SINDOLOR®

DIPYRONE SODIUM AND TRAMADOL HYDROCHLORIDE

VETERINARY USE

Oral analgesic for dogs

FORMULA

SINDOLOR® 250/20 mg
Each 375 mg tablet contains:
Dipyrone sodium ..... 250 mg
Tramadol hydrochloride ..... 20 mg
Excipients q.s.p ..... 375 mg

SINDOLOR® 750/60 mg
Each 1125 mg tablet contains:
Dipyrone sodium ..... 750 mg
Tramadol hydrochloride ..... 60 mg
Excipients q.s.p ..... 1125 mg

TECHNICAL INFORMATION

SINDOLOR® is a combination of two drugs (dipyrone sodium and tramadol hydrochloride) that act synergistically to provide analgesia. Tramadol is a mixed centrally-acting analgesic, since it acts as a (mu) opioid receptor agonist and inhibits norepinephrine and serotonin reuptake in the descending pain inhibitory pathways. Tramadol requires metabolic activation by cytochrome P450 (CYP2D15) hepatic enzymes. O-desmethyltramadol (M1), reported to be the major tramadol active metabolite, is 200 times more potent in the (mu)-type opioid receptor than tramadol itself. M1(+) interacts with opioid receptors, while M1(-) interacts with adrenergic receptors, to promote the analgesic effect. The absorption of tramadol by dogs, after oral administration (PO), is quite rapid, resulting in an average peak plasma concentration (Tmax) of 1 hour for tramadol and M1. Tramadol is mainly excreted through the liver and partially through the kidneys (30% of the dose), however, the main route of elimination of its metabolites is through the urine (80%), and a small portion undergoes biliary and fecal elimination (10%).
Dipyrone is classified as a non-opioid analgesic and antipyretic agent, widely known for its effective analgesic action in the treatment of acute pain in animals. Furthermore, as it is a pyrazolone derivative, it is classified as a non-steroidal anti-inflammatory drug (NSAID). Although it is classified as an NSAID, dipyrone has mild anti-inflammatory activity and low potential to cause nephrotoxicity, gastrointestinal ulceration and hematological changes. Dipyrone acts on the peripheral nervous system (PNS) and central nervous system (CNS), at different levels of processing of pain-related information. Dipyrone is known to reversibly inhibit the cycle of cyclooxygenase enzymes (COXs). It exerts a more potent inhibitory effect on type 3 cyclooxygenase (COX-3) than on type 1 (COX-1). Dipyrone is a prodrug rapidly hydrolyzed to its main metabolite, 4-methylaminoantipyrine (MAA), which is responsible for the therapeutic effect on dogs. MAA is about 50 times more effective as a COX-3 enzyme inhibitor than dipyrone. In dogs, the oral bioavailability of dipyrone is approximately 95%, while in the blood, around 58% is found to be bound to plasma proteins. Dipyrone provides analgesia approximately 15 minutes after dosing. Its plasma half-life in dogs is approximately 0.5 to 0.6 hour. Biotransformation occurs in the liver lasting between 4 and 7 hours, and 70% is excreted in urine 24 hours after dosing. In the case of the active metabolite MAA, the reported half-life is 4 to 5 hours, regardless of the route of administration.

INDICATIONS

SINDOLOR® is indicated as an analgesic for the treatment of acute postoperative pain in dogs.

DOSAGE AND HOW TO USE

SINDOLOR® should only be administered orally. The recommended dose is 25 mg/kg of dipyrone sodium and 2 mg/kg of tramadol hydrochloride every 8 hours for up to 7 days, according to the table below:

Animal weight (kg)	SINDOLOR® 250/20 mg Dose of 25 mg/kg of dipyrone sodium and 2 mg/kg of tramadol HCl every 8 hours	SINDOLOR® 750/60 mg Dose of 25 mg/kg of dipyrone sodium and 2 mg/kg of tramadol HCl every 8 hours
2.5	¼ tablet	-
5.0	½ tablet	-
7.5	¾ tablet	½ tablet
10	1 tablet	-
15	1 ½ tablet	½ tablet
17.5	1 ¾ tablet	-
20	2 tablets	-
22.5	-	¾ tablet
30	-	1 tablet
37.5	-	1 ¼ tablet
45	-	1 ½ tablet
52.5	-	1 ¾ tablet
60	-	2 tablets

According to the efficacy study carried out in dogs, SINDOLOR® was considered effective in the control of acute postoperative pain, when administered at the recommended dose of 25 mg/kg of dipyrone sodium and 2 mg/kg of tramadol hydrochloride every 8 hours for 5 consecutive days. For better control of inflammation, SINDOLOR® can be associated with a non-steroidal anti-inflammatory drug.

