PHYSICIAN'S GUIDE FOR PRESCRIBING

FENTORA®
BUCCAL TABLETS

This document has been reviewed and approved by the Ministry of Health on February 2023

FENTORA®
(fentanyl buccal tablet)

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INTRODUCTION

This guide is designed to help you understand the proper prescribing of FENTORA® (fentanyl) Buccal tablets for patients with breakthrough cancer pain (BTcP). Please read this guide carefully before prescribing FENTORA® and keep it for future reference. Critically, select patients based upon labelled information and use the Prescriber's Checklist provided. Encourage patients to talk about all medication-related issues.

FENTORA® buccal tablets may only be prescribed by physicians who are experienced, knowledgeable, and qualified in the use of opioid therapy in cancer patients. Special care should be taken when patients transition from hospital to home-based care.

The following materials are also available:

» A Patient/Carer Guide to the safe use of FENTORA® Buccal Tablet

» A Pharmacist's Guide for Dispensing FENTORA® Buccal Tablets

This Physician's Guide (and the other materials listed above) can be viewed or downloaded from:

https://www.gov.il/he/Departments/DynamicCollectors/patient-safety-information

REPORTING SIDE EFFECTS

Side effects can be reported to the Ministry of Health using the online form for side effect reporting that is found in the Ministry of Health homepage:

www.health.gov.il

or via the link:

https://sideeffects.health.gov.il

or through the marketing authorization holder:

Safety.Israel@Teva.co.il

FENTORA® (fentanyl buccal tablet)

WHAT IS FENTORA®?

FENTORA® for the treatment of cancer breakthrough pain

FENTORA® is a transmucosal form of fentanyl, an opioid analgesic. FENTORA® is indicated for the treatment of BTcP in adults who are already receiving maintenance opioid therapy for chronic cancer pain.[1]

FENTORA® is suitable for adult patients with BTcP who have been receiving maintenance opioid therapy for at least a week, consisting of:

- At least 60 mg of oral morphine daily, **or**
- At least 25 micrograms of transdermal fentanyl per hour, **or**
- At least 30 mg of oxycodone daily, **or**
- At least 8 mg of oral hydromorphone daily, **or**
- An equianalgesic dose of another opioid[1]

HOW IS FENTORA® USED?

Correct use of FENTORA®

Important:

The treatment of cancer pain must be initiated by, and remain under the supervision of, a physician who has sufficient knowledge and experience in the management of opioid therapy in cancer patients.

If left untreated, BTcP can have serious negative effects on a patient's quality of life.

As a prescribing physician, you must ensure your patient is appropriate for treatment with FENTORA® and that they understand how to use the medication. Specifically:

1 Buccal tablet	One tablet of FENTORA® per BTcP episode, with the option of taking a second FENTORA® tablet of the same strength after at least 30 minutes, if BTcP is not relieved
4 Hours	It is important to explain to the patient that there should generally be at least 4 hours between each treatment of a BTcP episode, highlighting the risks associated with more frequent use[1]
No more than 4 tablets	Dose readjustment of the background opioid therapy may be required if patients consistently present with more than four BTcP episodes per 24 hours[1]

Dosage and titration

- Do not compare FENTORA® Buccal tablets strengths with those of other fentanyl-containing products. Dose only according to the SmPC.
- To optimise BTcP treatment, please make use of the titration tool below with stepwise titration through the appropriate doses until adequate analgesia is achieved.
- The initial dose of FENTORA® should be 100 micrograms, titrating upwards as necessary through the range of available tablet strengths (100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg).
- During titration, if adequate analgesia is not obtained within 30 minutes after the start of administration of a single tablet FENTORA®, a second FENTORA® tablet of the same strength may be used.
- If treatment of a BTcP episode requires more than one tablet, an increase in dose to the next higher available strength should be considered to treat the next BTcP episode.

