Clinical Policy: Fentanyl IR (Actiq, Fentora, Lazanda, Subsys)

Reference Number: CP.PMN.127
Effective Date: 06.01.15
Last Review Date: 05.24
Line of Business: Commercial, HIM*, Medicaid Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

Description

The following are potent opioid agonist products requiring prior authorization: oral transmucosal fentanyl citrate lozenge (Actiq®), fentanyl buccal tablet (Fentora®), fentanyl nasal spray (Lazanda®), fentanyl sublingual spray (Subsys®).

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***For Health Insurance Marketplace (HIM),** if request is through pharmacy benefit, Fentora and Lazanda are non-formulary and should not be approved using these criteria; refer to the formulary exception policy, HIM.PA.103.*

FDA Approved Indication(s)

Transmucosal immediate release fentanyl products are indicated for the management of breakthrough pain in cancer patients (≥ 16 years old for Actiq and ≥ 18 years old for Fentora, Lazanda, and Subsys) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

Patients considered opioid tolerant are those who are taking, for one week or longer, around-the-clock medicine consisting of at least 60 mg of oral morphine per day, at least 25 mcg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone per day, at least 8 mg of oral hydromorphone per day, at least 25 mg oral oxymorphone per day, at least 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid daily for a week or longer. Patients must remain on around-the-clock opioids while taking Actiq, Fentora, Lazanda, or Subsys.

Limitation(s) of use:

- Not for use in opioid non-tolerant patients.
- Not for use in the management of acute or postoperative pain, including headache/migraine, dental pain, or in the emergency room.
- As a part of the Transmucosal Immediate Release Fentanyl Risk Evaluation and Mitigation Strategy (TIRF REMS) Access program, potent opioid agonist products may be dispensed only to outpatients enrolled in the program. For inpatient administration (e.g., hospitals, hospices, and long-term care facilities that prescribe for inpatient use), patient and prescriber enrollment is not required.

Policy/Criteria

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria.

It is the policy of health plans affiliated with Centene Corporation® that Actiq, Fentora, Lazanda, and Subsys are **medically necessary** when the following criteria are met:

I. Initial Approval Criteria
Please note: for HIM-Arkansas – if a member's covered prescription pain medication requires a prior authorization, then the prior authorization shall not be denied if the member has a terminal illness.

A. Cancer Pain (must meet all)**:**
1. Diagnosis of cancer pain;
2. Prescribed for the management of breakthrough pain;
3. Member is on fentanyl transdermal patches;
4. For Actiq requests, age ≥ 16 years;
5. For Fentora, Lazanda, or Subsys requests, age ≥ 18 years;
6. Request meets one of the following (a or b):
   a. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (see *Appendix E*);
   b. Failure of a trial of two formulary short-acting opioid analgesics, unless clinically significant adverse effects are experienced or all are contraindicated;
7. Request meets one of the following (a or b):
   a. Request is for treatment associated with cancer for a State with regulations against step therapy in certain oncology settings (see *Appendix E*);
   b. For brand Actiq, Fentora, Lazanda and Subsys requests: Member must use generic fentanyl citrate oral transmucosal lozenge (Actiq), unless contraindicated or clinically significant adverse effects are experienced;
8. A treatment plan is required, including:
   a. Pain intensity (scales or ratings);
   b. Functional status (physical and psychosocial);
   c. Patient`s goal of therapy (level of pain acceptable and/or functional status);
   d. Current analgesic (opioid and adjuvant) regimen;
   e. Current non-pharmacological treatment;
   f. Opioid-related side effects;
   g. Indications of medical misuse;
   h. Action plan if analgesic failure occurs;
9. For Actiq requests on the HIM plan: Dose does not exceed 4 lozenges per day.

Approval duration:
Medicaid/Commercial – 6 months
HIM – 6 months *(refer to HIM.PA.103 for Fentora and Lazanda)*

B. Other diagnoses/indications (must meet 1 or 2)**:**
1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business:

CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or

b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or

2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

II. Continued Therapy

Please note: for HIM-Arkansas – if a member's covered prescription pain medication requires a prior authorization, then the prior authorization shall not be denied if the member has a terminal illness.

