1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Robexera 20 mg/ml solution for injection for cats and dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Robenacoxib 20 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Sodium metabisulfite (E223)	1 mg
Macrogol 400	
Ethanol 96 per cent	128 mg
Poloxamer 188	
Citric acid	
Sodium hydroxide	
Water for injections	

Clear, colourless to slightly brownish-yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Cats and dogs.

3.2 Indications for use for each target species

For the treatment of pain and inflammation associated with orthopaedic or soft tissue surgery.

3.3 Contraindications

Do not use in animals suffering from gastrointestinal ulceration.
Do not use concomitantly with corticosteroids or other non-steroidal anti-inflammatory drugs (NSAIDs).
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
See also section 3.7.

3.4 Special warnings

None.

3.5 Special precautions for use

Special precautions for safe use in the target species:
The safety of the veterinary medicinal product has not been established in cats less than 4 months of age and in dogs less than 2 months of age, or in cats or dogs less than 2.5 kg body weight.

Use in animals with impaired cardiac, renal or hepatic function or those are dehydrated, hypovolaemic or hypotensive may involve additional risks. If use cannot be avoided, these animals require careful monitoring and fluid therapy.

Use this veterinary medicinal product under strict veterinary monitoring in cases at risk of gastrointestinal ulceration, or if the animal previously displayed intolerance to other NSAIDs.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
For pregnant women, particularly near-term pregnant women, accidental injection and prolonged dermal exposure increases the risk for premature closure of the ductus arteriosus in the foetus.

Wash hands and exposed skin immediately after use of the veterinary medicinal product.
In case of accidental oral exposure (hand-to-mouth), prolonged dermal exposure or self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Special precautions for the protection of the environment:
Not applicable.

3.6 Adverse events

Cats:

Common (1 to 10 animals / 100 animals treated):	Injection site pain Digestive tract disorder[1], Diarrhoea[1], Vomiting[1]
Uncommon (1 to 10 animals / 1 000 animals treated):	Bloody diarrhoea, Blood in vomit

[1]Most cases were mild and recovered without treatment.

Dogs:

Common (1 to 10 animals / 100 animals treated):	Injection site pain[1] Digestive tract disorder[2], Diarrhoea[2], Vomiting[2]
Uncommon (1 to 10 animals / 1 000 animals treated):	Tarry stool Decreased appetite

[1]Moderate or severe pain at injection site was uncommon.
[2]Most cases were mild and recovered without treatment.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or its local representative or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.
The safety of the veterinary medicinal product has not been established in cats and dogs used for breeding.

Pregnancy and lactation:
Do not use in pregnant and lactating animals.

Fertility:
Do not use in breeding animals.

3.8 Interaction with other medicinal products and other forms of interaction

This veterinary medicinal product must not be administered in conjunction with other NSAIDs or glucocorticosteroids. Pre-treatment with other anti-inflammatory medicines may result in additional or increased adverse effects and accordingly a treatment-free period with such substances should be observed for at least 24 hours before the commencement of treatment with this veterinary medicinal product. The treatment-free period, however, should take into account the pharmacokinetic properties of the veterinary medicinal products used previously.

Concomitant treatment with medicines displaying action on renal flow, e.g. diuretics or angiotensin-converting enzyme (ACE) inhibitors, should be subject to clinical monitoring.
In healthy cats or dogs treated with or without the diuretic furosemide, concomitant administration of this veterinary medicinal product with the ACE inhibitor benazepril for 7 days was not associated with any negative effects on plasma (cats) or urine (dogs) aldosterone concentrations, plasma renin activity or glomerular filtration rate. No safety data in the target population and no efficacy data in general exist for the combined treatment of robenacoxib and benazepril.

As anaesthetics may affect renal perfusion, the use of parenteral fluid therapy during surgery should be considered to decrease potential renal complications when using NSAIDs peri-operatively.

Concurrent administration of potentially nephrotoxic medicines should be avoided as there might be an increased risk of renal toxicity.

Concurrent use of other active substances that have a high degree of protein binding may compete with robenacoxib for binding and thus lead to toxic effects.

3.9 Administration routes and dosage

Subcutaneous use (**s.c.**).

The recommended dose is 2 mg robenacoxib/kg body weight (1 mL of the veterinary medicinal product per 10 kg body weight).
Administer the veterinary medicinal product approximately 30 minutes before the start of surgery, for example around the time of induction of general anaesthesia.
After surgery in cats, once daily treatment may be continued at the same dosage and at the same time every day for up to 2 days.
After soft tissue surgery in dogs, once daily treatment may be continued at the same dosage and at the same time every day for up to 2 days.

