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MITABAN®

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Pharmacia & Upjohn

NDC 0009-3118-01

brand of amitraz liquid concentrate

For topical use on dogs

For Use In Animals Only

WARNING

Toxicology studies conducted in the dog and other species suggest amitraz may alter the animal's ability to maintain homeostasis. Animals treated with MITABAN (amitraz) should not be subjected to stress for a period of at least 24 hours posttreatment. Adverse reactions including three fatalities were reported during the clinical studies. In excess of 1100 patients with generalized demodicosis were topically treated with MITABAN.

DESCRIPTION

MITABAN Liquid Concentrate (amitraz) contains 19.9% N'-(2,4-dimethylphenyl)-N-[[2,4-dimethylphenyl) imino] methyl]-N-methyl-methanimidamide (w/w), and also xylol, propylene oxide, and a blend of alkyl benzene sulfonates and exthoxylated polyethers. Amitraz, a diamide, is pale yellow, has a melting point of 86° to 87° C, is not hygroscopic, is stable to heating, soluble in most organic solvents, and sparingly soluble in water.

PHARMACOLOGY

Amitraz is hydrolyzed to 2,4-dimethyl-formanilide and N-(2,4-dimethylphenyl)-N'-methylformamidine; these metabolites are further metabolized to 2,4-dimethylaniline and ultimately to 4-amino-3-methylbenzoic acid, which was the principle metabolite in the urine and liver.

Radiolabeled amitraz was administered to beagles as a single oral treatment at a level of 4 mg/kg. Peak blood levels were reached between 1.5 and 6 hours posttreatment; the half-life was approximately 12 hours during the initial 48 hours. Radioactivity was extremely low in whole blood and plasma at 72 (0.05-0.06 ppm) and 96 (0.03-0.06 ppm) hours. The organs having residues at levels greater than plasma concentrations at 96 hours included: liver, skin, eyes, bile, kidney, medulla, cerebrum, lungs, gonads, fat, thyroid, spleen, and large intestine. The main metabolite isolated from these tissues was identified as 4-amino-3-methylbenzoic acid, which is nontoxic for the dog.

Studies have not been conducted to quantitatively determine absorption by the dog following topical or dermal treatment with amitraz. The technical drug (amitraz) and formulated material (MITABAN Liquid Concentrate) have been extensively evaluated in laboratory and domesticated animals in a series of acute, subchronic and chronic studies.

The mechanism of action for amitraz is unknown, however data currently available suggest the drug may act on the central nervous system. *In vitro* housefly tests indicated amitraz does not have significant cholinesterase inhibitory activity.

INDICATIONS

MITABAN (amitraz) is indicated for treatment of generalized demodicosis *(Demodex canis)* in dogs. Current data do not support use for treatment of localized demodicosis or scabies.

CONTRAINDICATIONS

Fertility impairment studies have not been conducted in the canine with MITABAN (amitraz). It is not known whether MITABAN may cause impairment of fertility in dogs. Reproduction studies during pregnancy have not been conducted with MITABAN. It is not known whether MITABAN may harm the embryo or fetus. The safety of MITABAN has not been established for dogs less than four months of age.

WARNINGS:

Please refer to warning at the beginning of the package insert. Not for human use. Keep out of reach of children. MITABAN (amitraz) may be harmful if swallowed by humans. If swallowed, do not induce vomiting (contains xylol) and immediately call a physician. Avoid inhalation of vapors (xylol) and contamination of feed and food stuffs. MITABAN is flammable; when diluted with water, the mixture is not flammable. MITABAN (concentrate or diluted) may cause eye or skin irritation in sensitive persons. Do not get in eyes, on skin or on clothing. If in eyes, wash with water for 15 minutes and call a physician immediately. Protect exposed skin (e.g. with rubber gloves, etc.) when mixing MITABAN with water and treating animals. Wash hands and arms with soap and water after treatment of the pet(s). Dispose of unused MITABAN-water solution by flushing down the drain. Rinse the MITABAN container with water and do not reuse. Avoid handling pets immediately after treatment. Contact may cause skin irritation in sensitive individuals during the first few days after treatment. Amitraz, the active ingredient in MITABAN, has been shown to cause liver tumors in female mice. Ingestion or inhalation may cause central nervous system depression.

PRECAUTIONS

Though eye or dermal irritation was not reported during controlled experiments, such effects have been infrequently reported from clinical use. Consistent with good veterinary practice, it is recommended that a protectant be used in the eyes of patients prior to facial treatment with any topical therapy. Well-controlled experiments with MITABAN® (amitraz) have not been conducted to determine the compatibility range with other products.

