1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Mirataz 20 mg/g transdermal ointment for cats

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.1 g dose contains:

Active substances:
Mirtazapine (as hemihydrate) 2 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Butylhydroxytoluene (E321)	0.01 mg
Macrogol 400	
Macrogol 3350	
Diethylene glycol monoethyl ether	
Caprylocaproyl polyoxyglycerides	
Oleyl alcohol	
Dimethicone	
Tapioca starch polymethylsilsesquioxane	

Non-greasy, homogeneous, white to off-white ointment.

3. CLINICAL INFORMATION

3.1 Target species

Cats.

3.2 Indications for use for each target species

For body weight gain in cats experiencing poor appetite and weight loss resulting from chronic medical conditions (see section 4.2).

3.3 Contraindications

Do not use in breeding, pregnant or lactating cats.
Do not use in animals less than 7.5 months of age or less than 2 kg body weight.
Do not use in cases of hypersensitivity to the active substance or to any of the excipients.
Do not use in cats treated with cyproheptadine, tramadol or monoamine oxidase inhibitors (MAOIs) or treated with an MAOI within 14 days prior to treatment with the veterinary medicinal product as there may be an increased risk of serotonin syndrome (see section 3.8).

3.4 Special warnings

The efficacy of the veterinary medicinal product has not been established in cats less than 3 years of age.

The efficacy and safety of the veterinary medicinal product has not been established in cats with severe renal disease and/or neoplasia.

Proper diagnosis and treatment of the underlying disease is key to managing weight loss, and treatment options are dependent on the severity of weight loss and underlying disease(s). The management of any chronic disease associated with weight loss should include providing appropriate nutrition and monitoring body weight and appetite.

The therapy with mirtazapine should not replace necessary diagnostics and/or treatment regimens needed to manage the underlying disease(s) causing unintended weight loss.

The efficacy of the veterinary medicinal product was only demonstrated with a 14-day administration corresponding to the current recommendations (see section 3.9). Repetition of the treatment has not been investigated and as such should only be done after benefit-risk balance assessment by the veterinarian.

The efficacy and safety of the veterinary medicinal product has not been established in cats weighing less than 2.1 kg or more than 7.0 kg (see also section 3.9).

3.5 Special precautions for use

Special precautions for safe use in the target species:
The veterinary medicinal product should not be applied on damaged skin.

In the case of hepatic disease, elevated hepatic enzyme levels may be observed. Kidney disease may cause reduced clearance of mirtazapine, which may result in higher drug exposure. In these special cases, biochemical hepatic and renal parameters should be regularly monitored during the treatment.

The effects of mirtazapine on glucose regulation have not been evaluated. In the case of use in cats with diabetes mellitus, glycaemia should be regularly monitored.

When used in hypovolemic cats, supportive treatment (fluid therapy) should be implemented.

Care should be taken that other animals in the household do not come in contact with the application site until it is dry.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:
The veterinary medicinal product can be absorbed via the cutaneous or oral use and can cause drowsiness or sedation.

Avoid direct contact with the veterinary medicinal product. Avoid contact with the treated animal for the first 12 hours after each daily application and until the application site is dry. It is therefore recommended to treat the animal in the evening. Treated animals should not be allowed to sleep with owners, especially children and pregnant women during all the period of the treatment.

Impermeable disposable protective gloves should be provided at the point of sale with the veterinary medicinal product and must be worn when handling and administering the veterinary medicinal product.

Thoroughly wash hands immediately after administration of the veterinary medicinal product or in case of skin contact with the product or the treated cat.

Limited data are available on the reproductive toxicity of mirtazapine. Given that pregnant women are considered a more sensitive population, it is recommended that pregnant women or women trying to conceive should avoid handling the veterinary medicinal product and avoid contact with treated animals throughout the treatment period.

The veterinary medicinal product may be harmful after ingestion.

Do not leave the child resistant tube out of its carton except during the application phase. The child resistant tube must be placed in the carton immediately after use.

Children must not be present when applying the treatment to the cat.