The interchangeable use of the veterinary medicinal products containing robenacoxib in the form of tablets and solution for injection has been tested in target animal safety studies and was shown to be well tolerated by cats and dogs.

The veterinary medicinal products containing robenacoxib in the form of solution for injection or tablets may be used interchangeably in accordance with the indications and directions of use approved

for each pharmaceutical form. Treatment should not exceed one dose (either tablet or injection) per day. Please note that the recommended doses for the two formulations may be different.

The stopper should be subjected to a maximum of 16 piercings.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

In healthy young dogs aged 6 months, once daily subcutaneous administration of robenacoxib at doses of 2 (recommended therapeutic dose; RTD), 6 (3 times RTD), and 20 mg/kg (10 times RTD) for 9 administrations over a 5 week period (3 cycles of 3 consecutive once daily injections) did not produce any signs of toxicity, including gastrointestinal, kidney or liver toxicity and had no effect on bleeding time. Reversible inflammation at the injection site was noted in all groups (including controls) and was more severe in the 6 and 20 mg/kg dose groups.

In healthy young cats aged 10 months, once daily subcutaneous administration of robenacoxib at doses of 4 mg/kg (twice RTD) for 2 consecutive days and 10 mg/kg (5 times RTD) for 3 consecutive days did not produce any signs of toxicity, including signs of gastrointestinal, kidney or liver toxicity and had no effect on bleeding time. Reversible, minimal injection site reactions were noted in both dose groups.

The interchangeable use of veterinary medicinal products containing robenacoxib in the form of tablets and solution for injection in 4-month old cats at overdoses of up to 3 times the maximum recommended dose (2.4 mg, 4.8 mg, 7.2 mg robenacoxib/kg orally and 2.0 mg, 4.0 mg and 6.0 mg robenacoxib/kg subcutaneously) resulted in a dose-dependent increase of sporadic oedema at the injection site and minimal to mild subacute/chronic inflammation of the subcutaneous tissue. A dose-dependent increase in the QT interval, a decreased heart rate and corresponding increased respiratory rate were observed in laboratory studies. No relevant effects on body weight, bleeding time or evidence of any gastrointestinal, kidney or liver toxicity were observed.

In overdose studies conducted in cats, there was a dose-dependent increase in the QT interval. The biological relevance of increased QT intervals outside of normal variations observed following overdose of robenacoxib is unknown. No changes in the QT interval were observed after single intravenous administration of 2 or 4 mg/kg robenacoxib to anaesthetised healthy cats.

The interchangeable use of veterinary medicinal products containing robenacoxib in the form of tablets and solution for injection in mongrel dogs at overdoses of up to 3 times the maximum recommended dose (2.0, 4.0 and 6.0 plus 4.0, 8.0 and 12.0 mg robenacoxib/kg orally and 2.0 mg, 4.0 mg and 6.0 mg robenacoxib/kg subcutaneously) resulted in dose-related oedema, erythema, thickening of the skin and skin ulceration at the subcutaneous injection site and inflammation, congestion, or haemorrhage in the duodenum, jejunum, and caecum.
No relevant effects on body weight, bleeding time or evidence of any kidney or liver toxicity were observed.

No changes to blood pressure or the electrocardiogram were observed after single administration to healthy dogs of 2 mg/kg robenacoxib subcutaneously or 2 or 4 mg/kg intravenously. Vomiting occurred 6 or 8 hours post-dosing in 2 of 8 dogs administered the solution for injection at a dosage of 4 mg/kg intravenously.

As with any NSAID, overdose may cause gastrointestinal, kidney, or liver toxicity in sensitive or compromised animals. There is no specific antidote. Symptomatic, supportive therapy is recommended consisting of administration of gastrointestinal protective agents and infusion of isotonic saline.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance.

Not applicable.

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code: QM01AH91

4.2 Pharmacodynamics

Robenacoxib is a non-steroidal anti-inflammatory drug (NSAID) of the coxib class. It is a potent and selective inhibitor of the cyclooxygenase 2 enzyme (COX-2). The cyclooxygenase enzyme (COX) is present in two forms. COX-1 is the constitutive form of the enzyme and has protective functions, e.g. in the gastrointestinal tract and kidneys. COX-2 is the inducible form of the enzyme and is responsible for the production of mediators including PGE_2 which induce pain, inflammation or fever.

