Important risk minimisation information for healthcare professionals

Abstral® (fentanyl)

Prescriber Guide
Abstral® (fentanyl)

This guide is approved by Saudi Food and Drug Authority (SFDA)

KYOWA KIRIN

November 22nd, 2020

Introduction

The Abstral® sublingual Fentanyl Citrate Prescriber Guide is designed to support health professionals in the diagnosis of breakthrough pain (BTP) in patients suffering with cancer, and in the initiation, administration and dose titration of Abstral®. This document should be referred to in conjunction with important information contained within the Abstral® Summary of Product Characteristics (SmPC) and the Abstral® Prescribing Information at the back of this booklet.

Healthcare professionals are asked to report any suspected adverse reactions to:

The National Pharmacovigilance Centre (NPC)
Saudi Food and Drug Authority (SFDA)
SFDA call center: 19999
Toll free phone: 8002490000
Fax: +966-11-2057662
E-mail: npc.drug@sfda.gov.sa
Website: http://ade.sfda.gov.sa

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Introduction

Abstral® Prescriber Guide

1. Background Cancer Pain

Chronic pain, usually termed background pain, is a common symptom for patients with cancer. Background cancer pain is defined as pain present for 12 hours or more per day in the previous week.[1]

Background Cancer Pain Treatment

The neurophysiology of cancer pain is complex and, consequently, management involves treatments and palliations including radiotherapy, chemotherapy, hormones, bisphosphonates and surgery. These combined with pharmacological and non- pharmacological methods of pain control, optimise pain relief.[2]

Opioids are the mainstay of pharmacological cancer pain management.[2] Guidelines recommend that background pain should be treated with an around the clock opioid analgesic, titrated to the optimum dose.[3]

If a patient is suffering from transient exacerbations of pain, the first action should be to assess whether their background pain is adequately controlled.[4] Options to consider are as follows:

- Increase the dosage of the background pain medication
- Change the medication
- Add another medication to the existing one
- Explore non-pharmacological treatments

If, after these options have been fully explored, the patient still suffers from transient exacerbations of pain, they may be suffering from BTP.