A. Cancer Pain (must meet all)**:**

1. Member meets one of the following (a or b):
   a. Currently receiving medication via Centene benefit or member has previously met initial approval criteria;
   b. Member is currently receiving medication and is enrolled in a state and product with continuity of care regulations (*refer to state specific addendums for CC.PHARM.03A and CC.PHARM.03B);*
2. Member is responding positively to therapy as evidenced by reduction in breakthrough pain without significant toxicity;
3. For Actiq requests on the HIM plan: Dose does not exceed 4 lozenges per day.

Approval duration:
Medicaid/Commercial – 12 months
HIM – 12 months *(refer to HIM.PA.103 for Fentora and Lazanda)*

B. Other diagnoses/indications (must meet 1 or 2)**:**

1. If this drug has recently (within the last 6 months) undergone a label change (e.g., newly approved indication, age expansion, new dosing regimen) that is not yet reflected in this policy, refer to one of the following policies (a or b):
   a. For drugs on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the no coverage criteria policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.33 for health insurance marketplace, and CP.PMN.255 for Medicaid; or
   b. For drugs NOT on the formulary (commercial, health insurance marketplace) or PDL (Medicaid), the non-formulary policy for the relevant line of business: CP.CPA.190 for commercial, HIM.PA.103 for health insurance marketplace, and CP.PMN.16 for Medicaid; or
2. If the requested use (e.g., diagnosis, age, dosing regimen) is NOT specifically listed under section III (Diagnoses/Indications for which coverage is NOT authorized) AND criterion 1 above does not apply, refer to the off-label use policy for the relevant line

of business: CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

III. Diagnoses/Indications for which coverage is NOT authorized:

A. Non-FDA approved indications, which are not addressed in this policy, unless there is sufficient documentation of efficacy and safety according to the off label use policies – CP.CPA.09 for commercial, HIM.PA.154 for health insurance marketplace, and CP.PMN.53 for Medicaid.

IV. Appendices/General Information

Appendix A: Abbreviation/Acronym Key

FDA: Food and Drug Administration
REMS: Risk Evaluation and Mitigation Strategy
TIRF: transmucosal immediate-release fentanyl

Appendix B: Therapeutic Alternatives

This table provides a listing of preferred alternative therapy recommended in the approval criteria. The drugs listed here may not be formulary agents for all relevant lines of business and may require prior authorization.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
morphine sulfate immediate-release	10 mg – 30 mg PO Q 4 H PRN Individualize dosage based on extent of pre-existing opioid tolerance	Varies
oxycodone immediate-release (Roxicodone®)	5 mg - 15 mg PO Q 4 to 6 H PRN Individualize dosage based on extent of pre-existing opioid tolerance	Varies
hydromorphone immediate-release (Dilaudid®)	2 mg – 4 mg PO Q 3 to 4 H PRN Individualize dosage based on extent of pre-existing opioid tolerance	Varies
oxymorphone immediate-release (Opana®)	5 mg – 20 mg PO Q 4 to 6 H PRN Individualize dosage based on extent of pre-existing opioid tolerance	Varies
fentanyl transdermal patches (Duragesic®)	Apply one patch topically every 72 hours	Varies

Therapeutic alternatives are listed as Brand name® (generic) when the drug is available by brand name only and generic (Brand name®) when the drug is available by both brand and generic.

Appendix C: Contraindications/Boxed Warnings

- Contraindication(s): opioid non-tolerant patients; management of acute or postoperative pain including headache/migraines dental pain or use in the emergency department; significant respiratory depression; acute or severe bronchial asthma in an unmonitored setting or in absence of resuscitative equipment; gastrointestinal obstruction, including paralytic ileus; hypersensitivity to fentanyl or components of the fentanyl product.
- Boxed Warning(s): life-threatening respiratory depression; accidental ingestion; cytochrome P450 3A4 interactions; risk of medication errors; risks from concomitant use

with benzodiazepines or other CNS depressants; addiction, abuse, and misuse; REMS access program; neonatal opioid withdrawal syndrome.