Do not eat, drink or smoke while handling the veterinary medicinal product.

The veterinary medicinal product is a skin sensitiser. People with known hypersensitivity to mirtazapine should avoid contact with the veterinary medicinal product.

This veterinary medicinal product may cause eye and skin irritation. Avoid hand to mouth and hand to eye contact until hands have been thoroughly washed. In the case of contact with eyes, rinse the eyes thoroughly with clean water. In the case of contact with the skin, wash thoroughly with soap and warm water. If skin or eye irritation occurs or in case of accidental ingestion, 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:

Very common (>1 animal / 10 animals treated):	Application site reactions[a] (erythema, crust/scab, residue, skin scaling/dry skin, flaking skin, dermatitis or irritation, alopecia and pruritus) Behavioural disorders[a,b] (vocalisation, hyperactivity, attention-seeking behaviour, aggression) Head shake[a] Disoriented state[a,b], ataxia[a,b] Lethargy[a,b] Weakness[a,b]
Common (1 to 10 animals / 100 animals treated):	Vomiting[a,b] Polyuria[a] (associated with a decreased urine concentration) Elevated blood urea nitrogen (BUN)[a] Dehydration[a,b]
Rare (1 to 10 animals / 10 000 animals treated):	Hypersensitivity reaction[c] Hypersalivation[d] Tremor[d]

[a] Resolved at the end of treatment period with no specific treatment.
[b] Depending on the severity, administration of the product may be discontinued according to the benefit-risk assessment of the veterinarian.
[c] Treatment should be immediately withdrawn.
[d] In case of oral ingestion, in addition to effects cited above (except local reactions).

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 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

Mirtazapine has been identified as potentially reprotoxic in rats and rabbits.

The safety of the veterinary medicinal product has not been established during pregnancy and lactation.

Pregnancy and lactation:
Do not use during pregnancy and lactation (see section 3.3).

Fertility:
Do not use in breeding animals (see section 3.3).

3.8 Interaction with other medicinal products and other forms of interaction

Do not use in cats treated with cyproheptadine, tramadol or monoamine oxidase inhibitors (MAOIs) or treated with an MAOI within 14 days prior to treatment with the veterinary medicinal product as there may be an increased risk of serotonin syndrome (see section 3.3).

Mirtazapine may increase sedative properties of benzodiazepines and of other substances with sedative properties (antihistamines H1, opiates). The plasma concentrations of mirtazapine may be also increased when used concomitantly with ketoconazole or cimetidine.

3.9 Administration routes and dosage

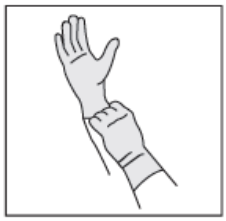
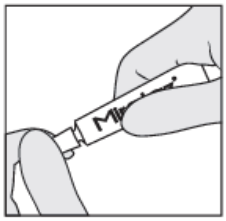
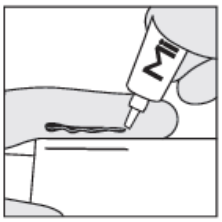
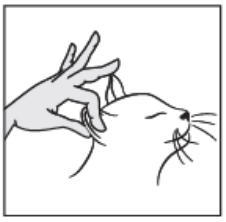
Transdermal use.

The veterinary medicinal product is applied topically to the inner pinna (inner surface of the ear) once daily for 14 days, at the dosage of 0.1 g ointment/cat (2 mg mirtazapine/cat). This corresponds to a 3.8 cm line of ointment (see below).

Alternate the daily application between the left and right ears. If desired, the inner surface of the cat's ear may be cleaned by wiping with a dry tissue or cloth immediately prior to the next scheduled dose. If a dose is missed, apply the veterinary medicinal product the following day and resume daily dosing.

The recommended fixed dose has been tested in cats weighing between 2.1 kg and 7.0 kg.

