

CHEQUE® DROPS

CII

Pharmacia & Upjohn

Estrous Preventive

Mibolerone drops

NADA No.: 102-709

Active Ingredient(s): Each mL contains 100 mcg mibolerone and propylene glycol, qs.

Indications: CHEQUE® (mibolerone) Drops are administered orally for estrous (heat) prevention in adult female dogs not intended primarily for breeding purposes. CHEQUE® Drops dosage should be discontinued after 24 months of use.

CHEQUE® Drops are effective in preventing estrus only when drug administration is initiated 30 days prior to the start of the proestrus. It should not be used in an attempt to abbreviate an estrous period. It should not be used in bitches prior to the first estrous period.

Pharmacology: CHEQUE® (mibolerone) Drops are 17-b-hydroxy-7a, 17-dimethyl-estr-4-en-3-one, generic name mibolerone, a non-progestational steroid. In its pure form, mibolerone is a white crystalline solid. The compound is stable under ordinary conditions and temperatures.

Actions: More than 90 percent of normal, mature cycling bitches did not exhibit estrus when administered CHEQUE® (mibolerone) Drops in adequate doses.

Mibolerone has been shown to be an anabolic and androgenic steroid in rats. When compared to methyltestosterone, it is 41 times more potent as an anabolic agent and 16 times more potent as an androgen. Mibolerone has no estrogenic activity in mice when used at levels up to 1.0 mg per animal per day. It is antiestrogenic in mice in intravaginal tests at 0.9 mcg and in subcutaneous tests at 10 mcg or less when tested against estradiol.

In the bitch, mibolerone has androgenic, anabolic and antigonadotrophic activity. Mibolerone selectively blocks the luteinizing hormone (LH) peak thereby preventing estrual activity. No significant progestational nor estrogenic activity has been demonstrated in the canine.

Metabolism: Based on tritium labeled studies in the bitch, approximately equal quantities of mibolerone were excreted via the urine and feces. Mibolerone was extensively metabolized, being excreted as over 10 metabolites. Mibolerone was present in most tissues with highest concentrations being in the liver, anal glands and reproductive organs. Significant levels of radioactivity occurred along the digestive tract.

Canine Efficacy: Mibolerone dosage for estrous prevention was evaluated in 13 breeds of purebred dogs in kennels. It was also field tested in a substantial number of bitches. Based on kennel trials and in home evaluations for various periods of time, more than 90 percent of normal, mature cycling bitches did not exhibit estrus when administered CHEQUE® (mibolerone) Drops in adequate dosage.

Drug Interaction: The following classes of drugs have been administered concurrently during mibolerone therapy without apparent problems being observed: general and local anesthetics, analgesic/antipyretics, anthelmintics-parasitacides, antibacterials-fungicides, corticosteroids and biologicals. However, dogs administered pharmaceuticals or biologicals concurrent with

CHEQUE® (mibolerone) Drops should be carefully monitored for possible interactions.

Data from a well controlled study support the concurrent uses of mibolerone and styrylpyridinium chloride-diethylcarbamazine citrate when the latter is used for prevention of heart worm infections. Concurrent therapy of the pharmaceuticals altered neither the efficacy nor safety of mibolerone or of styrylpyridinium chloride-diethylcarbamazine citrate.

Seizure activity has been reported in a previously controlled epileptic patient while simultaneously receiving mibolerone and diphenylhydantoin.

Dosage and Administration: CHEQUE® (mibolerone) Drops dosage is as follows (administer orally once each day by adding to a small amount of food or directly to the mouth):

Weight of Bitch (lbs)	CHEQUE® Drops Daily Dosage mL	mcg
1 to 25	0.3	30
26 to 50	0.6	60
51 to 100	1.2	120
101 and over	1.8	180
German Shepherd Dog or German Shepherd Mix (All Weights)	1.8	180

CHEQUE® Drops Dispensed
(Bottle Size)

Bottle Size	Approximate Days of Treatment for Different Dose Levels				
	Daily Dose (mL)	180	120	60	30
55.0 mL	.3	90	45	30	15
	.6	45	30	15	7.5
	1.2	22.5	15	7.5	3.75
	1.8	15	7.5	3.75	1.875

Contraindication(s): CHEQUE® (mibolerone) Drops should not be used in a pregnant bitch or female dogs with perianal adenoma, perianal adenocarcinoma, or other androgen dependent neoplastic conditions. CHEQUE® should not be administered to any animal with a prior history of liver or kidney disease.

