Prescriber's Guide For Prescribing ACTIQ® Lozenges

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, www.hpra.ie.

Adverse events may also be reported to Teva Pharmaceuticals Ireland *via* email to medinfo@tevauk.com or *via* phone on +44 (0) 207 540 7117.

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INTRODUCTION

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

Please read this guide carefully before prescribing ACTIQ® and keep it for future reference. This guide should be read in conjunction with the ACTIQ® Summary of Product Characteristics. 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 prescribers 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

This Prescribers Guide (and the other materials listed above) can be viewed or downloaded from the Health Products Regulatory Authority Website at: https://www.hpra.ie (enter 'Actiq' in Find a Medicines Search Area. click *'EdM' under the 'Documents' column for the relevant Actiq product).

*For a full list of medicines that have Educational Materials use the advanced search option and click on 'Only Medicines with Educational Materials'

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 breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain.[1]

ACTIQ® is suitable for patients aged 16 years and above with breakthrough pain 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]

Off-label use would include the following prescriptions:

- All indications except breakthrough pain, 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.

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.

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 prescriber who has sufficient knowledge and experience in the management of opioid therapy in cancer patients.

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

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

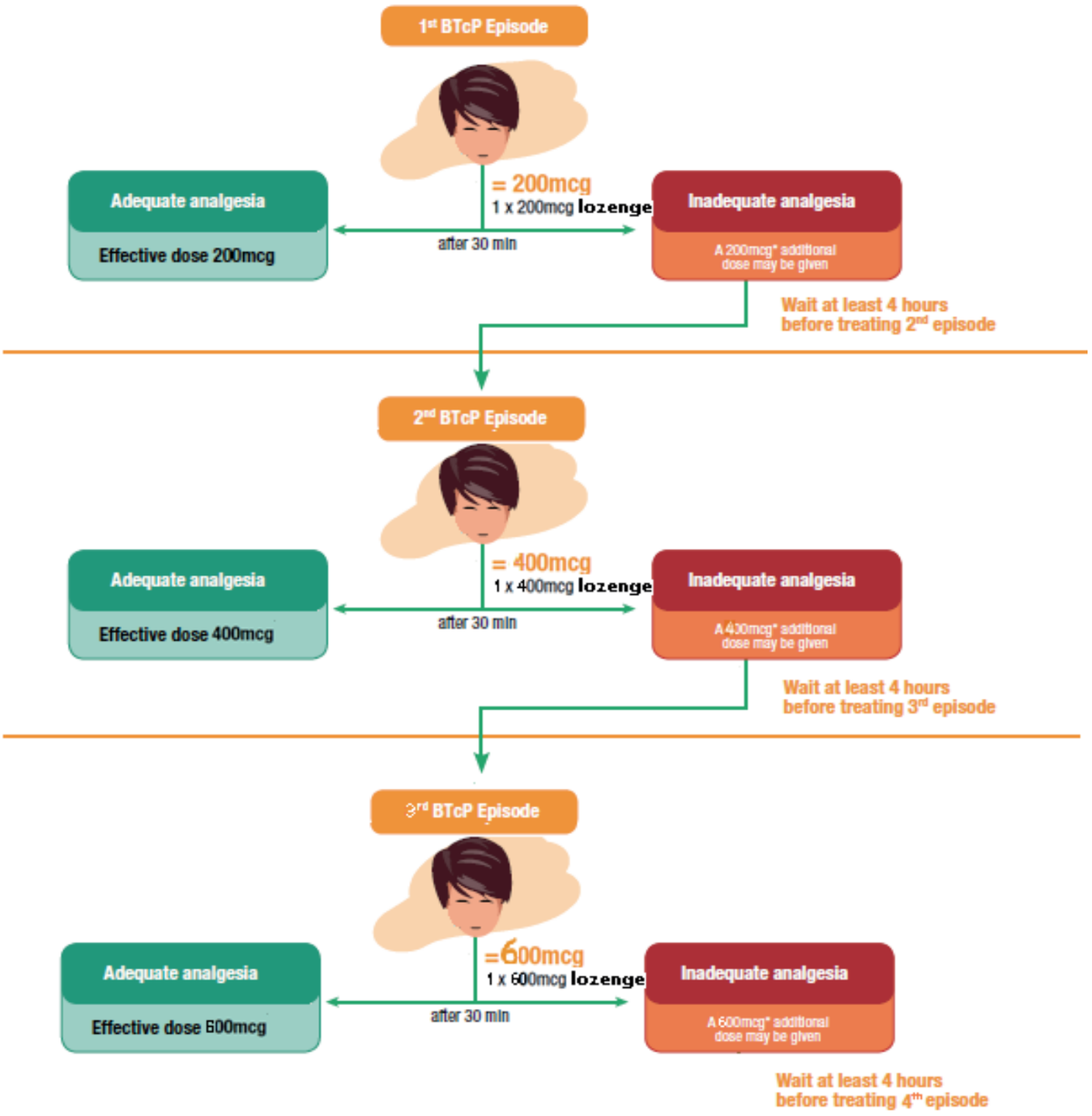
Medication errors are also particularly important to avoid when prescribing ACTIQ®.

