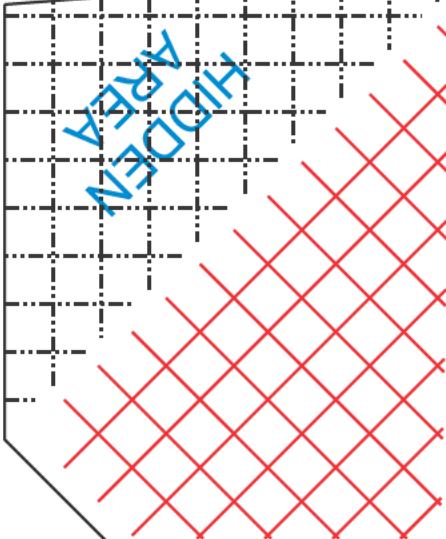
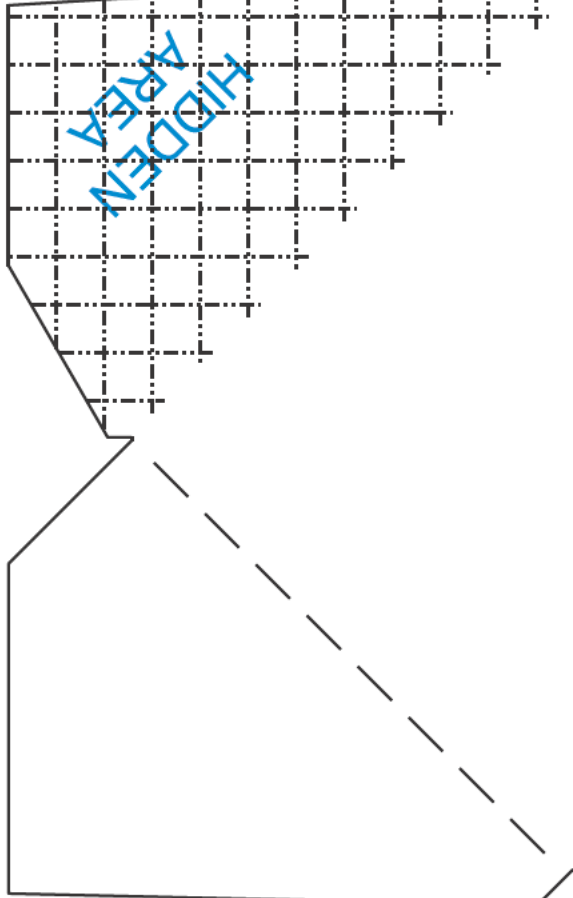
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY DO NOT SUBSTITUTE LAZANDA FOR OTHER FENTANYL PRODUCTS
Lazanda can be harmful or fatal if given to someone for whom it was not prescribed
Store the bottle in the child resistant container at all times, even when finished.