Not for use in Bedlington Terriers. A genetic defect (chronic progressive hepatitis) has been reported to occur in a high percentage of animals of this breed. Thus, irrespective of the existence or absence of liver disease in a given animal, every Bedlington Terrier should be

regarded as an animal with such a prior history.

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

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

Do not administer for more than 24 months. CHEQUE® (mibolerone) Drops should be administered only to normal, mature, nonpregnant, nonlactating bitches, as directed, and should not be administered to immature bitches, male dogs, puppies or cats. CHEQUE® Drops should not be administered to bitches intended primarily for breeding purposes.

CHEQUE® Drops should not be administered to any animal with prior history of liver or kidney disease. Liver serum enzyme elevations may be encountered. Some androgens may result in jaundice in particularly sensitive animals. This effect has been observed in a few animals administered CHEQUE® Drops at the therapeutic level. If jaundice does occur, CHEQUE® Drops treatment should be discontinued. Periodic liver function tests are recommended under prolonged administration. SGPT values were evaluated and appear to be an appropriate criterion for monitoring liver changes.

CHEQUE® Drops should be used with caution in the younger mature bitch (approximately 7 months old or less) in that steroids with androgenic activity can result in early epiphyseal closure. This effect on skeletal development has, however, not been observed with mibolerone treatment. Some immature bitches are especially responsive to the androgenicity of CHEQUE® Drops with marked clitoral enlargement and low grade vaginitis resulting from prolonged therapy. Topical antibiotic-corticosteroid ointments for genital application may be used if the irritation results in problem discharges. Failure to respond to topical treatment indicates the animal is no longer a candidate for CHEQUE® Drops. CHEQUE® Drops should be used with caution in animals with chronic epiphora or other conditions involving the lacrimal apparatus. Testing in Miniature and Toy Poodles has, however, not resulted in detectable aggravation of existing epiphora.

If CHEQUE® Drops dosage is started and then the bitch comes into estrus, CHEQUE® Drops may be continued but caution should be taken to prevent breeding. If breeding occurs, CHEQUE® Drops dosage should be stopped until such time as the bitch is determined not to be pregnant. CHEQUE® Drops should not be used concurrently with or following use of any progestational or estrogenic compound until potential clinical abnormalities associated with use of those compounds are eliminated.

For use in animals only.

Warning(s): Not for human use. One study in humans indicated a potential altered liver function that resulted in termination of the study.

Toxicology: Beagles treated orally for 28 days with mibolerone at a level of 300 mcg/kg had no drug related alterations in hematology or blood chemistry and no toxic symptoms were observed.

In a subsequent test, mibolerone was administered orally to Beagles at the rate of 3,000 to 30,000 mcg/kg daily for 28 days. Clinical chemistry, hematology, urinalysis, including urine concentration test, gross pathology and histopathology showed no drug related toxic effects. The only drug related effects included a reduction of the stainable lipid in the adrenal cortices, enlargement of the clitoris, thickening of the myometrium and endometrium, and inhibition of spermatogenesis (3,000 mcg/kg level). All treated dogs had periodic episodes of epiphora. There was an apparent drug related increase in renal, uterine, and prostatic weights and a decrease in the ovarian, testicular and thymic weights.