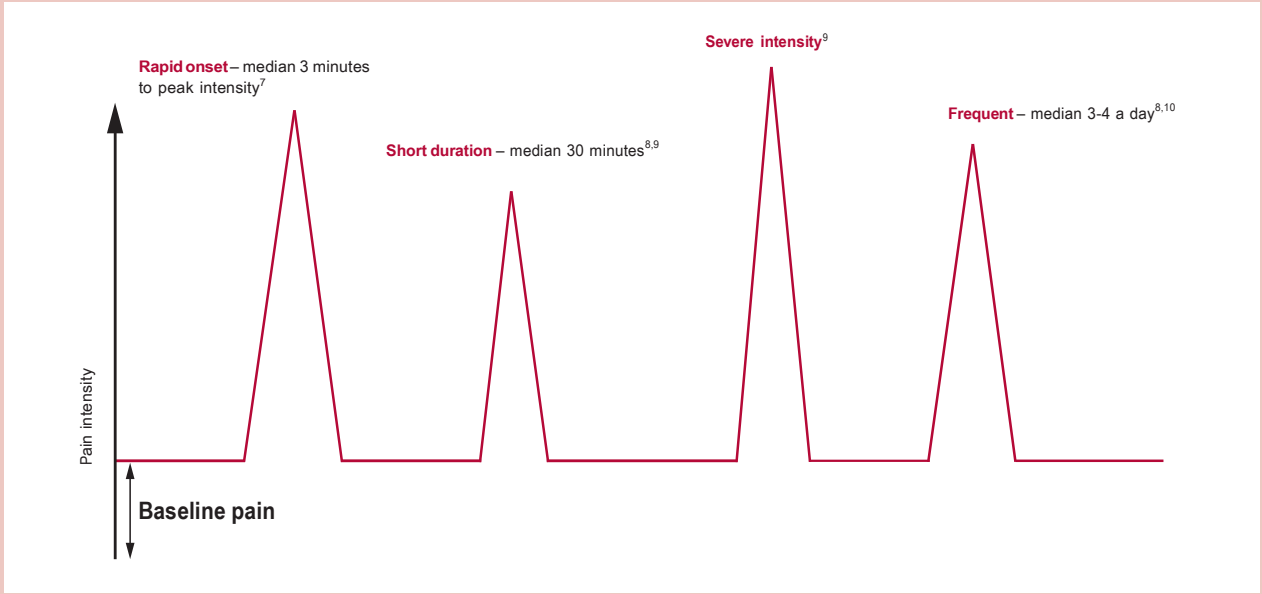
2. Breakthrough Cancer Pain

Defining Breakthrough Cancer Pain

- BTP is defined as a transient exacerbation of pain occurring in patients with otherwise stable, baseline persistent pain.[5]
- Breakthrough cancer pain is characterised by a short episode of severe pain that occurs **in addition** to persistent background pain in cancer patients
- BTP is a common problem in cancer patients, either as a direct or indirect result of cancer or cancer treatment
- Engaging with patients is a vital part of supporting them in the management of their BTP, from assessment through to diagnosis and treatment.

Types and Triggers of Breakthrough Cancer Pain

- **Predictable -** incident-related breakthrough cancer pain[6]
  - Voluntary – triggered by movement such as walking
  - Involuntary – triggered by reflex movement such as coughing
  - Procedural – related to a therapeutic intervention e.g. wound dressing
- **Unpredictable -** spontaneous breakthrough cancer pain, unrelated to any identifiable action[6]



Adapted from Coluzzi PH. *Am J Hosp Pall Care* 1998; **15**:13-22.

Diagnosing Breakthrough Cancer Pain

Before reaching a diagnosis of BTP, it is important to have assessed the patient's background pain medication, and to have explored the options as detailed in section1.

If background pain is adequately controlled, but the patient continues to experience transient episodes of severe pain, they should be asked to describe the nature of this pain. The following table details questions and diagnostic markers which can be used to form part of the assessment and diagnosis of BTP.

Questions for the patient	Breakthrough cancer pain diagnostic markers
1. Can you describe the pain?	2. Severe episodic pain in addition to controlled background pain[6]
2. Does the pain coincide with movement, e.g., walking or coughing?	3. Yes (predictable-incident-related) No (unpredictable-spontaneous, unrelated to any identifiable action)[6]
3. Does the pain occur at or around the time that your regular pain medicine is due?	4. Does not coincide with regular pain medication dosing[6]

Managing Breakthrough Cancer Pain

Once a patient has been diagnosed with BTP, it is important to consult on any preferences they may have on how to manage their condition.
Breakthrough pain can be treated using medications that belong to the opioid class of drugs. There are a variety of formulations and ways of administering these medications, e.g. oral, sublingual, transmucosal, subcutaneous, nasal. Advice should also be given to avoid volitional triggers, such as walking, where possible.

3. Managing Breakthrough Pain (BTP) with Abstral®

Product Overview

Abstral® is a sublingual fentanyl tablet indicated for the management of breakthrough pain in adult patients already receiving opioid therapy for chronic (background) cancer pain.[11]

Abstral® should be prescribed and administered in accordance with the licensing information contained within the Abstral® Summary of Product Characteristics (SmPC).

Selecting the Abstral® Patient

Before prescribing Abstral®, healthcare professionals should be familiar with guidance for using the product, including titration procedure (see section 4), recommended frequency of administration, symptoms of overdose and common side-effects.

Consideration should be given to whether the patient is suitable to take Abstral®. Factors may include their ability to understand and carefully follow dosing instructions, whether they might be at a heightened risk of addiction or accidental or intentional overdose.
Abstral® should only be administered to patients who are considered tolerant to their opioid therapy for persistent cancer pain. Patients can be considered opioid tolerant if they take at least 60 mg of oral morphine daily, at least 25 micrograms of transdermal fentanyl per hour, at least 30 mg of oxycodone daily, at least 8 mg of oral hydromorphone daily or an equianalgesic dose of another opioid for a week or longer.

Other factors to consider include the following:[11]

*Abstral® should only to be initiated in patients whose dose of long-acting opioid has been stabilised

*Abstral® should not be used in patients under 18 years of age

*Abstral® must not be used for treatment of acute pain other than breakthrough cancer pain

*Abstral® must not be used in patients with severe respiratory depression or severe obstructive lung conditions

*Use in patients without maintenance opioid therapy risks potentially serious adverse reactions including respiratory depression

*Ensure that the patient has no contra-indications for Abstral® including:

- Hypersensitivity to the active substance or any of the excipients
- Severe respiratory depression or severe chronic obstructive airways disease.
- Treatment of acute pain other than BTP.