CONTRAINDICATIONS

SINDOLOR® should not be administered to dogs with hypersensitivity to tramadol, any other opioid and dipyrone.
This product is not recommended for pregnant or lactating females or dogs under 12 months of age, as studies have not yet been carried out with these groups.
As it contains tramadol, **SINDOLOR®** should not be used in patients under treatment with monoamine oxidase inhibitors (MAOIs), for example amitraz and selegiline, serotonin reuptake inhibitor antidepressants, for example fluoxetine or other drugs that lower seizure threshold. The use of fluoxetine in patients treated with tramadol is not indicated, as fluoxetine can inhibit the metabolism of tramadol.
As it contains tramadol, **SINDOLOR®** is not recommended for decompensated epileptic dogs or dogs with increased intracranial pressure, as tramadol may lower the seizure threshold. As it contains dipyrone in its formulation, the use of **SINDOLOR®** is not recommended for dogs with a history or presence of blood dyscrasias.

DRUG INTERACTIONS

As it contains tramadol, **SINDOLOR®** should be avoided in dogs receiving serotonin and norepinephrine reuptake inhibitors (SNRIs), for example amitriptyline, nortriptyline and mirtazapine and alpha 2-adrenergic receptor agonists, for example xylazine and dexmedetomidine. The use of fluoxetine in patients treated with tramadol is not indicated, as fluoxetine may inhibit the metabolism of tramadol. Concomitant use of tricyclic antidepressants with tramadol, for example clomipramine and amitriptyline, may increase the risk of seizures and inhibit the metabolism of tramadol; in addition, the dose of tramadol can be reduced by 25% when associated with amitriptyline. Serotonin syndrome may occur when tramadol is associated with selective serotonin and norepinephrine reuptake inhibitors (SNRIs). This combination must be used according to the indication and under the guidance of a Veterinarian.
As it contains tramadol, **SINDOLOR®** should not be used in patients undergoing treatment with monoamine oxidase inhibitors (MAOIs), for example amitraz and selegiline.
As it contains tramadol, the analgesic effect of **SINDOLOR®** may be reduced when administered in combination with naloxone, due to its partial antagonistic action on μ (mu) opioid receptors.

The administration of quinidine to dogs may decrease the analgesic efficacy of SINDOLOR®, due to the relatively potent inhibitory action of quinidine on the formation of tramadol M1 metabolite.
As it contains tramadol, the analgesic effect of **SINDOLOR®** may be reduced when administered in combination with ondansetron.
As it contains dipyrone, **SINDOLOR®** may stimulate the cytochrome P450 system, therefore, the concomitant use of dipyrone with cyclosporine can reduce the plasma concentration of cyclosporine.
As it contains dipyrone, **SINDOLOR®** may increase the toxicity of methotrexate when used in combination. Studies suggest a possible occurrence of hematological adverse effects (leukopenia, thrombocytopenia, anemia), nephrotoxicity and mucosal ulcerations as a result of this association.

ADVERSE EFFECTS
Tramadol can cause adverse effects on the central nervous system (CNS), such as drowsiness or excessive sedation, excitement, anxiety and tremors, as well as on the gastrointestinal system, such as nausea, poor appetite, salivation, constipation, emesis and diarrhea.
Some effects on the central nervous system (CNS) have been associated with dipyrone, such as drowsiness and lethargy. The use of dipyrone may cause some common side effects, such as gastrointestinal disorders, nausea, vomiting, abdominal pain and diarrhea. However, compared to NSAIDs, reports indicate that dipyrone is safe, mainly for not causing gastric ulcers during its use. Other rare side effects described in dogs include rash, urticaria or erythema.
The safety study of **SINDOLOR®**, at the recommended doses, that is, dipyrone sodium 25 mg/kg and tramadol hydrochloride 2 mg/kg, administered orally every 8 hours, for up to 7 consecutive days, showed that the product is safe for use in dogs. The adverse effects observed were mild, transient in nature, and did not require interventions, such as emesis and sialorrhea observed at the time of the tablet administration, due to the characteristic bitter taste of the active ingredients. No hematological or biochemical abnormalities have been observed in dogs receiving **SINDOLOR®** at the recommended dose for 7 days. There were no changes in heart rate, respiratory rate and blood pressure parameters, nor in other clinical parameters in the animals studied.