Beagles, male and female, have been treated with levels of mibolerone of up to 500 mcg per day for 240 days and 200 mcg per day for up to 730 days. The incidence of vaginal irritation and clitoral enlargement was more pronounced in the immature than mature bitch. Other effects included: (1) blockage of tertiary but not primary or secondary follicular development, (2) maintenance of prepubertal ovarian and uterine-cervical weights in the immature treated bitches, (3) a slight decrease in adrenal weights without evidence of altered morphology or function, (4) an increase in kidney weight without evidence of altered morphology or function, (5) a decrease in prostate weight in high dose immature dogs. Treated males and females had slight increases in mean SGOT (serum glutamic oxalacetic transaminase, or aspartate transaminase) and SGPT (serum glutamic pyruvic transaminase or alanine transaminase) without evidence of hepatocellular damage (based on light microscopy) or alteration of hepatic function (based on BSP retention and clinical chemistry).

After terminating mibolerone treatment, Beagle bitches returned to cyclic estrous activity as soon as 7 days after last treatment with the longest interval being somewhat over 200 days. In a study involving 96 bitches bred starting their first estrus after the end of mibolerone treatment, bitches had a normal pregnancy and delivery and had normal pups. Mibolerone bitches had a lower conception rate for all breedings compared to untreated bitches (76% vs 100%). However, percent mibolerone treated bitches whelping of those conceiving (97%) was similar to untreated bitches (90%).

Weaned Beagle puppies (7-15 weeks of age, averaging 5.36 kg in weight) were treated daily with levels of mibolerone up to 200,000 mcg per day for 30 days. During the fourth week of treatment, the animals receiving 200,000 mcg per day showed excessive lacrimation, depression, anorexia, weight loss and myalgia. No gross lesions occurred at necropsy. An expected dose related uterotrophic response occurred as well as marked increase in prostate weight. A dose related decrease occurred in adrenal weight at 4,000 and 200,000 mcg/animal/day. Histologically there was a slight fatty change in the livers of 3 of 4 females receiving 200,000 mcg per day.

Mibolerone was administered six times a week for up to 9.6 years (average of 6.1 years) to bitches of seven breeds of dogs. The average age of all dogs at time of their termination was 9.7 years. Sixty-three bitches served as nontreated controls, 103 bitches received 30 to 180 mcg mibolerone per day to approximate the efficacious dose, and 61 bitches were given 90 to 900 mcg mibolerone per day as an exaggerated dose. Study bitches were evaluated with physical examinations, hematology, and clinical chemistry. Tissues of dogs which died during the study and those of dogs killed at study termination were evaluated histopathologically. Dogs were tested also for changes in peripheral circulation concentrations of both cortisol in response to ACTH and triiodothyronine and thyroxin to TSH.

Chronic oral administration of mibolerone was associated with an increased incidence of chronic liver disease with controls, 1X, and the exaggerated dose groups showing 57, 91, and 93 percent of the dogs with diseased livers, respectively. Drug administration was also associated with cirrhosis with controls, 1X, and exaggerated dose groups having 4, 10, and 28 percent of the dogs with cirrhosis, respectively. An increased prevalence of hepatocellular intranuclear crystalline inclusion bodies was found in many treated bitches.

Treatment related reproductive tract lesions included ovarian arterial mineralization, endometrial atrophy, endometrial cysts, endocervical cysts, vaginal mucosal atrophy, invaginations and cysts of the vaginal mucosa, vaginitis, clitoral ossification and clitoritis at the efficacious and exaggerated doses. A 10% incidence of ovarian fibroma was found in bitches given the approximate efficacious dose only; an increased incidence of ovarian follicular cysts was found in bitches given the exaggerated dose.

Chronic mibolerone exposure was also associated with decreased numbers of corpora lutea

and vaginal fibromas at the efficacious and exaggerated doses.

Treatment related findings from other organs included increased incidences of mineral deposition in the kidneys, adrenal cortical lipidosis and a reduction in the incidence of mammary neoplasms and total neoplasms, all at the efficacious and exaggerated doses.

The Beagle, but not the other six breeds, appeared to have a reduced response to ACTH challenge. Epiphora appeared to be mibolerone related in Toy Poodles and Beagles.

The therapeutic dose of mibolerone kept females out of heat and did not elicit side effects or clinical health problems that would prevent the animal from being a functional pet. The dogs fed mibolerone at exaggerated doses were not compromised as judged by their fitness to be a functional pet, based on clinical evaluations.