Patients and/or carers should be given clear instruction on the importance of taking Abstral® exactly as prescribed, and that Abstral® must not be given to anyone else. The importance of careful storage and disposal should also be stressed.

Inform patients/carers that it is important to keep Abstral® out of the reach and sight of children because it contains an active substance in an amount that can be fatal to a child.

For further detailed information relating to contra-indications, special warnings and precautions, interactions and the use of Abstral® in pregnancy and during breastfeeding refer to the SmPC (sections 4.3, 4.4, 4.5 and 4.6).

Route of Administration

Patients selected to use Abstral® for the management of their breakthrough cancer pain should be given the following important information about administering their medication:

1. Take tablet at onset of breakthrough cancer pain episode
2. Place tablet directly under the tongue at the deepest part
3. Do not swallow, chew or suck the tablet
4. Allow the tablet to dissolve
5. Do not consume anything until the tablet has completely dissolved

In patients who have a dry mouth water may be used to moisten the buccal mucosa before taking Abstral®.

4. How to administer Abstral®

Titrating to the correct dose:

The dose of Abstral® must be individually titrated, under supervision, until the optimal maintenance dose is reached. The optimal dose is defined as that which provides adequate analgesia to manage BTP episodes with an acceptable level of adverse effects.

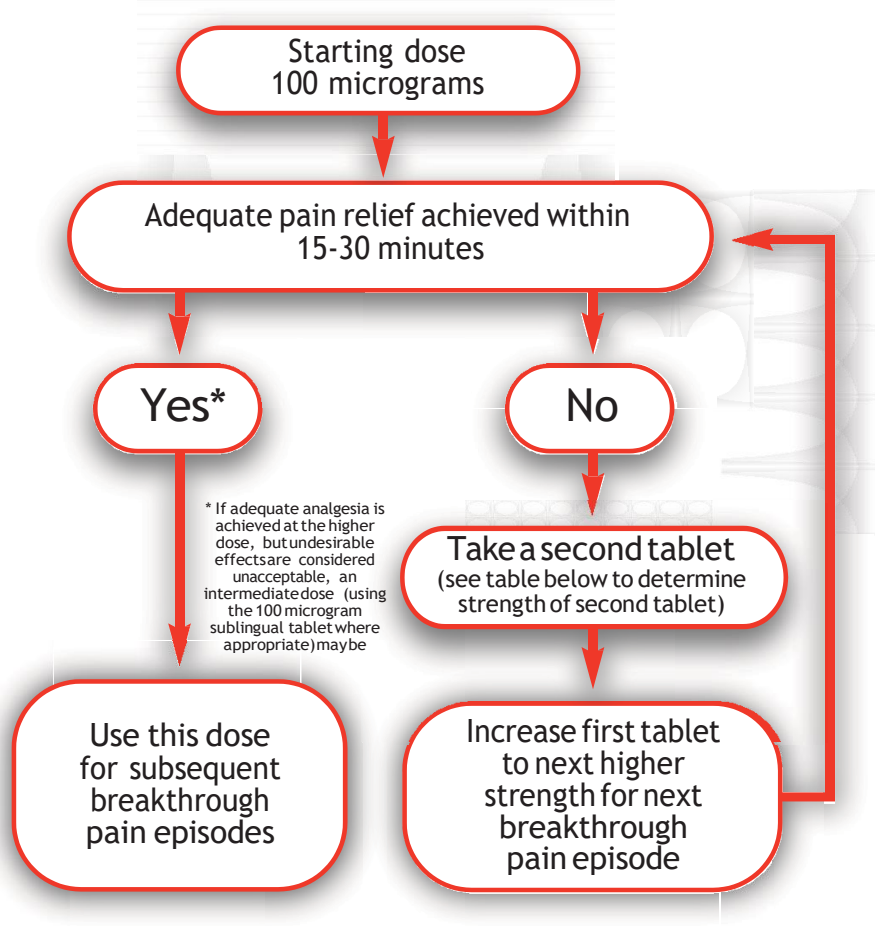
Particular caution should be exercised during dose titration with Abstral® in patients with chronic obstructive pulmonary disease or other medical conditions predisposing them to respiratory depression (e.g. myasthenia gravis), because of the risk of further respiratory depression which could lead to respiratory failure.[11]

The starting dose of Abstral® is 100 micrograms in all cases, titrating upwards as shown in the table opposite.[11] This includes patients switching to Abstral® from other opioids for BTP.