In cats, using an *in vitro* whole blood assay, robenacoxib was approximately 500 fold selective for COX-2 (IC_{50} 0.058 μM) as compared to COX-1 (IC_{50} 28.9 μM). *In vivo*, robenacoxib solution for injection produced marked inhibition of COX-2 activity and had no effect on COX-1 activity. At the recommended dosage (2 mg/kg), analgesic, anti-inflammatory and anti-pyretic effects were demonstrated in an inflammation model, and in clinical trials, robenacoxib reduced pain and inflammation in cats undergoing orthopaedic or soft tissue surgery.

In dogs, robenacoxib was *in vitro* approximately 140 fold selective for COX-2 (IC_{50} 0.04 μM) as compared to COX-1 (IC_{50} 7.9 μM). *In vivo*, robenacoxib solution for injection produced marked inhibition of COX-2 activity and had no effect on COX-1 activity. At dosages ranging from 0.25 to 4 mg/kg, robenacoxib had analgesic, anti-inflammatory and anti-pyretic effects in an inflammation model with a rapid onset of action (1 h). In clinical trials at the recommended dose (2 mg/kg), robenacoxib reduced pain and inflammation in dogs undergoing orthopaedic or soft tissue surgery, and reduced the need for rescue treatment in dogs undergoing soft tissue surgery.

4.3 Pharmacokinetics

Cats:

Absorption
Peak blood concentrations of robenacoxib are attained rapidly after subcutaneous injection.
After a dosage of 2 mg/kg a T_{max} of 1 h, a C_{max} of 1,464 ng/ml and an AUC of 3,128 ng·h/ml is obtained. After a subcutaneous administration of 1 mg/kg the systemic bioavailability is 69%.

Distribution
Robenacoxib has a relatively small volume of distribution (Vss of 190 ml/kg) and is highly bound to plasma proteins (>99%).

Biotransformation
Robenacoxib is extensively metabolised by the liver. Apart from one lactam metabolite, the identity of other metabolites is not known.

Elimination
After intravenous administration robenacoxib was rapidly cleared from blood (CL of 0.44 L/kg/h) with an elimination $t_{1/2}$ of 1.1 h. After subcutaneous administration, the terminal half-life from blood was 1.1 h.
Robenacoxib persists longer and in higher concentrations at sites of inflammation than in blood.

Robenacoxib is excreted predominantly via the biliary route (~70%) and the remainder via the kidneys. Repeated subcutaneous administration at dosages of 2–20 mg/kg produced no change in the blood profile, with neither bioaccumulation of robenacoxib nor enzyme induction. Bioaccumulation of metabolites has not been tested. The pharmacokinetics of robenacoxib injection do not differ between male and female.

Dogs:

Absorption
Peak blood concentrations of robenacoxib are attained rapidly after subcutaneous injection. After a dosage of 2 mg/kg a T_{max} of 1 h, a C_{max} of 615 ng/ml and an AUC of 2,180 ng·h/ml is obtained. After a subcutaneous administration of 1 mg/kg the systemic bioavailability is 88%.

Distribution
Robenacoxib has a relatively small volume of distribution (240 ml/kg) and is highly bound to plasma proteins (>99%).

Biotransformation
Robenacoxib is extensively metabolised by the liver. Apart from one lactam metabolite, the identity of other metabolites is not known.

Elimination
After intravenous administration robenacoxib was rapidly cleared from blood (CL of 0.81 L/kg/h) with an elimination $t_{1/2}$ of 0.8 h. After subcutaneous administration, the terminal half-life from blood was 1.2 h.
Robenacoxib persists longer and in higher concentrations at sites of inflammation than in blood.
Robenacoxib is excreted predominantly via the biliary route (~65%) and the remainder via the kidneys. Repeated subcutaneous administration at dosages of 2–20 mg/kg produced no change in the blood profile, with neither bioaccumulation of robenacoxib nor enzyme induction. Bioaccumulation of metabolites has not been tested. The pharmacokinetics of robenacoxib injection do not differ between male and female, and are linear over the range of 0.25–4 mg/kg.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must not be mixed with other veterinary medicinal products.

5.2 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.

5.3 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).
After first broaching the vial, store at temperature below 25 °C.
Store in the original package in order to protect from light.

5.4 Nature and composition of immediate packaging

A cardboard box containing one amber type I glass vial of 20 ml, closed with a type I bromobutyl rubber stopper and an aluminium seal with plastic tear-off tab.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

KRKA, d.d., Novo mesto

7. MARKETING AUTHORISATION NUMBER(S)

VPA10774/078/001

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database (https://medicines.health.europa.eu/veterinary).