

Recommendation for use of Ethiq XR® in mice

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Authors:

Prof. Margarete Arras, DVM, Dr. Med. Vet., Diplomate of the European College of Laboratory Animal Medicine (ECLAM)

PD Dr. Alessandra Bergadano, DVM, Dr. Med. Vet., Diplomate of the European College of Veterinary Anaesthesia and Analgesia (ECVAA),
Dipl. ECLAM, PhD, Head of Experimental Animal Center (EAC) at the University of Bern (UNIBE)

Corina Berset, DVM, Dr. Med. Vet., Dipl. ECLAM, Diplomate Specialised Veterinarian in Laboratory Animal Science (SVLAS), Animal Welfare
Officer at the University of Zurich (UZH)

with support from:

Stefan Mitrea, Dr. Med. Vet., Animal Welfare Officer at UNIBE

A. Disclaimers

1. There is only limited experience with the administration of Ethiq XR® in mice in Switzerland, so amendments may arise in the future with more frequent use.
2. Up to date there is no published pharmacokinetic/pharmacodynamic study to analyze the efficacy and safety of analgesics co-administered with Ethiq XR®.
3. Recommendations are based on practical experience and on the feedback received from the researchers, animal welfare officers and veterinarians from research institutions in Switzerland where Ethiq XR was used for mice.
4. It is good practice to always take a case-by-case decision.

B. Preliminary remarks

1. Ethiq XR® should be used **only** when the post-procedural pain is expected to last 48-72 hours or beyond.
2. Local, loco-regional anaesthesia should be used whenever possible. Please see here for more information: https://www.gv-solas.de/wp-content/uploads/2020/09/Schmerztherapie_2025.pdf
3. The manufacturers of Ethiq XR® mention in the “frequently asked questions” (<https://ethiqxr.com/>) and in the product labelling that: *“Adverse effects, including death, have been reported when NSAIDs (nonsteroidal anti-inflammatory drugs) and Ethiq XR® have been administered concomitantly in mice.”*
4. Based on the experience made from 2023 to 2026, the following recommendations were issued, when using Ethiq XR® in mice:
 - If NSAIDs can be used, carprofen is the drug of choice as:
 - Rescue analgesic within 72 hours post injection of Ethiq XR®: carprofen 10 mg/kg via subcutaneous (s.c.) injection.
 - Analgesic after more than 72 hours post injection of Ethiq XR®: carprofen 10-25 mg/kg s.c. (every 12 hours) or carprofen 25 mg/kg in drinking water.

C. Recommended protocols for using Ethiq XR® in mice

1. If opioids and NSAIDs could be administered (if neither are contraindicated):

a. If **inhalation anaesthesia** is used for the procedure => **30-60 minutes before the procedure**, administer **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg**;

or

b. If **injectable anaesthesia** with the triple mix fentanyl (0.05 mg/kg s.c.), medetomidine (0.5 mg/kg s.c.), midazolam (5 mg/kg s.c.) is used for the procedure, 2 options are possible:

b.1. antagonize anaesthesia at the end of the procedure with Buprenorphine (0.1 mg/kg s.c.), Flumazenil (0.5 mg/kg s.c.) and Atipamezole (2.5 mg/kg s.c.). Administer **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg, 4 hours after the end of the procedure**.

b.2. antagonize anaesthesia at the end of the procedure with **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg**. Inject separately Flumazenil (0.5 mg/kg s.c.) and Atipamezole (2.5 mg/kg s.c.).

The following apply to both scenarios (a or b):

- Check the wellbeing of the animals at least 2x/day for 3 days;
- Provide local, loco-regional anaesthesia as appropriate;
- **Rescue analgesia** with carprofen 10 mg/kg subcutaneous injection, single administration, recheck after 2 hours => euthanize if the animal still shows signs of pain. If the animal does no longer show signs of pain, recheck after 12 hours after injection of Carprofen to decide on how to continue analgesia.