In order to minimise the risk of medication errors, all ACTIQ® labels are color-coded differently for each of the strengths of action.

- 200 mcg - Grey
- 400 mcg - Blue
- 600 mcg - Orange

Dosage and titration

- Do not compare ACTIQ® Lozenge strengths with those of other fentanyl-containing products. Dose only according to the SmPC.
- To optimise breakthrough pain 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 (200 mcg, 400 mcg and 600 mcg). Patients should be carefully monitored until a dose is reached that provides adequate analgesia with acceptable adverse reactions using a single unit per episode of breakthrough pain. This is defined as successful dose.
- During titration, if adequate analgesia is not obtained within 30 minutes after starting the first unit (i.e., 15 minutes after the patient completes consumption of a single ACTIQ® unit), a second ACTIQ® unit of the same strength may be consumed.
- If treatment of consecutive breakthrough pain episodes requires more than one unit per breakthrough pain episode, an increase in dose to the next higher available strength should be considered.[1]



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

Maintenance therapy

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

Dose re-adjustment

- The maintenance dose of ACTIQ® should be increased when a breakthrough pain episode is not effectively treated with a single unit for several consecutive breakthrough pain episodes.
- If more than four breakthrough pain 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 breakthrough pain 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 breakthrough pain. 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]

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.

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]

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 before and during therapy.**
   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 and recognise the symptoms of addiction and withdrawal.**
   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).

   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]

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. For patients with signs and symptoms of OUD, consultation with an addiction specialist should be considered. Several treatment options for patients with OUD can be considered and tailored to individual needs.[4]

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:

HPRA Pharmacovigilance, www.hpra.ie.

Adverse events should also be reported to Teva Pharmaceuticals Ireland *via* email at medinfo@tevauk.com or *via* phone on +44 (0) 207 540 7117.

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.)

CHECKLIST FOR PRESCRIBING ACTIQ® LOZENGES

- [ ] Ensure that all the criteria of the approved indication are fulfilled. ACTIQ® should only be prescribed for breakthrough pain in patients who are already receiving opioid maintenance therapy for background cancer pain
- [ ] Give the patient and/or carer instructions on how to use ACTIQ® lozenges
- [ ] Make sure the patient/carer reads the Package Leaflet inside the ACTIQ® package
- [ ] Supply the patient/carer with the ACTIQ® Patient/Carer Guide and explain the use of the dose monitoring card.
- [ ] Instruct the patient/carer on how to open the blister packaging as described in the Patient/Carer Guide
- [ ] Explain the risks of using more than the recommended amount of ACTIQ®
- [ ] Advise the patient/carer of signs of fentanyl overdose and the need for immediate medical assistance
- [ ] Explain secure storage and the need to keep ACTIQ® out of the reach and sight of children
- [ ] Explain the correct process for disposal of ACTIQ®
- [ ] Encourage the patient/carer to discuss their maintenance opioid therapy, breakthrough pain, and their use of opioids with you.
- [ ] Remind the patient and/or caregiver that they should ask their doctor if they have any questions or concerns about how to use ACTIQ® or about the associated risks of misuse and abuse.

References

1. ACTIQ® Lozenges — Summary of Product Characteristics (SmPC). Teva Pharma 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 25 January 2023)

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 18 October 2022)

4. European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).Opioids: health & social responses. https://www.emcdda.europa.eu/publications/mini-guides/opioids-health-and-social-responses_en. (Accessed on 18 October 2022)