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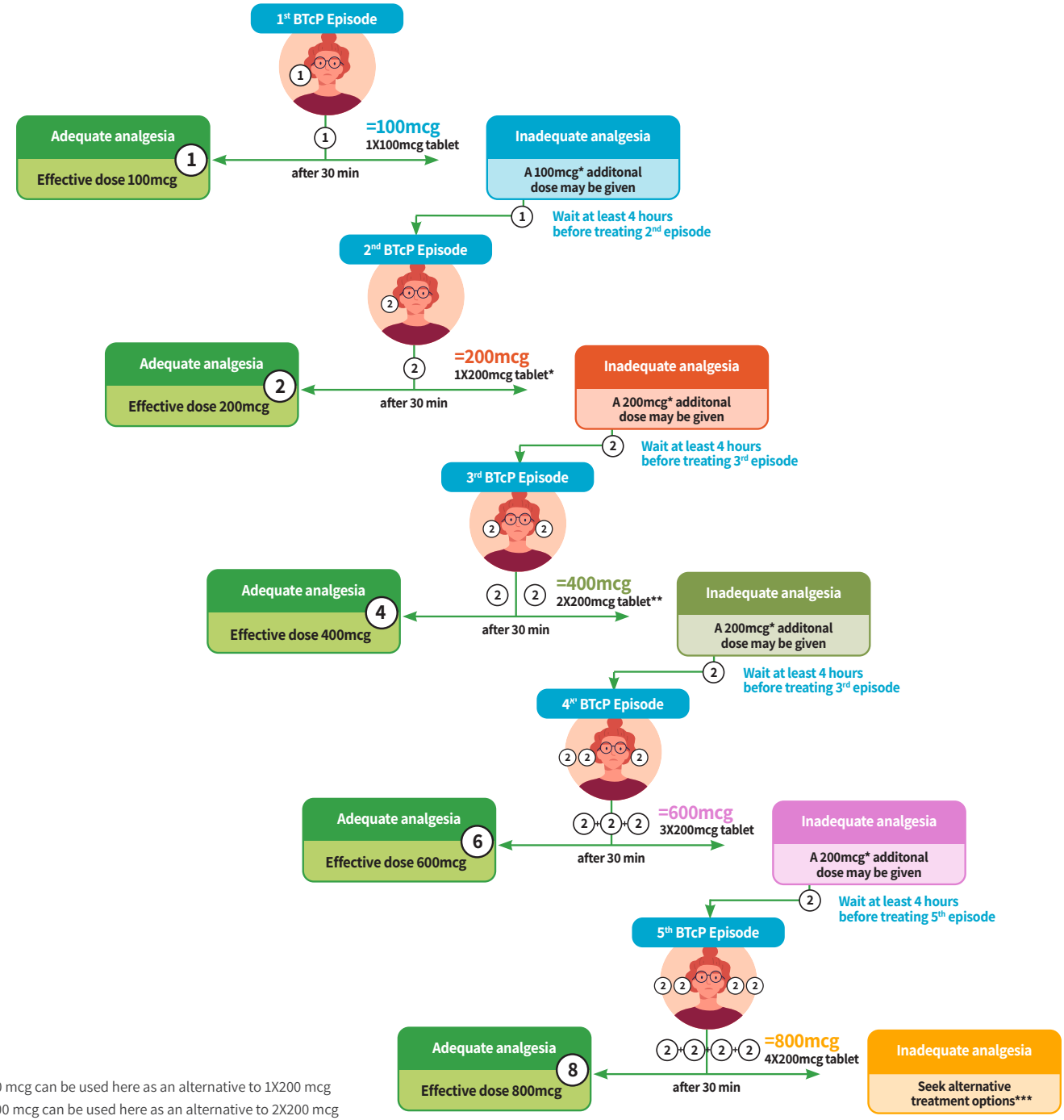

* 2x100 mcg can be used here as an alternative to 1X200 mcg

** 4X100 mcg can be used here as an alternative to 2X200 mcg

*** Doses above 800 mcg Fentora® have not been evaluated in clinical trials

Maintenance therapy

- Once a successful dose has been established during titration patients should continue to take this dose as a single tablet of that given strength.
- Breakthrough pain episodes may vary in intensity and the required FENTORA® dose might increase over time due to progression of the underlying cancer disease. In these cases, a second tablet of the same strength may be used. If a second tablet of FENTORA® was required for several consecutive times, the usual maintenance dose is to be readjusted.
- Patients should wait at least 4 hours before treating another BTcP episode with FENTORA® during maintenance therapy.[1]

Dose re-adjustment

- The maintenance dose of FENTORA® should be increased when a patient requires more than one tablet per BTcP episode for several consecutive BTcP episodes.
- Dose readjustment of the background opioid therapy may be required if a patient consistently present with more than four BTcP episodes per 24 hours.
- In absence of adequate pain control, the possibility of hyperalgesia, tolerance and progression of underlying disease should be considered.[1]

Discontinuation of therapy

- FENTORA® should be discontinued immediately if the patient no longer experiences BTcP episodes. The treatment for persistent background pain should be kept as prescribed.
- If discontinuation of all opioid therapy is required, the patient must be closely followed by the doctor in order to manage the risk of abrupt withdrawal effects.

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Overdose and Unintentional exposure

Unintentional exposure to FENTORA® is considered a medical emergency and a potentially life-threatening event.

