SOP 002 – Analgesia with Ethiqa XR® (buprenorphine extended-release injectable suspension)

SOP 002	Species: **Mouse**
Version 01	Date: 03.04.2024
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Indication for use of Ethiqa XR®:

- Extended release buprenorphine suspension (1.3 mg buprenorphine/ml) for analgesia in mice that will undergo experimental procedures expected to cause pain for 48-72 hours.
- Administer **exclusively subcutaneously**, **30-60 minutes prior to start of the painful procedure.**
- Inject at a different location than other substances, **do not mix** with other substances (Ethiqa XR® **must not be diluted**)
- Before using Ethiqa XR® always read the manufacturer instructions on the website.
- Before each planned use, check the expiry date of the vial and use it only if valid.
- At first use of each vial: write the date of opening on the vial. At subsequent uses of each vial: check written date of opening and use only within 90 days.
- **Store only in original vial** (see Figure 1) at room temperature (15° to 25°C) in a locked cabinet/locked safe.
- Unfinished vials > 90 days after broaching and expired vials must be sent to the drug control unit ("Heilmittelkontrolle"). The form that needs to be filled out and the address can be found here: https://www.zh.ch/de/gesundheit/heilmittel-betriebe/arznei-betaeubungsmittel.html#-1033478754

Figure 1 Ethiqa XR® vials

1. Preparation

1.1. Material and additional tools/supplies

- Ethiqa XR® (1.3 mg buprenorphine/ml), 5 ml glass vial containing 3 ml viscous, oil-based suspension.

- Sterile syringe (0.5 or 1ml) to withdraw Ethiqa XR® (viscous suspension) from the vial. Sterile Luer Lock syringes are recommended (see Figure 2).

Figure 2 Luer Lock 1 ml syringe

- Sterile needle (23 G or larger) to withdraw Ethiqa XR® from the vial
- Sterile needle, 23 G for subcutaneous injection of Ethiqa XR®
- Scale for weighing the animal
- Clean paper tissue/sterile gauze
- Ethanol 70%
- Sharps dispenser
- Protective clothing to prevent direct contact of Ethiqa XR® with human skin or mucous membranes when handling the suspension

1.2. Procedure prior to administration of Ethiqa XR®

a. Weigh the mouse and record the weight in writing on the relevant form.

b. The **dose** for a **mouse** is **a single subcutaneous injection** of **3.25 mg buprenorphine/kg body weight**, i.e.2.5 **ml Ethiqa XR®/kg** body weight = 2.5 **microl** Ethiqa XR®/**g** body weight.

Calculate the dose and volume of administration for Ethiqa XR® based on the weight of the animal e.g.: **0.05 ml Ethiqa XR® suspension per 20-gram mouse**

c. **Shake the Ethiqa XR® vial well before each use** to ensure uniform suspension.

d. Use **aseptic technique** to withdraw the suspension from the vial:

- **1st use of a vial:**

  i. remove the blue plastic cap of the Ethiqa XR® vial (depicted in Figure 1) without touching the gray rubber stopper underneath it (see Figure 3 below):

Figure 3 Grey rubber stopper on top of an Ethiqa XR® vial

  ii. use a 1 ml or 0.5 ml sterile syringe fitted with a sterile needle to puncture the rubber stopper of the vial in the middle and to withdraw the suspension slowly. Discard the needle in a sharps dispenser.

  iii. carefully fit a 23G sterile needle on the syringe containing Ethiqa XR®: these will be used for the subcutaneous injection. **Beware of the small volume to be injected**.

- **2nd use and subsequent uses of the same vial:**

i. wipe the rubber stopper of the vial with a clean paper tissue/sterile gauze sprayed with/soaked in 70% ethanol prior to inserting the needle to withdraw the suspension. Then follow steps ii. and iii. (see above).

2. Subcutaneous injection of Ethiqa XR®

a. Immobilize the mouse on the cage grid with one hand, allowing it to grasp the grid with its paws.
b. While restraining the mouse with the hand (by pressing it down moderately) use the forefinger and thumb to lift the skin on the back of the mouse. Pull a tent of skin to separate the epidermal/dermal layers from the musculature of the animal, creating a subcutaneous space.
c. The injection can be performed on the back of the mouse above the shoulder blades (scapular injection, preferred) or on the flank of the mouse.
d. Have the needle bevel up. Inject into the lifted skin well below your fingers, holding the needle parallel to the body of the mouse to avoid damage to underlying structures.
e. Inject the suspension **very slowly and carefully.** Keep the needle shortly in place after injecting to avoid reflux.
f. Withdraw the needle slowly and check that no suspension is running out of the skin.
g. Place the mouse back into the home cage.
h. Dispose of the needle into sharps container.
i. Record the administration of Ethiqa XR® (at least: animal ID, date, time, dose, route of administration, visum/signature) in writing on the relevant forms: documentation for animal experiments (according to Art. 144 Animal Welfare Ordinance) and documentation for use of controlled substances.
j. **Monitor and score the animal according to the experimental animal license.**

3. What to do in case of adverse or unexpected effects of Ethiqa XR® on mice

- Please refer to the "Recommendations for the use of Ethiqa XR® in mice"

4. Precautions and considerations regarding storage, use and safety

4.1. Ethiqa XR®

- Do not freeze.
- Do not return any unused drug suspension from the syringe back into the vial.
- Beware of interactions with other drugs (e.g**. do not use it prior to midazolam-medetomidine-fentanyl anaesthesia, use with caution when used together with drugs that cause respiratory depression, do not use buprenorphine as rescue analgesia within 72 hours after administration of Ethiqa XR®**)

- Buprenorphine is excreted in the feces. Coprophagy may lead to ingestion of buprenorphine or its metabolites by mice treated with Ethiqa XR® and untreated cage mates
- The safety of Ethiqa XR® has not been evaluated in pregnant, lactating, neonatal, or immunodeficient mice.
- Ethiqa XR® forms a depot near the injection site. Granulomatous inflammation nodules have been observed in nude mice administered Ethiqa XR®.
- **Adverse effects, including death, have been reported when non-steroidal anti-inflammatory drugs (NSAIDs) and Ethiqa XR® have been administered concomitantly in mice. For further information, please consult the "Recommendations for the use of Ethiqa XR® in mice"**

4.2. Human safety considerations

- **Protective covering:** To prevent direct contact of Ethiqa XR® with human skin or mucous membranes when handling the suspension, protective clothing is recommended.
- **Mucous membrane or eye contact during administration**: Direct contact of Ethiqa XR® with the eyes, oral or other mucous membranes of humans could result in absorption of buprenorphine and the potential for adverse reactions. If accidental eye, oral or other mucous membrane contact is made during administration, flush the area with water and contact a physician.
- **Skin contact during administration:** If human skin is accidentally exposed to Ethiqa XR®, wash the exposed area with soap and water and contact a physician. Accidental exposure could result in absorption of buprenorphine and the potential for adverse reactions.