ADVERSE REACTIONS AND SIDE EFFECTS

Ingestion of MITABAN may increase the risk of adverse effects. Therefore, appropriate care should be exercised both during and immediately after MITABAN application to minimize the opportunity for exposure by the oral route.

The most frequently observed adverse reaction in the clinical studies was transient sedation, which occurred in approximately 8% of the generalized demodicosis patients. This effect was observed within 2 to 6 hours posttreatment, and usually dissipated within 24 to 72 hours. In approximately 40% of the affected generalized demodicosis patients, the effect dissipated in less than 24 hours. Sedation often was less apparent when additional MITABAN (amitraz) treatments were applied, however in approximately 35% of the generalized demodicosis patients sleepiness was observed after each treatment. Transient pruritus, which clinical investigators considered to be an indirect effect due to an inflammatory reaction associated with dead mites, occurred in less than 3% of the generalized demodicosis patients. This effect usually occurred and dissipated within 24-48 hours posttreatment. Other observations noted by the clinical investigators and/or clients were a low incidence (less than 1%) of convulsions, ataxia, hyperexcitability, personality change, hypothermia, appetite stimulation, bloat, polyuria, vomition, diarrhea, anorexia, edema, erythema and other varying degrees of skin irritation. Three fatalities were recorded.

Toxicology:

Dermal Studies - Dog

Acute and subchronic dermal toxicity studies were conducted with nondiseased beagles using the recommended concentration (250 ppm active drug) and exaggerated concentrations of MITABAN (amitraz). A single treatment with 250 ppm, 1250 ppm or 2500 ppm was topically applied to healthy dogs. Transient sedation was observed within 8 hours posttreatment in 1 of 6 dogs at 250 ppm, and all of the animals at 1250 ppm and 2500 ppm; all of the animals were normal at 24 hours posttreatment. There was a significant depression of rectal temperatures at 4 hours posttreatment in the 1250 ppm and 2500 ppm groups. Blood glucose values were elevated at 4 hours posttreatment in the 250 ppm female group, and in both sexes at the 1250 ppm and 2500 ppm concentrations. Rectal temperatures and glucose values returned to normal within 24 hours posttreatment. In another study, groups of healthy beagles were topically treated with either 250 ppm, 750 ppm or 1250 ppm of active drug at 14 day intervals and for 12 weeks. Blood glucose values were elevated at the 750 ppm concentration at 4 hours posttreatment after 3 of 6 treatments, and after 5 of 6 treatments at the 1250 ppm level. In the 750 ppm group, serum glucose values returned to normal at 24 hours posttreatment, however for the 1250 ppm group, at 24 hours and after 3 of 6 treatments the levels remained significantly elevated.

Dermal or ocular responses were not observed when MITABAN was applied at recommended or exaggerated concentrations to the skin and incidentally to the eyes of dogs (in controlled experiments simulating recommended use). However, such responses have been infrequently reported from clinical use. (See PRECAUTIONS).

Oral Studies - Dog

An acute oral toxicity study was conducted with amitraz utilizing nondiseased beagles. Death occurred in one of two dogs given a single oral dose of 100 mg/kg. Clinical signs included CNS depression, ataxia, hypothermia,

bradycardia, muscular weakness, vomition, uncontrolled vocal spasm and micturition. Clinical laboratory data indicated a hemoconcentration, and transient elevations in blood glucose, blood urea nitrogen, serum potassium and alkaline phosphatase values. Dogs given 20 mg/kg (single oral dose) showed similar, though less pronounced, clinical signs and were clinically normal at three days posttreatment. Hemoconcentration and increased blood urea nitrogen were noted in both dogs; increased and transient blood glucose and serum alkaline phosphatase values were observed in one dog. Dogs given 4 mg/kg (single oral dose) had decreased rectal temperatures within three hours and were normal at 24 hours posttreatment.

Amitraz was orally administered to nondiseased beagles at levels of 0, 0.25, 1 and 4 mg/kg once daily for 90 days. There were no deaths in any of the groups. At 3 hours posttreatment and for only the initial three days of the 90 day experiment, dogs treated with 4 mg/kg exhibited CNS depression and ataxia; the effects remained for 3 to 6 hours and the dogs were normal within 24 hours posttreatment. Vomition occurred in two dogs on only the initial two days of the study. Thereafter (days 4 through 90) the dogs appeared to be subdued for approximately 6 hours after dosing, and ataxia was nearly impossible to detect. In the initial 48 to 72 hours, dogs treated with 1 mg/kg/day exhibited signs of depression (without ataxia) for 4-6 hours; subsequently the depression became less marked and of shorter duration. At 3 hours after dosing, dogs treated with 1 or 4 mg/kg consistently had subnormal rectal temperatures and pulse rates; both parameters returned to normal within 24 hours posttreatment. At 0.25 mg/kg/day, the dogs appeared normal throughout the experiment. Hyperglycemia consistently occurred in dogs treated with 1 and 4 mg/kg/day and rarely occurred in dogs at the 0.25 mg/kg level; this response was maximal within 6 hours posttreatment and serum glucose values returned to normal within 24 hours after treatment. Grossly there was a significant increase in liver weights for dogs treated at the 4 mg/kg level, however microscopically the findings were minimal and consisted of a slight enlargement of the central and midzonal hepatocytes; the degree of enlargement was not dose related. However, at the two higher doses the area affected appeared more prominent as reflected by an increase of the periportal hepatocytes. In the adrenal gland, several dogs treated with the two higher levels had thinning of the zonae fasiculata and reticularis, which may be associated with slight hyperplasia of the zona glomerulosa.

