1. NAME OF THE VETERINARY MEDICINAL PRODUCT
NaltrexoneHCl injection 50 mg/ml, vial 7 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
One ml contains:
Active substance: naltrexone hydrochloride 50 mg
Excipients: benzylalcohol, sodiumchloride, HCl, water for injection

3. PHARMACEUTICAL FORM
Solution for injection.
Clear colourless solution.

4. CLINICAL PARTICULARS
4.1 Target species
Experience with large animals like elephants, rhino's, buffalo's, but also hoof stock like antelopes, giraffes and zebra's.

4.2 Indications for use, specifying the target species
Naltrexone hydrochloride is used for the antagonism of any opiate sedation in any species. It has the advantage over naloxone in that it has a longer metabolic half- life and thus renarcotization is rarely a problem when naltrexone hydrochloride is used. Naltrexone hydrochloride is primarily used for antagonism of etorphine sedation and immobilisation of zoo and wild life animals. Naltrexone hydrochloride will reverse signs or symptoms of opiate intoxication like
- dizziness, incoordination, lethargy, sedation
- nausea, vomiting
- pin point pupil
- respiratory depression, apnoea
- cold skin, weak pulse
- unconsciousness, coma
- cardiovascular collapse due to hypoxia

4.3 Contraindications
There are no known contraindications to the use of naltrexone hydrochloride in veterinary medicine. If animals are to be re-immobilized with opiates within 24 hours or less of a previous dose of naltrexone hydrochloride, the opiate used may be less effective and alpha-two/dissociative combinations may be considered as an alternative protocol.

4.4 Special warnings for each target species
Not applicable.

4.5 Special precautions for use
After administering naltrexone hydrochloride to an animal that has been immobilized with etorphine or other opiate agonists, the animal may rise quickly and be fully conscious in as little as 2 minutes. All necessary procedures should have been accomplished and personnel advised that the reversal agent has been administered. Side effects associated with etorphine administration, such as muscle tremors or heavy panting, may not immediately abate upon administration of the reversal agent. In case of intoxication with an opiate, intubation for breathing, hart massage or defibrillation may be necessary even after administration of naltrexone hydrochloride.

4.6 Adverse reactions (frequency and seriousness)
Naltrexone has few, if any, intrinsic actions besides its opioid blocking properties. However, it does produce some pupillary constriction, by an unknown mechanism.

4.7 Use during pregnancy or lactation
Can be used during pregnancy and lactation.

4.9 Amounts to be administered and administration route
To reverse etorphine, a ratio of 25 mg naltrexone hydrochloride to 1 mg etorphineHCl administered has proved successful in hoof stock. In general 1 ml Etorphine 2.25 mg/ml can be antagonized with 1 ml NaltrexoneHCl 50 mg/ml.

Administer one-quarter of the calculated dose intravenously and three-quarters of the calculated dose subcutaneously. If a vein cannot be accessed, field experience indicates that reversal is accomplished completely by an intramuscular injection of the full dose.

Fentanyl plasters 12 microg/hr contains approx. 7-11 mg fentanyl (brand depending): 0.5 ml NaltrexoneHCl 50 mg/ml i.m. will antagonize the effects of unintended consumption of one plaster.

Opiate	potency	mg naltrexone to reverse effect of **10 mg opiate**	amount of iv/sc/im NaltrexoneHCl 50 mg/ml
Codeine	0.1	0.025 mg	0.0005 ml
Morfine	1	0.25 mg	0.005 ml
Butorfanol	1-7	1 mg	0.02 ml
Oxycodon	3-6	1 mg	0.02 ml
Buprenorfine	25	6.25 mg	0.125 ml
Alfentanyl	~50	12.5 mg	0.25 ml
Fentanyl	100	25 mg	0.5 ml
Sufentanil	500-700	125 mg	2.5 ml
Etorfine	1,000-3,000	250 mg	5 ml
Carfentanil	10,000	2,500 mg	50 ml