To apply the veterinary medicinal product:

Step 1: Put on impermeable gloves.	**Step 2: Press down and twist cap on tube anticlockwise to open.**	**Step 3: Gently apply even pressure on tube and squeeze a 3.8 cm line of ointment onto your index finger using the measured line on the carton/bottle or in this leaflet as a guide.**	**Step 4: Using your finger, gently rub ointment on inside surface of cat's ear (pinna) spreading it evenly over the surface. If contact with your skin occurs wash with soap and water.**

The line below coincides with the appropriate length of ointment to be applied:

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

The known symptoms of a mirtazapine overdose of > 2.5 mg/kg in cats include: vocalisation and behavioural changes, vomiting, ataxia, restlessness and tremors. In case of an overdose, symptomatic/supportive treatment should be instituted if needed.

In the case of overdose, the same effects as those observed at the recommended therapeutic dose were noted but with a higher incidence.

Transient increased hepatic alanine transferase can be observed uncommonly. It is not associated with clinical signs.

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: QN06AX11

4.2 Pharmacodynamics

Mirtazapine is an α2-adrenergic receptor antagonist noradrenergic and serotonergic antidepressant drug. The exact mechanism by which mirtazapine induces weight gain appears to be multifactorial. Mirtazapine is a potent antagonist of 5-HT2 and 5-HT3 receptors in the central nervous system (CNS), and a potent inhibitor of histamine H1 receptors. Inhibition of 5-HT2 and histamine H1 receptors may account for the orexigenic effects of the molecule. Mirtazapine-induced weight gain may be secondary to changes in leptin and the tumour necrosis factor (TNF).

The product has an expected positive effect on feed intake by stimulating the appetite but this effect was not measured in the pivotal field trial. The only effect tested under field practice was on body weight: client-owned cats presented with a weight loss ≥ 5 %, deemed clinically significant by the investigator, gained a statistically significant ($p < 0.0001$) amount of weight, after 14 days of product administration (3.39 % weight gain or average of 130 grams) compared to those cats administered placebo (0.09 % weight gain or average of 10 grams).

4.3 Pharmacokinetics

In a crossover study conducted with the product at 0.5 mg/kg in eight cats to determine the relative bioavailability of oral and transdermal 2 % mirtazapine, the mean terminal half-life (25.6 ± 5.5 hours) with topical administration was over 2X longer than the mean terminal half-life (8.63 ±3.9 hours) with oral administration. Bioavailability following topical administration was 34 % (6.5 to 89 %) compared to oral administration during the first 24 hours and 65 % (40.1 to 128.0 %) based on $AUC_{0-\infty}$. After a single topical administration, the mean peak plasma concentration of 21.5 ng/ml (± 43.5) is reached in t_{max} mean of 15.9 hours (1-48 hours). The mean AUC_{0-24} was 100 ng*h/ml (± 51.7).
After administration of the product to 8 cats at a dose of 0.5 mg/kg once daily for 14 days, mean peak plasma concentration of 39.6 ng/ml (± 9.72) is reached in t_{max} mean of 2.13 hours (1-4 hours). The mean terminal half-life of mirtazapine was 19.9 h (± 3.70) and the mean AUC_{0-24} was 400 ng*h/ml (±100).
In the target animal safety study, where cats received a higher dose (2.8 to 5.4 mg) than the label dose (2 mg) once daily for 42 days, steady state was achieved within 14 days. The median accumulation between first and 35th dose was 3.71X (based on AUC ratio) and 3.90X (based on C_{max} ratio).

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

Not applicable.

5.2 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 3 years.
Shelf life after first opening the immediate packaging: 30 days.

5.3 Special precautions for storage

This veterinary medicinal product does not require any special storage conditions.

The child resistant tube should be closed and returned to the carton immediately after every use.

5.4 Nature and composition of immediate packaging

Polyethylene laminate tube with a high-density polyethylene (HDPE) child resistant screw cap.

Cardboard box containing one 3 g child resistant tube.

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

Dechra Regulatory B.V.

7. MARKETING AUTHORISATION NUMBER(S)

EU/2/19/247/003

8. DATE OF FIRST AUTHORISATION

Date of first authorisation: 10/12/2019

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

{DD/MM/YYYY}

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).