2. If opioids are not contraindicated and if NSAIDs are contraindicated:

a. If **inhalation anaesthesia** is used for the procedure => **30-60 minutes before the procedure**, administer **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg**;

or

b. If **injectable anaesthesia** with the triple mix fentanyl (0.05 mg/kg s.c.), medetomidine (0.5 mg/kg s.c.), midazolam (5 mg/kg s.c.) is used for the procedure => 2 options are possible:

b.1. antagonize anaesthesia at the end of the procedure with Buprenorphine (0.1 mg/kg s.c.), Flumazenil (0.5 mg/kg s.c.) and Atipamezole (2.5 mg/kg s.c.). Administer **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg, 4 hours after the end of the procedure**.

b.2. antagonize anaesthesia at the end of the procedure with **Ethiq XR® via s.c. injection, 3.25 mg buprenorphine/kg**. Inject separately Flumazenil (0.5 mg/kg s.c.) and Atipamezole (2.5 mg/kg s.c.).

The following apply to both scenarios (a or b):

- Check the wellbeing of the animals at least 2x/day for 3 days;
- Provide local, loco-regional anaesthesia as appropriate;
- **Either no rescue analgesia** (i.e., euthanize if in pain) **or rescue analgesia with oral paracetamol** (200 mg paracetamol/kg body weight in drinking water) could be an option.

D. Side effects of Ethiq XR®

1. Expected side effects of Ethiq XR® on mice that have been observed by the time this recommendation was last updated:

- Mice may exhibit hyperactivity/"antenna-tail" after receiving Ethiq XR®.
- An oily sheen may be observed on the fur of the mouse after injection due to leakage of the oil-based drug suspension from the injection site. The oily sheen may last for 4 to 5 days post-injection of Ethiq XR®.

2. Other expected side effects of Ethiq XR® on mice that have been reported by the manufacturer:

- Ethiq XR® may cause sedation, decreased blood pressure, decreased heart rate, decreased gastrointestinal mobility, and respiratory depression.
- Animals may exhibit diminished responsiveness to stimuli up to 4 hours after receiving Ethiq XR®.

E. Adverse effects of Ethiq XR®

How to address adverse effects of Ethiq XR®, including deaths:

1. Read the information available here regarding reporting adverse effects:

<https://www.swissmedic.ch/swissmedic/en/home/tierarzneimittel/veterinary-medicines/report-adverse-drug-reaction-to-a-veterinary-medicinal-product.html>

2. Fill out the form "MU101_40_001d_Meldung unerwünschter Tierarzneimittelwirkungen Synthetika oder Impfstoffe (UAW Tamvigilance) (DOCX, 61 kB, 01.01.2023)" available here for reporting adverse effects:

<https://www.swissmedic.ch/swissmedic/en/home/tierarzneimittel/veterinary-medicines/report-adverse-drug-reaction-to-a-veterinary-medicinal-product/forms.html>

3. Contact the Veterinary Services of your Laboratory Animal Facility, send them the form mentioned at point 2.

4. Pathological examination is recommended in case of premature euthanasia of animals that received Ethiq XR®. In such a case, it is recommended to contact in advance the relevant laboratory (e.g. for UZH: Laboratory for Animal Model Pathology (LAMP):

<https://www.vetpathology.uzh.ch/de/lamp.html>) to discuss the adequate protocol to be followed and the preparation of the samples for analysis.

F. Appendix: practical tips for administration

1. Use a vortex mixer for 10-15 seconds at maximum power in order to resuspend the lipid particles and ensure a uniform suspension in the vial of Ethiq XR®, thus avoiding overdosing or underdosing.
2. Use a 0.5-1 ml sterile syringe with low dead volume for administration of Ethiq XR®. Example: B. Braun Injekt H Fine Dosing Syringe 1ml Solo
3. Use a separate needle for withdrawal from the vial.
4. The rubber of the vial should be wiped with a gauze sprayed with ethanol 70%.
5. Before injection, the needle should be well fixed to the syringe.
6. Do not inject in the same location with another drug (not to be mixed with other drugs).