Appendix D: General Information

- Because of the potential risk for misuse, abuse, and overdose, the fentanyl sublingual and transmucosal products listed below are only available through restricted distribution programs. Under the TIRF REMS program, only prescribers, pharmacies, and patients registered with TIRF REMS are able to prescribe, dispense, and receive these products. Additional information is available at: www.tirfremsaccess.com/TirfUISplashWeb/index.html or by calling 1-866-822-1483.
- These products are not interchangeable and must not be used in opioid non-tolerant patients because life-threatening hypoventilation could occur at any dose in patients not taking chronic opiates. Substantial differences exist in the pharmacokinetic profiles of these drugs that result in clinically important differences in the extent of absorption of fentanyl. As a result of these differences, the substitution of these products may result in fatal overdose. Patients considered opioid tolerant are those who are taking around the clock medicine consisting of at least 60 mg morphine/day, at least 25 mcg transdermal fentanyl/hour, at least 30 mg of oxycodone daily, at least 8 mg oral hydromorphone daily, or an equianalgesic dose of another opioid for a week or longer.
- Fentanyl absorption with different formulations of transmucosal delivery systems can be substantially different. Patients should not be converted on a mcg per mcg basis between any transmucosal fentanyl products.
- The initial dose of Fentora and Subsys is always 100 mcg with the only exception being patients already using Actiq. Patients switching from Actiq to Fentora or Subsys should be initiated as shown:

Actiq dose (mcg)	Fentora dose (mcg)	Subsys dose (mcg)
200	100	100
400	100	100
600	200	200
800	200	200
1200	400	400
1600	400	400

Appendix E: States with Regulations against Redirections in Cancer

State	Step Therapy Prohibited?	Notes
FL	Yes	For stage 4 metastatic cancer and associated conditions
GA	Yes	For stage 4 metastatic cancer. Redirection does not refer to review of medical necessity or clinical appropriateness
IA	Yes	For standard of care stage 4 cancer drug use, supported by peer-reviewed, evidence-based literature, and approved by FDA
LA	Yes	For stage 4 advanced, metastatic cancer or associated conditions. Exception if "clinically equivalent therapy, contains identical active ingredient(s), and proven to have same efficacy

State	Step Therapy Prohibited?	Notes
MS	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
NV	Yes	Stage 3 and stage 4 cancer patients for a prescription drug to treat the cancer or any symptom thereof of the covered person
OH	Yes	**Applies to Commercial and HIM requests only** For stage 4 metastatic cancer and associated conditions
OK	Yes	**Applies to HIM requests only** For advanced metastatic cancer and associated conditions
PA	Yes	For stage 4 advanced, metastatic cancer
TN	Yes	For advanced metastatic cancer and associated conditions
TX	Yes	For stage 4 advanced, metastatic cancer and associated conditions

V. Dosage and Administration

Drug Name	Dosing Regimen	Maximum Dose
Oral transmucosal fentanyl citrate (Actiq)	Initiate dosing with 200 mcg PO and if breakthrough episode is not relieved in 30 minutes, patients may take only 1 additional dose using the same strength and must wait at least 4 hours before taking another dose. Individually titrate to a dose that provides adequate analgesia using single dosage unit per breakthrough cancer pain episode and minimizes side effects. Initial prescription recommendation for maximum of 6 units; Once a successful dose has been found, use no more than 4 doses per day; separate by at least 4 hours.	Varies If more than 4 episodes of breakthrough pain are experienced per day, the dose of the long-acting opioid used for persistent underlying cancer pain should be re-evaluated
Oral transmucosal fentanyl citrate (Fentora)	Initiate dosing with 100 mcg PO and if breakthrough episode is not relieved in 30 minutes, patients may take only 1 additional dose using the same strength and must wait at least 4 hours before taking another dose. Maximum: 4 tablets simultaneously	Varies If more than 4 episodes of breakthrough pain are experienced per day, the dose of the long-acting opioid used for persistent underlying cancer pain should be re-evaluated
Fentanyl nasal spray (Lazanda)	Initial dose of Lazanda for all patients is 100 mcg (one spray) into one nostril. 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. Dose is a single spray into one nostril or a single spray into each nostril (2	Varies If more than 4 episodes of breakthrough pain are experienced per day, the dose of the long-acting opioid used for persistent

