PHYSICIAN'S GUIDE FOR PRESCRIBING

ACTIQ® LOZENGES

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

ACTIQ® oral transmucosal fentanyl citrate

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For full information about the drug please refer to Prescribing Information of ACTIQ® LOZENGES.

INTRODUCTION

This guide is designed to help you understand the proper prescribing of ACTIQ® (fentanyl) lozenges for patients with breakthrough cancer pain (BTcP). Please read this guide carefully before prescribing ACTIQ® 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.

ACTIQ® lozenges 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 ACTIQ® Lozenges

» A Pharmacist's Guide for Dispensing ACTIQ® Lozenges

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.

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WHAT IS ACTIQ®?

ACTIQ® for the treatment of cancer breakthrough pain

ACTIQ® is a transmucosal form of fentanyl, an opioid analgesic. ACTIQ® is indicated for the management of BTcP in patients already receiving maintenance opioid therapy for chronic cancer pain.[1]

ACTIQ® is suitable for patients aged 16 years and above 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 ACTIQ® USED?

Correct use of ACTIQ®

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 ACTIQ® and that they understand how to use the medication. Specifically:

1 Lozenge	One ACTIQ® lozenge per BTcP episode, with the option of taking a second lozenge of the same strength after at least 30 minutes (15 minutes after the patient completes consumption of a single ACTIQ® unit) if the BTcP episode is not relieved. No more than two ACTIQ® lozenges should be used to treat any individual BTcP episode
No more than 4 lozenges	Patients should limit consumption to a maximum of four ACTIQ® lozenges per day[1]

Dosage and titration

- Do not compare ACTIQ® Lozenge 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 scheme through the appropriate doses until adequate analgesia is achieved
- The initial dose of ACTIQ® used should be 200 micrograms, titrating upwards as necessary through the range of available dosage strengths (200mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable adverse reactions using a single lozenge per episode of BTcP. This is defined as successful dose
- During titration, if adequate analgesia is not obtained within 30 minutes after starting the first lozenge (i.e., 15 minutes after the patient completes consumption of a single ACTIQ® lozenge), a second ACTIQ® lozenge of the same strength may be consumed
- If treatment of consecutive BTcP episodes requires more than one lozenge per BTcP episode, an increase in dose to the next higher available strength should be considered[1]

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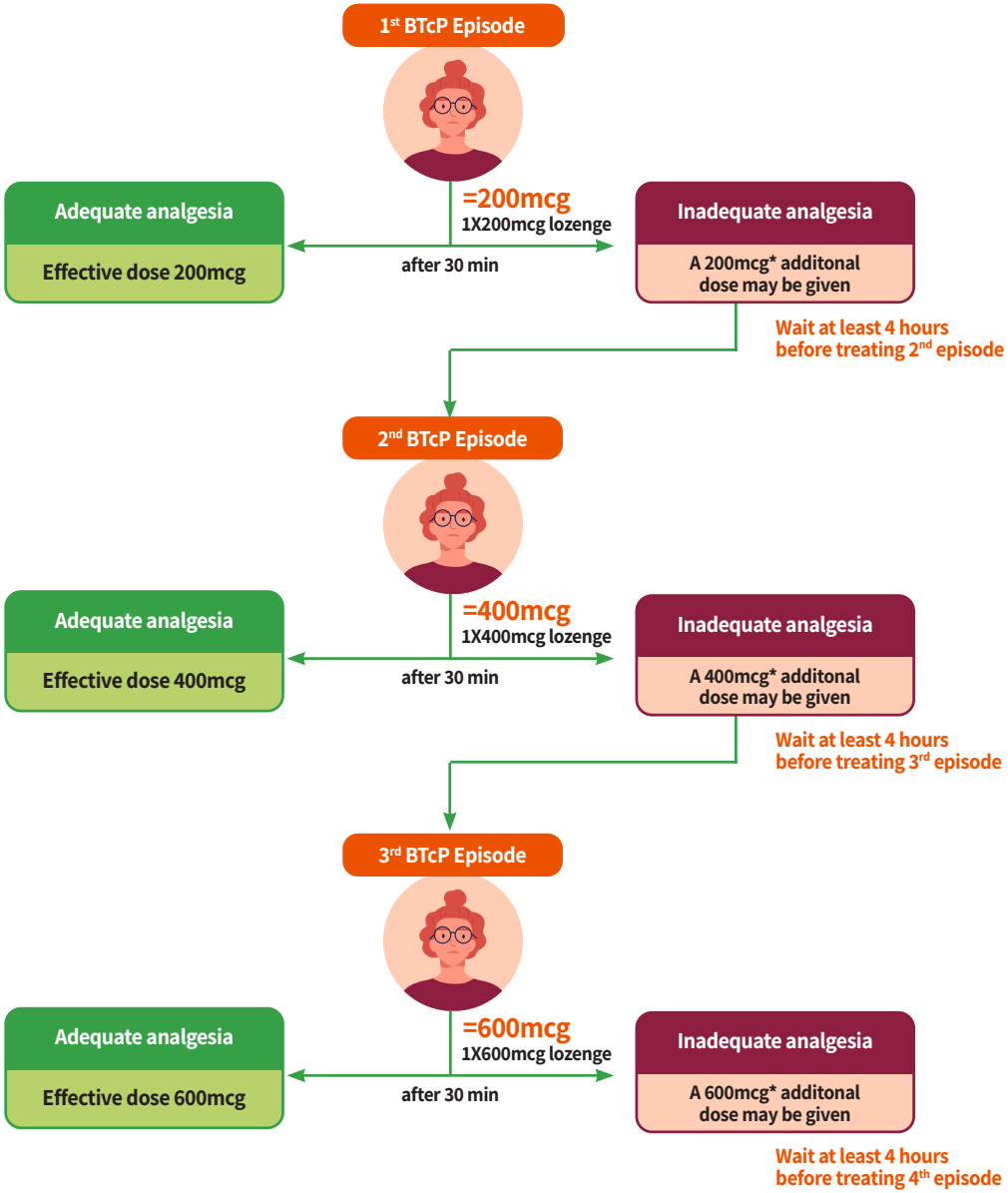