Adult bitches of mixed breeding receiving 60 mcg of mibolerone daily for up to 1,574 days showed no signs of toxicity. A drug related increase in clitoral size occurred but it was not deemed to be objectionable.

Adult Beagle bitches were started on mibolerone treatment orally at 20 or 60 mcg per animal per day starting 1, 3 or 6 days after the first two breedings and were continued on treatment until weaning. Conception and implantation were not prevented in bitches started on treatment after breeding. Gestation, parturition, and lactation were normal in all bitches. Female pups from the animals receiving mibolerone were masculinized. No other lesions were observed.

One study indicated liver tissue changes such as cellular swelling, obliterations of sinusoids, vascular degeneration, leukocyte infiltration and fibrosis.

The acute oral LD50 in the rat is greater than 1,600,000 mcg/kg while the intraperitoneal LD50 in the mouse is 555,600 mcg/kg.

Mibolerone has been well tolerated in rats at levels of 3,000 or 10,000 or 30,000 mcg/kg orally for up to 28 days. Changes observed included hypertrophy of the myometrium, reduction of the amount of stainable lipid in all three zones of the adrenal cortices, arrest of spermatogenesis and atrophy of the accessory sex gland of male rats at 3,000 and 10,000 mcg/kg. Treated animals ate less than the controls and required more food per unit of body weight gain.

The dose of mibolerone was increased at equal increments weekly from 600 mcg/kg the first week to 4,800 mcg/kg the fourth week in rats. A reduction in food consumption and a reduction in weight gain were noted. Treated males had a leukocytosis. No other toxic effects or changes in hematology or in gross or microscopic pathology were observed in either males or females. Rats exposed under dynamic conditions for one hour to a dust aerosol of mibolerone at a concentration of 5.03 mg/liter of air did not have any signs of toxicity during exposure or during a 14 day post treatment observation period.

Ointment containing mibolerone at a concentration of 0.25% was applied to abraded and unabraded rabbit skin daily for five days. The ointment was slightly irritating to the unabraded skin of the abdomen while it was not irritating to abraded skin.

Side Effects: Some animals, particularly immature females, have shown increased sensitivity to mibolerone. This sensitivity has been expressed by clitoral enlargement and white viscid discharge consisting of leukocytes originating from the clitoral fossa. If irritation of the vaginal vestibule persists some bitches may develop mounting behavior. Occasional bitches have had a musky body odor.

In clinical evaluation of CHEQUE® (mibolerone) Drops the following side effects have been attributed to CHEQUE® at estrus inhibiting doses (listed as a % of total clinical cases

reporting): Clitoral enlargement (20%); vaginal discharge (10%); riding behavior (1.6%); epiphora (5.6%), objectionable body odor (4.3%). Percent of all reported side effects was 45.4. A common finding after prolonged dosage was the presence of small (<1mm diameter) vesicles on the vaginal mucosa posterior to the urethral orifice. The clinical significance of these vesicles has not been determined.

Since the market introduction of CHEQUE® Drops, certain clinical signs have been reported as being associated with dogs receiving the drug. The actual role of mibolerone in the elicitation of those signs has not in all cases been determined. In decreasing order of frequency, they are:

1. Expression of estrus - generally due to failure to receive proper dose.
2. Vaginal/uterine discharge - may lead to diagnostic problems; e.g. mimic heat, confuse diagnosis of uterine disease.
3. Mating - may occur during estrus break or false estrus due to genital discharge.
4. Hepatic dysfunction as evidenced by jaundice, hepatomegaly, cirrhosis, and occasional deaths has been reported.
5. Increased aggressiveness - a recognizable side effect of androgenic substances.

Presentation: CHEQUE® (mibolerone) Drops are available in a bottle of 55 mL fill with graduated dropper.

Disclaimer: Every effort has been made to ensure the accuracy of the information published. However, it remains the responsibility of the readers to familiarize themselves with the product information contained on the product label or package insert. Compendium Code No.:
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