INFORMATION FOR CLIENTS

Clients should be informed that animals treated with MITABAN (amitraz) should not be subjected to additional stress for a period of at least 24 hours posttreatment. Refer to information in italics under **WARNINGS**.

DOSAGE AND ADMINISTRATION

Long and medium-haired dogs should be clipped closely before treating. Prior to the initial treatment, all dogs should be bathed with a mild soap and water and towel dried. The entire animal should then be topically treated with MITABAN (amitraz) at a rate of 10.6 milliliters (contents of one bottle) per 2 gallons of warm water (250 ppm active drug). Two bottles (21.2 milliliters) per four gallons of water may be necessary to treat large dogs. The entire dog should be thoroughly and completely wetted with the mixture, and then allowed to air dry. Do not rinse or towel dry the dog after treatment with MITABAN. A fresh MITABAN-water mixture should be prepared for each patient; using the same mixture for more than one patient can spread other dermal infections and also the concentration of MITABAN could be reduced to a level which would be less effective than the recommended concentration.

Three to six topical treatments (14 days apart) are recommended for treatment of generalized demodicosis. It is important to continue the treatment until no viable (alive) mites are found in the skin scrapings at two successive treatments, or until six treatments have been applied. Severe (chronic) cases and dogs which are reinfested may require a second and third series of treatments, and again the treatment should be applied at 14 day intervals. Discontinue treatment of dogs which do not respond clinically.

When employing MITABAN for treatment of demodicosis, other dogs in the home also should be examined for lesions to ascertain whether treatment of these animals is warranted.

CANINE EFFICACY

Controlled Studies

The efficacy of MITABAN (amitraz) was extensively evaluated on dogs experimentally or naturally parasitized with *Demodex canis*. Three to six MITABAN treatments (250 ppm active drug), at 14 day intervals, were highly efficacious for treatment of naturally acquired demodicosis. MITABAN treatment was continued until all *Demodex* in the skin scrapings were dead or the dogs no longer harbored mites at two successive treatments, or the animal received six treatments. Ninety-six percent of the dogs were cleared of mites.

Clinical Studies

Investigators at university veterinary clinics, small animal practitioners, and dermatology specialists clinically evaluated MITABAN. A total of 1107 generalized demodicosis patients were included in these investigations. A variety of breeds, ages, hair conditions and lengths, and weights of dogs were included in these field investigations. The pre- and posttreatment demodicosis indices were used to quantify the degree and extent of involvement. Of the generalized cases, greater than 95% clinically improved (posttreatment clinical condition better than pre-treatment condition), and the average clinical response [(mean pretreatment index - mean posttreatment index) X 100 ÷ mean pretreatment index] was greater than 90%; these patients received an average of 5 treatments. Seventy-five percent of the generalized demodicosis patients were negative for viable mites prior to administration of the final MITABAN treatment.

Eighty percent of the generalized demodicosis patients were returned to clinical normalcy and did not require additional therapy after receiving one treatment series. Twenty percent of all patients with generalized demodicosis required a second treatment series. When retreated, the 14 day treatment interval was again followed, and these patients received an average of 5 treatments. Greater than 90% of the dogs clinically improved, and the average clinical response of these patients was approximately 80%. Greater than 96% of all generalized demodicosis patients returned to normalcy after receiving one or two treatment series and did not require further therapy. Between 3 and 4% of all generalized demodicosis patients were returned to the investigators and required therapy beyond the second treatment series; these patients received a third or fourth series of MITABAN treatments. Greater than 99% of all generalized demodicosis patients returned to normalcy after receiving one, two, or three treatment series, and did not require further therapy; less than 1% of the patients required additional therapy.

HOW SUPPLIED

MITABAN Liquid Concentrate (amitraz) is available in cartons of 12-10.6 mL bottles.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Caution: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

NADA #120-299, Approved by FDA

Made in Canada

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