*If adequate analgesia is not obtained with one ACTIQ® lozenge, dose should be increased to the next highest strength. Available dosage strengths include: 200mcg, 400 mcg, 600 mcg, 800 mcg, 1200 mcg and 1600 mcg

Maintenance therapy

- Once a successful dose has been established (i.e., on average, a BTcP episode is effectively treated with a single lozenge), patients should be maintained on this dose and should limit consumption to a maximum of four ACTIQ® lozenges per day
- Patients should be monitored by a health professional to ensure that the maximum of four ACTIQ® lozenges per day is not exceeded[1]

Dose re-adjustment

- The maintenance dose of ACTIQ® should be increased when a BTcP episode is not effectively treated with a single lozenge for several consecutive BTcP episodes
- If more than four BTcP episodes are experienced per day, the dose of the maintenance opioid therapy used for persistent pain should be re-evaluated. If the dose of the maintenance opioid therapy is increased, the dose of ACTIQ® to treat BTcP may need to be reviewed.
- In absence of adequate pain control, the possibility of hyperalgesia, tolerance, and progression of underlying disease should be considered
- It is imperative that any dose re-titration of any analgesic is monitored by a health professional[1]

Discontinuation of therapy

- ACTIQ® should be discontinued immediately if the patient no longer experiences BTcP. 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 as gradual downward opioid titration is necessary in order to avoid the possibility of abrupt withdrawal effects[1]

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Overdose and Unintentional exposure

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

If a child is accidentally exposed to the product, 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.

The most serious signs of overdose/toxicity are:

- Altered mental status
- Loss of consciousness
- Coma
- Cardiorespiratory arrest
- 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 ACTIQ® as prescribed and should be made aware of the serious risks associated with misuse, abuse, overdose, and addiction.[1]

Safety, Storage, and disposal

- ACTIQ® 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
- ACTIQ® lozenges should be stored in protective blister until ready for use.
- ACTIQ® should not be stored above 30°C
- Please draw the attention of patients and their carers to the danger if a child is exposed to ACTIQ®
- Please ensure that patients understand that in order to prevent theft, diversion (misuse for illegal purposes) or other misuse, fentanyl should be stored in a suitably secure place. Fentanyl, the active ingredient in ACTIQ® 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: ACTIQ® lozenges with residual active substance should at no time be discarded or misplaced. Any used or unused but no longer required product or waste material should be disposed of in accordance with local requirements[1]

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

Importance of preventing off-label use

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

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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 16 years of age

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

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 ACTIQ® labels are color-coded differently for each of the strengths of action:

200 mcg- gray | 400 mcg- blue | 600 mcg- orange | 800 mcg- purple | 1200 mcg- green | 1600 mcg- red

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)

3. **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 ACTIQ® (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 ACTIQ®

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

1. The following adverse reactions have been reported with ACTIQ® 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 or limited amount of 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. ACTIQ® should not be used in pregnancy unless clearly necessary. (See SmPC Section 4.6)

6. Dental decay and tooth loss: Normal oral hygiene is recommended to reduce any potential harm to the teeth. Because ACTIQ® contains approximately 2 grams of sugar, frequent consumption increases the risk of dental decay. The occurrence of dry mouth associated with the use of opioid medicinal products may add to this risk. During treatment with ACTIQ®, regular dental visits are advised (see SmPC Section 4.4)

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References

1. ACTIQ® Lozenges — Summary of Product Characteristics (SmPC). Teva B.V.
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 ACTIQ®

No.	Description	Done
1	Ensure that all the criteria of the approved indication are fulfilled. ACTIQ® should only be prescribed for BTcP in patients who are already receiving opioid maintenance therapy for background cancer pain	☐
2	Give the patient and/or carer instructions on how to use ACTIQ® lozenges	☐
3	Make sure the patient/carer reads the Package Leaflet inside the ACTIQ® package	☐
4	Supply the patient/carer with the ACTIQ® A 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 ACTIQ®	☐
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 ACTIQ® out of the reach and sight of children	☐
9	Explain the correct process for disposal of ACTIQ®	☐
10	Encourage the patient/carer to discuss their maintenance opioid therapy, BTcP, and their use of opioids with you	☐

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