PRECAUTIONS
For treatments that need to be extended beyond the period recommended in the leaflet, it is advisable to seek the guidance and monitoring of a Veterinary doctor, besides carrying out hematological and biochemical tests. Although a relationship between dipyrone intake and the development of blood dyscrasias has not been established in veterinary medicine to date, some authors recommend caution and monitoring of these animals through laboratory tests, especially during long-term treatment. It should be used with caution in geriatric or severely debilitated animals.
The use in stable epileptic dogs should be monitored, as recommended by a veterinary doctor.
The use of cyclobenzaprine concomitantly with tramadol may potentiate the occurrence of seizures, and veterinary monitoring is indicated.
As it contains tramadol in its formulation, it is important to be alert to the concomitant use of **SINDOLOR®** with opiates, type 2 adrenergic receptor agonists, selective norepinephrine and serotonin reuptake inhibitors, such as antidepressants and/or behavior modulators, as they can cause respiratory depression.
Caution should be exercised when administering **SINDOLOR®** to animals with hepatic or renal disorders, since tramadol and dipyrone undergo hepatic metabolism and are excreted via the kidneys.
Caution should be exercised when administering **SINDOLOR®** to dogs undergoing treatment with phenylbutazone or barbiturates, due to the interactions with the hepatic enzyme system.
Caution should be exercised when administering **SINDOLOR®** to dogs undergoing treatment with quinidine, since quinidine has an inhibitory action on the formation of M1 and, thus, reduces the analgesic efficacy of tramadol.
Caution should be exercised when administering **SINDOLOR®** to dogs undergoing treatment with naloxone, as the partial antagonistic action of naloxone on type (mu) opioid receptors may reduce the analgesic efficacy of tramadol.

POISONING AND OVERDOSE
When administered in overdose regimens, for example, 75 mg/kg of dipyrone sodium and 6 mg/kg of tramadol hydrochloride every 8 hours, orally, for 7 days, that is, three times the recommended dose, **SINDOLOR®** proved to be unsafe, as it showed to potentially cause sialorrhea at the moment of tablet administration (incidence of 100%) hiporexia (incidence of 80%) and emesis (incidence of 60%). Furthermore, hematological changes have been reported, such as a significant reduction in hematocrit, erythrocyte and hemoglobin levels (all below the reference levels), in addition to increased alkaline phosphatase concentrations (above the reference levels). Therefore, the use of this product in overdoses is contraindicated.
The use of tramadol overdose can cause serotonin syndrome, especially when combined with drugs that inhibit the reuptake of norepinephrine and serotonin. Studies carried out to evaluate acute oral toxicity reported that tramadol overdose can cause respiratory depression, lethargy, coma, seizures, cardiac arrest and death. Studies carried out with laboratory animals receiving an overdose regimen of tramadol, ranging from 3 to 15 times the recommended dose, have demonstrated the occurrence of embryotoxicity and fetotoxicity. Both tramadol and its active metabolite pass into breast milk at very low levels, but the safety of the drug in neonates has not been established yet.
Studies carried out to evaluate the acute oral toxicity of dipyrone, when administered in an overdose regimen, reported the occurrence of sedation and convulsion in all species tested. Studies involving long-term overdose regimens, such as the dose of 600 mg/kg body weight/day of dipyrone, reported the occurrence of sialorrhea, emesis, hyporexia, significant reduction in erythrocyte and hemoglobin counts, significant increase in reticulocyte and Heinz body levels, increased serum concentrations of urea and bilirubin, in addition to a tendency towards increased serum activity of the enzyme aspartate aminotransferase (AST) in the species tested.
In cases of poisoning or overdose, seek a Veterinary doctor for evaluation and supportive treatment and to carry out hematological and biochemical tests.

WARNING
Veterinary products must be kept out of the reach of children and pets. They should not be stored near food, drinks or personal hygiene products. **SINDOLOR®** is not indicated for pregnant or lactating females or dogs under 12 months of age, as studies have not been carried out with these groups. Doses adjustments should only be made following the Veterinary doctor's recommendation and guidance.

WARNING: USE BY HUMANS MAY CAUSE SERIOUS RISKS TO HEALTH.

HOW SUPPLIED
Cartridge with 1 blister containing 10 bisected tablets each (presentation of **SINDOLOR®** 375 mg).
Cartridge with 2 blisters containing 5 bisected tablets each (presentation of **SINDOLOR®** 1125 mg).

STORAGE RECOMMENDATIONS
Keep it in a dry place, at room temperature (15°C to 30°C), away from direct sunlight and out of reach of children and pets. In cases of accidental ingestion, seek the advice of a doctor and take the product package with you.
Exposing the product to extreme conditions of heat, sunlight and humidity, disregarding the correct storage recommendations, may result in a decrease or loss of activity of active ingredients.

After splitting the tablet, the parts obtained must be used within 24 hours.

Lot, manufacturing and expiration date: see packaging.

SALE UNDER VETERINARY DOCTOR'S PRESCRIPTION WITH MANDATORY RETENTION OF PRESCRIPTION RECORDS

Product licensed at the Ministry of Agriculture, Livestock and Supply under number SP 001692-6.000006 on July 15/2022.

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Responsible technician:
Daniela Ziolkowski
CRF-SP 29486

Expiry date:
24 months from the manufacturing date.

Avert