If a child is accidentally exposed to the FENTORA®, it is considered a medical emergency and may, without professional treatment, cause death.

Make sure that both yourself and colleagues likely to come into contact with patients on fentanyl therapy are aware of the signs of fentanyl overdose/toxicity and the appropriate protocol for its management. Ensure medications such as naloxone are readily accessible and staff are trained in their use.1

The most serious signs of opioid overdose/toxicity are:

- Altered mental status
- Loss of consciousness
- Coma
- Hypotension
- Respiratory depression, respiratory distress, and respiratory failure, which have resulted in death
- Cases of Cheyne-Stokes respiration have been observed in case of fentanyl overdose, particularly in patients with history of heart failure

Please ensure that your patients and their carers are aware of the signs of fentanyl overdose/toxicity and understand the need to seek urgent medical attention.

Patients should be monitored for signs that they are not using FENTORA® as prescribed and should be made aware of the serious risks associated with misuse, abuse, overdose, and addiction.[1]

Safety, Storage, and disposal

- FENTORA® should only be handled by the patient or their carers. Please advise the patient never to allow anyone else to handle or use the product.
- Store FENTORA® in the original package in order to protect from moisture. The tablet should not be stored once removed from the blister package as the tablet integrity cannot be guaranteed and a risk of accidental exposure to a tablet can occur.
- Please draw the attention of patients and their cares to the danger if children are exposed to FENTORA®.
- Please ensure that patients understand that in order to prevent theft, diversion (ie., misuse for illegal purposes) or other misuse, fentanyl should be stored in a suitably secure place. Fentanyl, the active ingredient in FENTORA® is a target for people who abuse narcotic medicines or other street drugs, and therefore storage instructions must be closely followed.
- Information about proper disposal: Patients and carers must be advised to dispose of any unopened tablets remaining from a prescription as soon as they are no longer needed. Any used or unused but no longer required medicinal product or waste material should be disposed of in accordance with local requirements.

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WHAT ARE THE RISKS ASSOCIATED WITH OFF-LABEL USE OF FENTORA®?

Importance of preventing off-label use

The use of FENTORA® outside the approved indication is considered off-label use. **Please note that different fentanyl formulations have different indicationss**. Make sure that you are familiar with the specific indication for FENTORA® before prescribing. The use of FENTORA® for indications other than those approved increases the risk of misuse, abuse, medication error, overdose, addiction and death.

Off-label use would include the following prescriptions

- All indications except BTcP, including any other pain therapy
- Patients who do not already receive maintenance opioid therapy
- More frequent dosing than recommended
- Patients under 18 years of age

Medication errors are also particularly important to avoid when prescribing FENTORA®

Types of medication errors include

- Unintentional drug prescribing error
- Drug administration error
- Drug dispensing error
- Incorrect dosage administered
- Use of an incorrect route of administration

In order to minimize the risk of medication errors, all FENTORA® labels are color-coded differently for each of the strengths of action:

100 mcg- blue | 200 mcg- orange | 400 mcg- green | 600 mcg- pink | 800 mcg- yellow

RISKS ASSOCIATED WITH "OPIOID USE DISORDER" (OUD)

How to recognize abuse-related side effects and OUD

The following considerations may help you identify patients who have developed OUD. In patients where OUD is strongly suspected, a consultation with an addiction specialist should be considered.

1. **Pay particular attention to patients who have an increased risk of OUD**
   The risk of developing OUD is increased in patients with a personal or family history (parents or siblings) of substance use disorders (including alcohol use disorder), in current tobacco users and in patients with a personal history of other mental health problems (e.g. depression, anxiety and personality disorders).

2. **Carefully monitor prescription requests**
   Patients must be observed for signs of drug-seeking behavior (e.g. desire for early follow-up prescriptions). This includes monitoring concomitant use of other opioids and other psychoactive drugs (such as benzodiazepines).

Recognize the symptoms of addiction and withdrawal

Withdrawal symptoms are one of the criteria associated with OUD. The context of withdrawal symptoms must be accurately assessed. A patient suffering from withdrawal symptoms may complain of nausea and vomiting, anxiety, insomnia, heat and cold flushes, excessive sweating, muscle cramps, watery discharge from the eyes and nose, and/or diarrhea.[3]

Some OUD criteria may be difficult to distinguish from behaviors that are frequently observed in cancer patients receiving opioid pain therapy. Some classical opioid withdrawal symptoms are also "normal" side effects that have been reported after the use of FENTORA® (e.g. flushing, insomnia, sweating).[1] The complexity of treating BTcP, together with the risks associated with off-label use, poses unique challenges to OUD diagnosis.