Prescribe a maximum of four (4) doses per day and at least two (2) hours in between doses in order to minimise the risk of addiction/potential overdose.

For further information on titration, please refer to the guidance chart opposite and the SmPC section 4.2. For further information on ongoing maintenance, dose re-adjustment and discontinuation, please refer to SmPC section 4.2.

Abstral® Titration Process



Range of tablet strengths for flexible dosing and titration

Distinctive tablet shapes and colour coded packs for easy dose identification

Tablets shown above are not actual size

Strength (micrograms) of first sublingual tablet per episode of breakthrough pain	Strength (micrograms) of supplemental (second) sublingual tablet to be taken 15-30 minutes after first tablet, if required
100 micrograms	100 micrograms
200 micrograms	100 micrograms

300 micrograms	100 micrograms
400 micrograms	200 micrograms
600 micrograms	200 micrograms
800 micrograms	No supplemental tablets

Patients with uncontrolled pain:

If after titration, patients do not experience relief for their BTP episodes, they should first be reassessed so that their pain management strategy can be reviewed and modified as appropriate. Following continued monitoring, patients who continue to receive inadequate pain relief should be referred to a pain or palliative care specialist.

Treatment with opioid-based formulations can be associated with adverse effects. The risk of serious adverse effects is reduced if these medications are used under the following conditions:

- In the right patient (refer to Patient selection - section 3)
- Within the parameters of the titration schedule (refer to Titrating to the correct dose - section 4)
- In accordance with product license indications and licensing information (refer to Abstral® SmPC).

5. Important Considerations

Undesirable Effects

In order to minimise the risk of opioid related adverse reactions including early evidence of respiratory depression (somnolence, confusion) it is imperative that patients be monitored closely by health professionals during the titration process and thereafter.

Undesirable effects typical of opioids are to be expected with Abstral®; they tend to decrease in intensity with continued use. The most serious potential adverse reactions associated with opioid use are respiratory depression (which could lead to respiratory arrest or apnoea), somnolence, confusion, hypotension and shock.[11]

The most frequently observed adverse reactions with Abstral® include nausea, constipation, somnolence, headache, dizziness, dyspnoea, stomatitis, vomiting, dry mouth, hyperhidrosis and fatigue.[11]

Ensure appropriate instructions are provided to patients regarding monitoring for the signs of respiratory depression.

During patient selection, it is important to assess whether the patient might be at risk from accidental or intentional overdose. Instruct patients/carers about the symptoms of, and what to do in case of, overdose.

In addition, patients may experience symptoms of opioid withdrawal upon discontinuation, please refer to section 4.2 of the SmPC.

For more detailed information refer to section 4.8 of the SmPC.

Serotonin Syndrome:

As with other fentanyl products, caution is advised when Abstral® is co-administered with drugs that affect the serotonergic neurotransmitter systems.

The development of potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs such as Selective Serotonin Re-Uptake Inhibitors (SSRIs) and Serotonin Norepinephrine Re-Uptake Inhibitors (SNRIs), and with drugs that impair metabolism of serotonin (including Monoamine Oxidase Inhibitors (MAOIs)). This may occur within the recommended dose. Abstral® is not recommended in patients who have received MAOIs within the previous 14 days.[11]

Serotonin syndrome may include mental-status changes (e.g. agitation, hallucinations, coma), autonomic instability (e.g. tachycardia, labile blood pressure, hyperthermia), neuromuscular abnormalities (e.g. hyperreflexia, incoordination, rigidity), and/or gastrointestinal symptoms (e.g. nausea, vomiting, diarrhoea).[11]

If serotonin syndrome is suspected, treatment with Abstral® should be discontinued.[11]

Further details on serotonin syndrome can be found within SmPC section 4.4.

Switching to an alternative transmucosal fentanyl (TMF) formulation.