Drug Name	Dosing Regimen	Maximum Dose
	sprays), three single sprays (alternating nostrils), or two sprays into each nostril (4 sprays). 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. Wait at least 2 hours before treating another episode of breakthrough pain with Lazanda.	underlying cancer pain should be re-evaluated
Fentanyl sublingual spray (Subsys)	Initial dose of Subsys: 100 mcg SL except patients already using Actiq. Individually titrate to a tolerable dose that provides adequate analgesia using a single Subsys dose per breakthrough cancer pain episode. No more than two doses can be taken per breakthrough pain episode. Wait at least 4 hours before treating another episode of breakthrough pain with Subsys. Limit consumption to four or fewer doses per day once successful dose is found.	Varies If more than 4 episodes of breakthrough pain are experienced per day, the dose of the long-acting opioid used for persistent underlying cancer pain should be re-evaluated

VI. Product Availability

Drug Name	Availability
Oral transmucosal fentanyl citrate (Actiq)	Lozenges: 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg (30 lozenges per package)
Oral transmucosal fentanyl citrate (Fentora)	Buccal tablet: 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg (Package of 7 blister cards containing 4 tablets in each card)
Fentanyl nasal spray (Lazanda)	Metered dose nasal spray: 100 mcg, 300 mcg, 400 mcg per spray (Each 5 mL bottle contains 8 sprays)
Fentanyl sublingual spray (Subsys)	Single spray units: 100 mcg, 200 mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg, 1600 mcg per spray

VII. References

1. Actiq Prescribing Information. Parsippany, NJ: Teva Pharmaceuticals USA, Inc.; December 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/020747s062lbl.pdf. Accessed January 18, 2024.
2. Fentora Prescribing Information. North Wales, PA: Teva Pharmaceuticals USA, Inc.; December 2023. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/021947s043lbl.pdf. Accessed January 18, 2024.
3. Lazanda Prescribing Information. North Brook, IL: West Therapeutic Development, LLC; March 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/022569s030lbl.pdf. Accessed January 18, 2024.

4. Subsys Prescribing Information. Northbrook, IL: West Therapeutics Development, LLC; March 2021. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/202788s023lbl.pdf. Accessed January 18, 2024.
5. Aronoff GM, Brennan MJ, Pritchard DD, et al. Evidence-based oral transmucosal fentanyl citrate (OTFC) dosing guidelines. Pain Medicine. 2005;6(4):305-14.
6. Micromedex® Healthcare Series [Internet database]. Greenwood Village, Colo: Thomson Healthcare. Updated periodically. Accessed February 13, 2024.
7. Dowell D, Ragan KR, Jones CM, Baldwin GT, and Chou R. CDC clinical practice guideline for prescribing opioids for pain – United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1-95.

Reviews, Revisions, and Approvals	Date	P&T Approval Date
2Q 2020 annual review: added requirement for Brand Actiq to step through the generic lozenge product; references reviewed and updated.	02.18.20	05.20
2Q 2021 annual review: no significant changes; revised prior trial requirement of generic Actiq to "must use" language; added notation throughout that Abstral, Fentora, and Lazanda are NF on HIM, and thus this policy doesn't apply to those agents; revised HIM.PHAR.21 to HIM.PA.154; references reviewed and updated.	03.02.21	05.21
2Q 2022 annual review: no significant changes; references reviewed and updated.	02.28.22	05.22
Template changes applied to other diagnoses/indications and continued therapy section.	10.03.22	
2Q 2023 annual review: no significant changes; removed references to Abstral due to discontinuation of product; references reviewed and updated.	02.03.23	05.23
2Q 2024 annual review: no significant changes; references reviewed and updated.	01.18.24	05.24
Added by-passing of redirection if state regulations do not allow step therapy in certain oncology settings along with Appendix E.	06.05.24	

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment, or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of members. This clinical policy is not intended to recommend treatment for members. Members should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members and their representatives agree to be bound by such terms and conditions by providing services to members and/or submitting claims for payment for such services.

Note:
For Medicaid members, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.