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WHAT TO DO IF YOU SUSPECT THAT YOUR PATIENT IS SUFFERING FROM OUD?

A patient suffering from OUD can still receive cancer treatment and have their pain relieved. Several treatment options for patients with OUD can be considered and tailored to individual needs.[5] These include:

- Treatment with opioid agonists (Opioid Agonist Treatment, OAT), including methadone or buprenorphine, currently the most effective drugs for opioid dependence and addiction.[4]
- Behavioral medicine and psychosocial interventions.

A combination of behavioral and pharmacotherapeutic approaches (so-called drug-assisted therapy) has proven to be the most successful in helping patients overcome OUD.[2] If you do not feel qualified to offer effective behavioral and/or pharmacotherapeutic treatment for OUD, please refer your patient to an appropriately qualified specialist.

Report any known off-label use, misuse, abuse, addiction, and overdose via:

Side effects can be reported to the Ministry of Health using the online form for side effect reporting that is found in the Ministry of Health homepage: **www.health.gov.il** or via the link: **https://sideeffects.health.gov.il** or through e-mail to the marketing authorization holder: **safety.israel@teva.co.il**

OTHER IMPORTANT POINTS ABOUT FENTORA®

Please counsel the patient on the following points from the FENTORA® SmPC:

1. The following adverse reactions have been reported with FENTORA® and/or other fentanyl- containing compounds during clinical studies and post-marketing experience: dyspnoea, drug dependence (addiction), drug abuse, neonatal withdrawal syndrome, loss of consciousness. (See SmPC Section 4.8)

2. Hyperalgesia: As with other opioids, in case of insufficient pain control in response to an increased dose of fentanyl, the possibility of opioid-induced hyperalgesia should be considered. Fentanyl dose reduction or discontinuation of fentanyl treatment or treatment review may be indicated. (See SmPC Section 4.2 and 4.4)

3. Concomitant use of medicinal products containing sodium oxybate and fentanyl is contraindicated. (See SmPC Sections 4.3 and 4.5.)

4. Co-administration of fentanyl with other central nervous system depressants, including other opioids, sedatives or hypnotics, (including benzodiazepines), general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines, gabapentinoids (gabapentin and pregabalin) and alcohol can produce additive depressant effects which may result in a fatal outcome. (See SmPC Section 4.5)

5. Pregnancy: There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown reproductive toxicity (see SmPC Section 5.3). The potential risk for humans is unknown. FENTORA® should not be used in pregnancy unless clearly necessary. (See SmPC Section 4.6)

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References

1. FENTORA® Buccal tablets — Summary of Product Characteristics (SmPC).
2. Centers for Disease Control and Prevention. Web site. Module 5. Assessing and addressing opioid use disorder (OUD). https://www.cdc.gov/drugoverdose/training/oud/accessible/index.html. Accessed on 31 March 2020.
3. Clinical guidelines for withdrawal management and treatment of drug dependence in closed settings. Geneva: World Health Organization (WHO); 2009. 4, Withdrawal management. https://www.ncbi.nlm.nih.gov/books/NBK310652/. Accessed on 31 March 2020
4. Degenhardt L, Grebely J, Stone J, et al. Global patterns of opioid use and dependence: harms to populations, interventions, and future action. Lancet. 2019;394:1560–1579.
5. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Policy and practice briefings: tackling opioid dependence. http://www.emcdda.europa.eu/print/best-practice/briefings/tackling-opioid-dependence_en. Accessed on 31 March 2020

CHECKLIST FOR DISPENSING FENTORA®

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No.	Description	Done
1	Ensure that all the criteria of the approved indication are fulfilled. FENTORA® should only be prescribed for BTcP in adults who are already receiving opioid maintenance therapy for background cancer pain	☐
2	Give the patient and/or carer instructions on how to use the FENTORA®	☐
3	Make sure the patient/carer reads the Package Leaflet inside the FENTORA® package	☐
4	Supply the patient/carer with the FENTORA® Patient/Carer Guide and explain the use of the dose monitoring card	☐
5	Instruct the patient/carer on how to open the blister packaging as described in the Patient/Carer Guide	☐
6	Explain the risks of using more than the recommended amount of FENTORA®	☐
7	Advise the patient/carer of signs of fentanyl overdose and the need for immediate medical assistance	☐
8	Explain secure storage and the need to keep FENTORA® out of the reach and sight of children	☐
9	Explain the correct process for disposal of FENTORA®	☐
10	Encourage the patient/carer to discuss their maintenance opioid therapy, BTcP, and their use of opioids with you	☐

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