Before the decision is taken to switch from Abstral® to another TMF, the patient should be assessed to determine whether they have been titrated to the correct dose on the first TMF. Switching from other fentanyl containing products to Abstral® must not occur at a 1:1 ratio because of differences in absorption profiles and can result in fatal respiratory depression. If patients are switched from another fentanyl containing product, a new dose titration with Abstral® is required, starting at 100 micrograms.

Other drug interactions:

Abstral® should be used with caution if administered concomitantly with CYP3A4 inhibitors as fentanyl is metabolized by CYP3A4.

Patients on concomitant CNS depressants (including alcohol) must be monitored for a change in opioid effects that may require adjustment to the dose of Abstral®.

Abstral® is not recommended for use in patients who have received monoamine-oxidase (MOA) inhibitors within 14 days.

The concomitant use of partial opioid agonists/antagonists is not recommended. They partially antagonize the analgesic effect of fentanyl and may induce withdrawal symptoms in opioid dependent patients.

Please refer to the SmPC for further drug interactions.

Stopping Abstral® altogether:

- Abstral® should be discontinued immediately if the patient no longer experiences BTP episodes. The treatment for the persistent background pain should be kept as prescribed
- If discontinuation of all opioid therapy is required, the patient must be closely monitored in order to avoid the possibility of abrupt withdrawal effects.
- Refer to section 4.2 of the SmPC for further information about stopping treatment with Abstral®

Breastfeeding:

Fentanyl should not be used by breastfeeding women and breastfeeding should not be restarted until at least 5 days after the last administration of fentanyl.[11]

Further details can be found in section 4.6 of the SmPC.

6. Providing Guidance for Patients & Carers

Patients and carers should be referred to the Abstral® patient information leaflet, ensuring they are aware of and understand the information contained within it. They should also be given a copy of Abstral® Patients and Carer Guide. In addition, patients and their carers should be made aware of the information specified below:

Correct Treatment Administration & Adherence

- Abstral® must be taken exactly as prescribed and must not be given to anyone else
- The patient should remain on background opioids when taking Abstral®
- There are other restrictions of use, including not taking certain medications and avoiding alcohol (Refer to section 4.5 of the SmPC)
- Abstral® is designed for sublingual administration and must not be chewed, sucked or swallowed whole[11]
- No more than four (4) episodes of breakthrough pain should be treated per day, with patients waiting at least two (2) hours before treating a subsequent episode with Abstral®[11]
- The different strengths of Abstral® tablets are shaped differently and the packaging for each strength is colour-coded. Advise patients about the different strengths and the colour/shape differentiation
- If Abstral® is not used according to instructions, there is an increased risk of side-effects and addiction

Monitoring Effectiveness

The patient should continually monitor the effectiveness of Abstral® in providing relief for their BTP during the titration phase, and report the following back to their health professional:

- Did they achieve pain relief at the prescribed dose?
- How long did it take to achieve pain relief?
- Was a supplemental tablet needed in order to achieve pain relief?
- How long after the first tablet did, they take the supplemental tablet?

Action in the Event of an Accidental Overdose

During patient selection it is important to assess whether the patient might be at risk from accidental or intentional overdose.

The symptoms of fentanyl overdose are an extension of its pharmacological actions, the most serious effect being respiratory depression, which may lead to respiratory arrest. Instruct patients/carers about the symptoms of, and what to do in case of, overdose.

Abuse/Diversion/Dependence/medication errors

During patient selection, it is important to assess whether the patient has demonstrated an abuse or may be at risk of abuse of their pain medication.

There is potential for abuse and diversion with this product so patients should be informed about the risk of abuse, addiction and diversion with opioids, including Abstral®. Please refer also to **Patient selection (**section 3).

Patients should be advised about the importance of correct storage/disposal of this medicine, as inappropriate storage/disposal could put someone else (not the patient) at risk of accidental opioid-naïve use, or drug diversion.

Advise patients about the different strengths and the color/shape differentiation.

Safe Keeping, Dispensing & Disposal

- Tablets must be stored in a locked storage space out of the reach of children to avoid risk of death
- Tablets must be kept in the original blister pack to protect them from moisture
- Any unused tablets should be returned to the pharmacy where they will be disposed of in accordance with national and local requirements.

Misuse and overdose:

- Any situation where Abstral® is intentionally and inappropriately used not in accordance with authorised product information should be reported as a safety report.