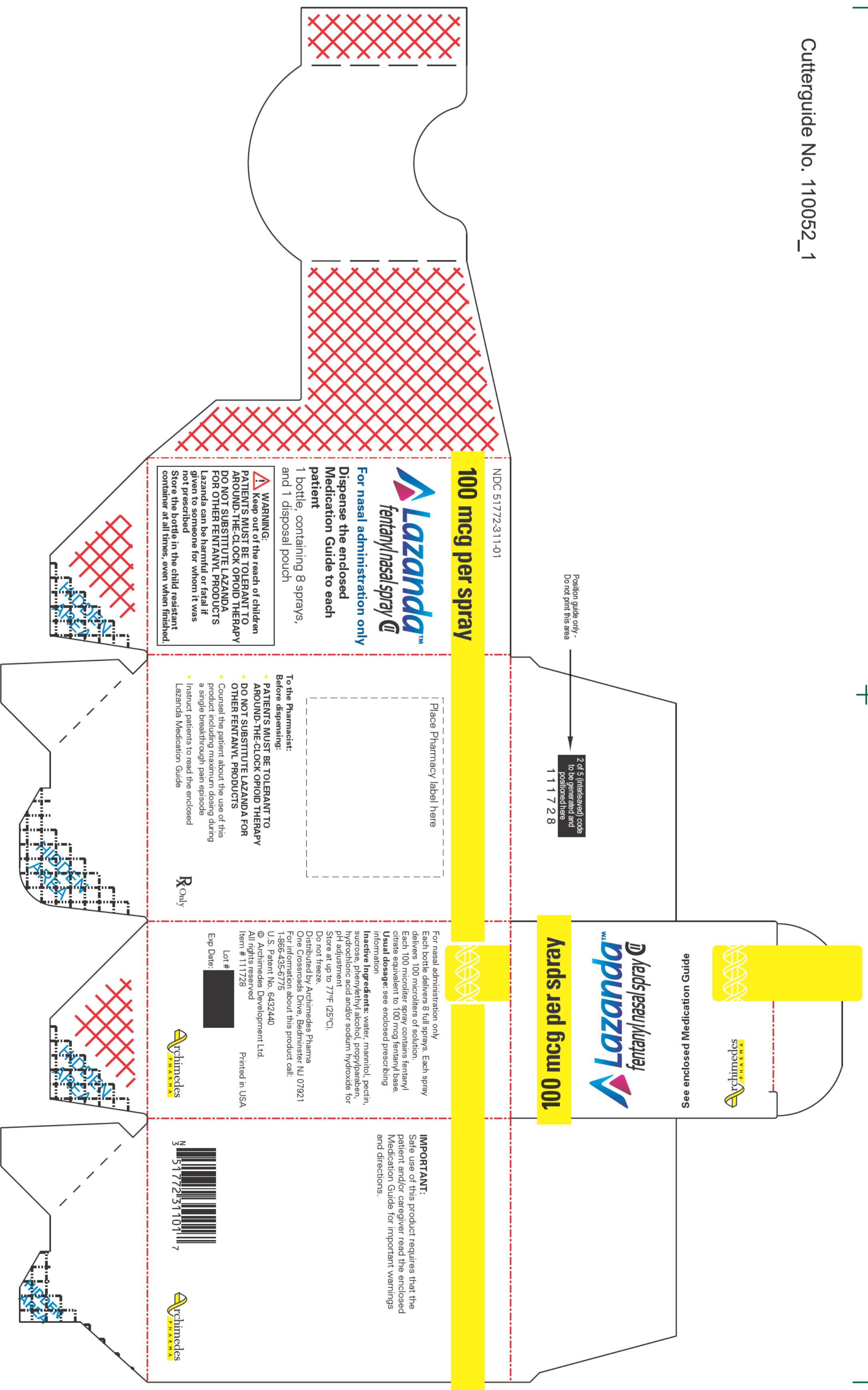
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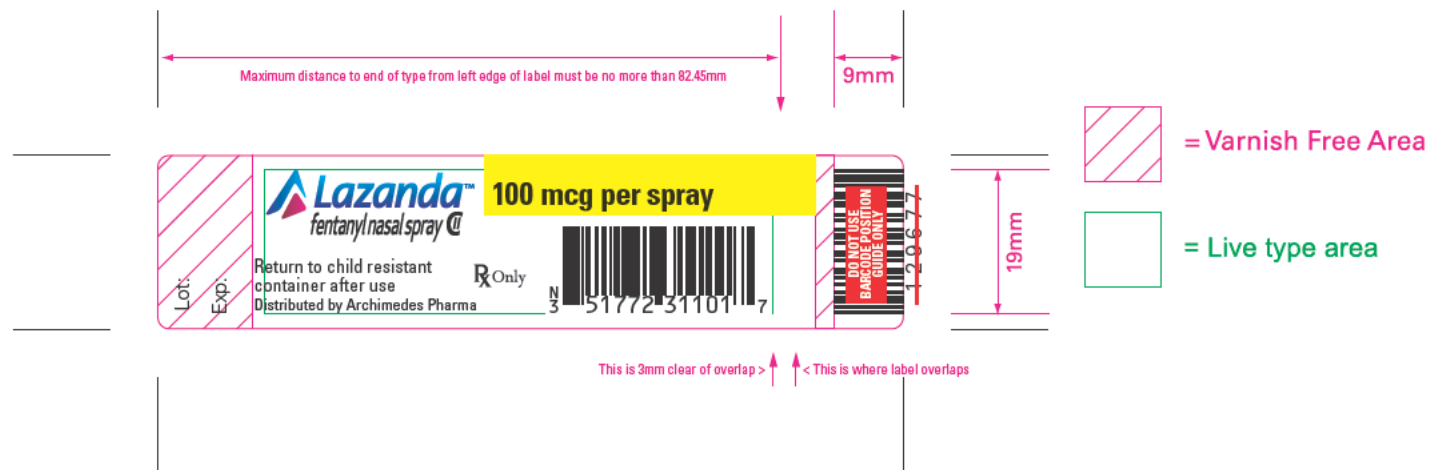
2 of 5 (interleaved) code
to be printed and
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IMPORTANT:

Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.