4.10 Dosing of naltrexone hydrochloride in case of accidental overdose of etorphine
In case of human emergencies:
Remain calm and evaluate the possible exposure to etorphine. In case of superficial scratches without systemic exposure, remove all contaminants immediately with plenty of water and stay with the exposed person for 15 minutes. If no effects are observed in this period, no further actions are needed, although it is advisable to maintain an observation period for several hours. In case of symptoms or accidental injection of etorphine immediate administration of opiate antagonists is warranted. Naloxone (Narcan) or naltrexone hydrochloride are safe in humans, don't use diprenorphine.

Naltrexone hydrochloride 20-25 mg antagonizes 1 mg of etorphine, therefor NaltrexoneHCl 50mg/ml can be given intravenously in the same volume as the accidently administered volume of Etorphine 2.25 mg/ml, the minimum dose naltrexone hydrochloride is 10 mg = 0.2 ml. Re-dosing is possible in case of recurring symptoms, although naltrexone's activity (>24 hours) lasts longer than etorphine. Naltrexone is well tolerated in humans.

4.11 Withdrawal periods
Not applicable, animals treated with naltrexone are excluded from human consumption.

5. PHARMACOLOGICAL PROPERTIES
Naltrexone HCl is 17-(cyclopropylmethyl)-4,5-epoxy-3, 14 dihydroxy-morphinan-6-one hydrochloride. Naltrexone hydrochloride is a cyclopropyl derivative of oxymorphone.
Pharmacotherapeutic group: other nervous system drugs, drugs used in addictive disorders, drugs used in alcohol dependence
ATCvet code: QN07BB04

5.1 Pharmacodynamic properties
Naltrexone, and its active metabolite 6-β-naltrexol, are competitive antagonists at the μ- and κ- opioid receptors, and to a lesser extent at the δ- opioid receptor. It reversibly blocks or attenuates the effects of opioids. Its relative antagonistic potency is approximately twice that of naloxone and 17 times that of nalorphine, to both of which naltrexone hydrochloride is structurally similar.

5.2 Pharmacokinetic particulars
Absorption
Reversal of the effects of opiate immobilization is usually accomplished within 3 to 10 minutes of administration of naltrexone hydrochloride. In clinical trials, however, some animals required as little as 2 minutes or a period of greater than 10 minutes to reverse from the effects of carfentanil citrate or etorphine. Doses naltrexone hydrochloride lower than the proposed dose resulted in signs of renarcotization, including open-mouth breathing, hypermetria, ataxia, and subtle changes in behaviour and responsiveness.

Metabolism
Naltrexone hydrochloride is metabolized in the liver, the 6-β-naltrexol metabolite is active.

Elimination
Both parent drug and metabolites are excreted primarily by the kidney (53% to 79% of the dose), however, urinary excretion of unchanged naltrexone accounts for less than 2% of an oral dose and fecal excretion is a minor elimination pathway. The mean elimination half-life (T-1/2) values for naltrexone and 6-β-naltrexol are 4 hours and 13 hours, respectively. Naltrexone and 6-ß-naltrexol are dose proportional in terms of AUC and Cmax over the range of 50 to 200 mg.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
benzylalcohol
sodiumchloride
HCl qs
water for injection

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf-life after first opening the immediate packaging: 28 days.

6.4 Special precautions for storage
This veterinary medicinal product should be stored at room temperature.

6.5 Nature and composition of immediate packaging
Injection vial of 7 ml closed with a rubber stopper and sealed with an aluminium cap.

6.6 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products
Any unused veterinary medicinal product or waste materials derived from such veterinary medicinal products should be disposed of in accordance with local requirements.

7. MANUFACTURER
Pharmacy Faculty Veterinary Medicine Utrecht University
Yalelaan 106
3584 CM Utrecht
The Netherlands

10. DATE OF REVISION OF THE TEXT
August 2017