- This includes situations where incorrect or no titration (including incorrect switching) has been performed.
- During patient selection it is important to assess whether the patient might be at risk from accidental or intentional overdose.
- Instruct patients/carers about the symptoms of, and what to do in case of, overdose.

References:

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- 10. Überall MA, Müller-Schwefe GHH. *Curr Med Res Opin* 2011; 27(7) 1385-94
- 11. Abstral Summary of Product Characteristics: http://www.nrls.npsa.nhs.uk/resources/?EntryId45=59888 Accessed September 2019

Further Information:

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2132NP Hoofddorp
The Netherlands

7. Prescribing Information

Abstral® (fentanyl (as citrate)) 100 micrograms, 200 micrograms, 300 micrograms, 400 micrograms,
600 micrograms and 800 micrograms Sublingual Tablets

Prescribing Information
Please refer to Summary of Product Characteristics before prescribing. **Name:** Abstral sublingual tablets. **Active Ingredient:** Each tablet contains 100mcg, 200mcg, 300mcg, 400mcg, 600mcg or 800mcg fentanyl (as citrate). **Indication:** Management of breakthrough pain (BTP) in adult patients using opioid therapy for chronic cancer pain. **Dosage and administration:** Administer directly under the tongue, and allow to dissolve without chewing, sucking or swallowing the tablet. ***Adults;*** Initially 100mcg, titrating upwards as necessary to establish an appropriate dose. Patients must be monitored closely during titration. Patients should wait at least 2 hours before treating another episode of breakthrough pain and take no more than 4 doses/ day. Abstral should be discontinued immediately if the patient no longer experiences breakthrough pain episodes. The treatment for the persistent background pain should be kept as prescribed. If discontinuation of all opioid therapy is required, the patient must be closely monitored to avoid the possibility of abrupt withdrawal effects. ***Elderly and patients with renal and hepatic impairment;*** Take particular care during titration and monitor for signs of fentanyl toxicity. ***Children and adolescents;*** Must not be used in patients under 18 years of age. **Adverse effects:** The most serious adverse effects include respiratory depression, hypotension and shock. The most frequent adverse reactions include nausea, constipation, somnolence, headache, dizziness, dyspnea, stomatitis, vomiting, dry mouth, hyperhidrosis and fatigue. Other serious but uncommon adverse reactions include hypersensitivity, tachycardia, bradycardia, hypotension and drug withdrawal syndrome. Prescribers should consult the summary of product characteristics for further details of side-effects. **Precautions:** Abstral must be kept out of reach and sight of children. Ensure patients and carers use correctly and know what to do in case of overdose. Before starting Abstral, ensure long-acting opioid treatment for persistent pain is stable. Dependence may develop upon repeated administration of opioids. There is a risk of significant respiratory depression. Take care during dose titration in patients with COPD or at risk of respiratory depression. Administer with extreme caution in patients susceptible to the intracranial effects of hypercapnia. Opioids may mask the clinical course in patients with head injuries. Use with caution in patients mouth wounds or mucositis. Monitor use carefully in elderly, cachectic and debilitated patients, and patients with liver or kidney dysfunction. A potentially life-threatening serotonin syndrome may occur with the concomitant use of serotonergic drugs. Discontinue Abstral if serotonin syndrome is suspected. **Interactions:** Use with caution if given concomitantly with CYP3A4 inhibitors (e.g. macrolide antibiotics, azole antifungal agents, protease inhibitors or grapefruit juice), other CNS depressants, alcohol or partial opioid agonists/ antagonists (e.g. buprenorphine, pentazocine). Co-administration of a serotoninergic agent, such as a Selective Serotonin Reuptake Inhibitor, a Serotonin Norepinephrine Reuptake Inhibitor or a Monoamine Oxidase Inhibitor, may increase the risk of serotonin syndrome. Not recommended for use in patients who have received an MAOI within 14 days. **Pregnancy:** Fentanyl should only be used during pregnancy when clearly necessary. Do not use during labour and delivery. **Lactation:** Fentanyl should not be used by breastfeeding women. **Contraindications:** Hypersensitivity to any of the ingredients; opioid-naïve patients; severe respiratory depression or severe obstructive lung conditions. Treatment of acute pain other than BTP.