See enclosed Medication Guide



400 mcg per spray

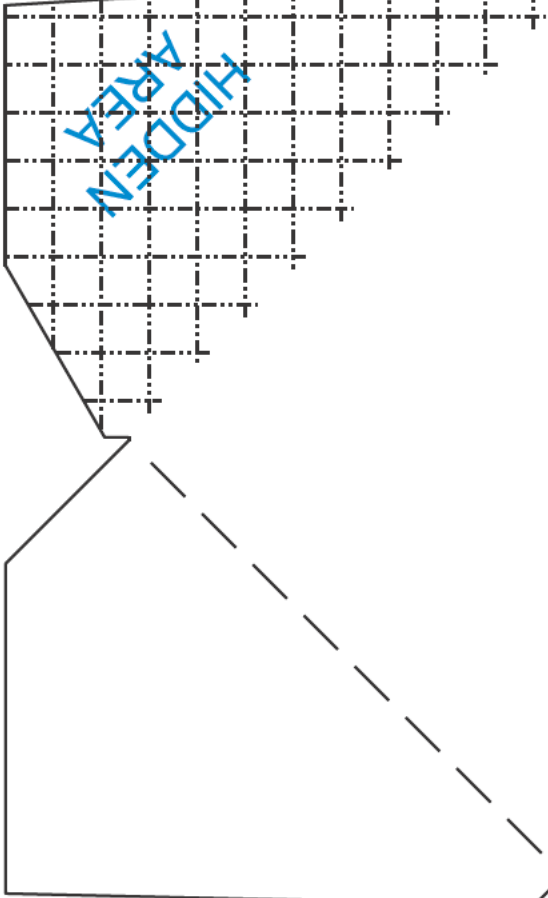


For nasal administration only
Each bottle delivers 8 full sprays. Each spray delivers 100 microliters of solution.
Each 100 microliter spray contains fentanyl citrate equivalent to 400 mcg fentanyl base.

Usual dosage: see enclosed prescribing information
Inactive ingredients: water, mannitol, pectin, sucrose, phenylethyl alcohol, propylparaben, hydrochloric acid and/or sodium hydroxide for pH adjustment
Store at up to 77°F (25°C).
Do not freeze.

Distributed by Archimedes Pharma
One Crossroads Drive, Bedminster NJ 07921
For information about this product call: 1-866-435-6775
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Item # 111651
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Lot #
Exp Date



Place Pharmacy label here

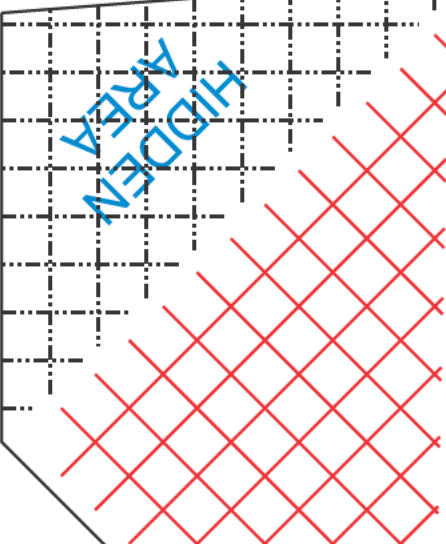
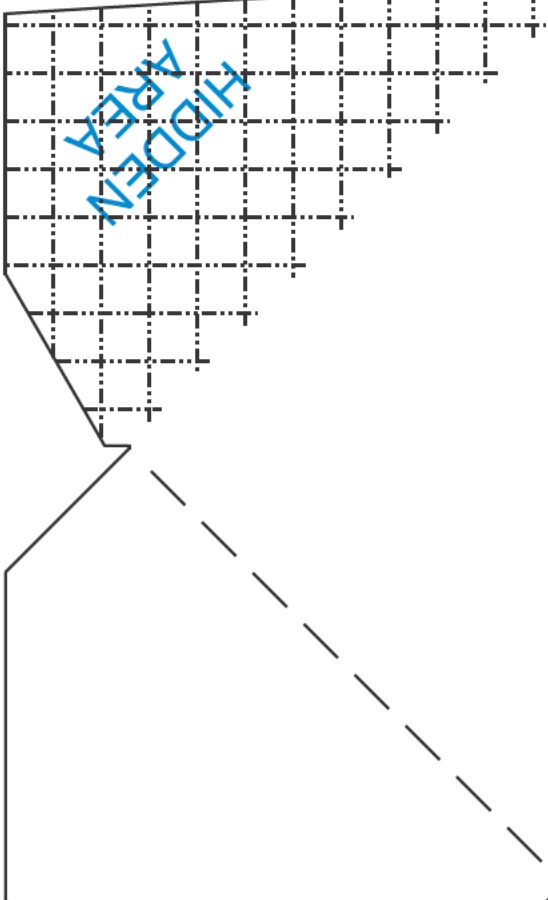
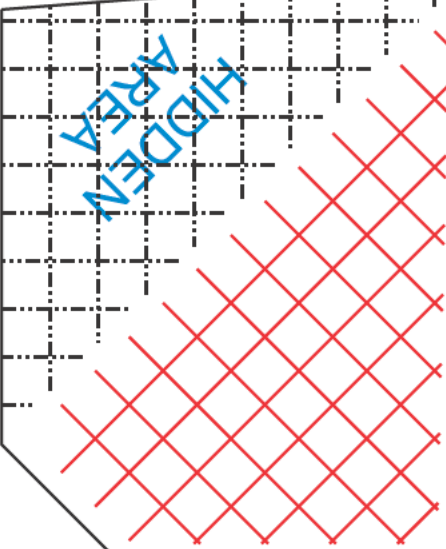
To the Pharmacist:
Before dispensing:

- PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
- DO NOT SUBSTITUTE LAZANDA FOR OTHER FENTANYL PRODUCTS

Counsel the patient about the use of this product including maximum dosing during a single breakthrough pain episode

- Instruct patients to read the enclosed Lazanda Medication Guide

R Only



NDC 51772-314-04

400 mcg per spray



For nasal administration only
Dispense the enclosed Medication Guide to each patient
4 bottles, containing 8 sprays each, and 4 disposal pouches

WARNING: Keep out of the reach of children
PATIENTS MUST BE TOLERANT TO AROUND-THE-CLOCK OPIOID THERAPY
DO NOT SUBSTITUTE LAZANDA FOR OTHER FENTANYL PRODUCTS
Lazanda can be harmful or fatal if given to someone for whom it was not prescribed
Store the bottle in the child resistant container at all times, even when finished.

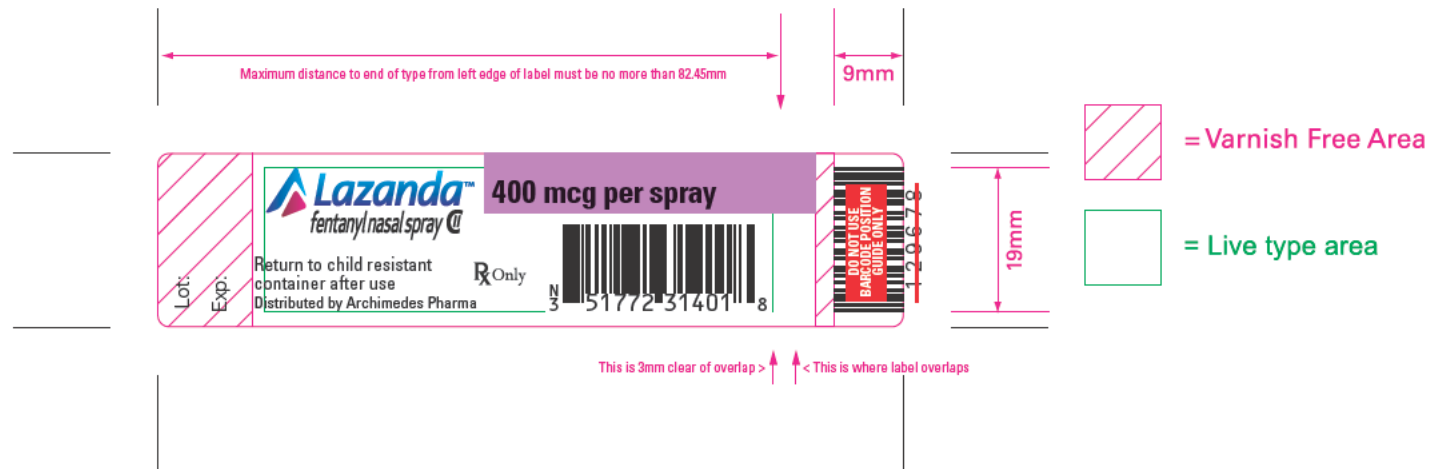


2 of 5 (interleaved) code
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Do not print this area -

IMPORTANT:
Safe use of this product requires that the patient and/or caregiver read the enclosed Medication Guide for important warnings and directions.

Cutterguide No. 110052_1



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/s/

BOB A RAPPAPORT
06/30/2011