



Trilostane

Trilostane is a synthetic steroid analog that inhibits the adrenal enzyme 3 β -hydroxysteroid dehydrogenase.

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Overview

- ⚠ Trilostane suppresses production of progesterone and its end products, including cortisol and aldosterone.
 - Additional enzymes, (eg, 11 β -hydroxylase, 11 β -hydroxysteroid dehydrogenase) may also be affected.

Treatment Protocol

- ⚠ Clinical doses currently being used are lower than originally believed necessary.¹
 - The current FDA-approved labeled dose is 2.2-6.7 mg/kg administered once a day.²
 - The author recommends starting treatment as close as possible to the low end of that dose range.
 - Large dogs (ie, >25 kg body weight) generally require lower doses on a per-kilogram basis to control clinical signs.³
- ⚠ Despite label recommendations for once-a-day administration,² trilostane may begin to lose its

effectiveness 8 to 10 hours after administration.⁴

- Administration twice a day delivered good efficacy and may increase chance of remission in dogs with pituitary-dependent hyperadrenocorticism (HAC).⁵
- The need to increase the frequency to 3 times a day has been reported in some dogs.⁶
 - If twice a day results in ideal or acceptable cortisol concentrations but clinical signs are not controlled, 3 times a day should be considered.

- ⚠ The author likewise recommends administration twice a day in all dogs with HAC.
 - This protocol is especially indicated in patients for which breaks in control of HAC could be detrimental if the drug effects wear off (eg, dogs with concurrent diabetes mellitus or serious complications of HAC, such as proteinuria or hypertension).

- ⚠ Trilostane should be given with

food to increase absorption from the GI tract.²

- ⚠ Use of the trademark product Vetoryl (Dechra) is recommended by the author.
 - Compounded products can contain 40% to 150% of the labeled amount and may have variable dissolution properties.⁷
 - The bioavailability and pharmacokinetics of compounded trilostane are unknown, as is stability of liquid formulations.⁷

Monitoring

- ⚠ Adrenocorticotropic hormone (ACTH) stimulation testing is necessary for monitoring patient response to therapy.⁸
 - Alternatives (eg, baseline cortisol, endogenous ACTH, cortisol:ACTH ratio, urinary cortisol:creatinine ratio) have been assessed and were found to be unreliable.⁸
 - The test should start 2 to 6 hours after drug administration; the ideal interval is unknown.

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- It is important that the interval always be the same for an individual patient (eg, if the first test is done 5 hours postadministration, all subsequent tests should also start 5 hours postadministration).⁹
- Variations in sampling time (ie, start time of ACTH stimulation test relative to drug administration) of 2 hours can result in significant differences in cortisol levels and may influence dose and/or frequency recommendations.⁹
- The first ACTH stimulation test should be performed after 10 to 14 days of treatment or if decreased appetite, vomiting, diarrhea, listlessness, or normalization of water intake occurs.¹
- Because the full effect of the drug may not be seen for ≈30 days, the first recheck is to ensure against overdosing.
- The dose should not be increased at the first recheck but should be decreased if

serum cortisol concentrations are too low.

- ⚠ The ideal cortisol concentrations pre- and post-ACTH testing are ≈1-5 µg/dL (30-150 nmol/L).
 - A cortisol concentration of up to ≈9 µg/dL (250 nmol/L) post-ACTH testing is considered acceptable if the patient is doing well and clinical signs of HAC are controlled.⁸
- ⚠ Dose adjustments (ie, increases and decreases) based on ACTH stimulation test results and clinical signs will need to be made over time in most patients.

Adverse Effects

- ⚠ In most patients, adverse effects are relatively mild and include lethargy, weakness, decreased appetite, vomiting, and diarrhea.² Fatality has occurred but is rare.²
 - It is important to differentiate minor adverse effects from hypocortisolism, which causes the same clinical signs.
 - ACTH stimulation testing may be necessary.

- ⚠ Because cortisol is a natural antiinflammatory, when concentrations are decreased by trilostane administration, concurrent inflammatory conditions (eg, osteoarthritis) can worsen.
- ⚠ Theoretically, trilostane effects should be reversible within 1 to 2 days; however, suppression of cortisol secretion can last weeks to years.¹⁰⁻¹²
 - Adrenal necrosis is possible, to the extent that aldosterone secretion becomes deficient and complete hypoadrenocorticism results.^{13,14}
 - Aldosterone secretion can be suppressed independently of cortisol, potentially leading to signs of hypoadosteronism.¹⁵
- ⚠ If hormone deficiency occurs, trilostane administration should be stopped until adrenocortical recovery is documented by ACTH stimulation testing and electrolyte measurements.



WORDS OF CAUTION

PEER REVIEWED

ELLEN N. BEHREND, VMD, PhD, DACVIM, is the Joezy Griffin Professor in the department of clinical sciences at Auburn University. She has authored or co-authored more than 100 abstracts, journal articles, and book chapters. Her area of interest is endocrinology, with a focus on canine hyperadrenocorticism. After receiving her VMD, Dr. Behrend completed an internship at Michigan State University and a residency in internal medicine at Colorado State University.

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16 plumbstherapeuticsbrief.com November 2015

CLARO™

(florfenicol, terbinafine, mometasone furoate)
Otic Solution

Antibacterial, antifungal, and anti-inflammatory
For Otic Use in Dogs Only

CAUTION: Federal (U.S.A.) law restricts this drug to use by or on the order of a licensed veterinarian.

DESCRIPTION:

CLARO™ contains 15.0 mg/mL florfenicol, 13.3 mg/mL terbinafine (equivalent to 15.0 mg/mL terbinafine hydrochloride) and 2.0 mg/mL mometasone furoate. Inactive ingredients include purified water, propylene carbonate, propylene glycol, ethyl alcohol, and polyethylene glycol.

INDICATIONS:

CLARO™ is indicated for the treatment of otitis externa in dogs associated with susceptible strains of yeast (*Malassezia pachydermatis*) and bacteria (*Staphylococcus pseudintermedius*).

DO dosage AND ADMINISTRATION:

Shake before use.

CLARO™ should be administered by veterinary personnel.

Administer one dose (1 dropperette) per affected ear. The duration of effect should last 30 days.

- Clean and dry the external ear canal before administering the product.
 - Verify the tympanic membrane is intact prior to administration.
 - Remove single dose dropperette from the package.
 - While holding the dropperette in an upright position, remove the cap from the dropperette.
 - Turn the cap over and push the other end of the cap onto the tip of the dropperette.
 - Twist the cap to break the seal and then remove cap from the dropperette.
 - Screw the applicator nozzle onto the dropperette.
 - Insert the tapered tip of the dropperette into the affected external ear canal and squeeze to instill the entire contents (1 mL) into the affected ear.
 - Gently massage the base of the ear to allow distribution of the solution.
 - Repeat with other ear as prescribed.
- Cleaning the ear after dosing may affect product effectiveness.

CONTRAINDICATIONS:

Do not use in dogs with known tympanic membrane perforation (see **PRECAUTIONS**).

CLARO™ is contraindicated in dogs with known or suspected hypersensitivity to florfenicol, terbinafine hydrochloride, or mometasone furoate.

WARNINGS:

Human Warnings: Not for use in humans. Keep this and all drugs out of reach of children. In case of accidental ingestion by humans, contact a physician immediately. In case of accidental skin contact, wash area thoroughly with water. Avoid contact with eyes. Humans with known hypersensitivity to florfenicol, terbinafine hydrochloride, or mometasone furoate should not handle this product.

PRECAUTIONS:

Do not administer orally.

The use of CLARO™ in dogs with perforated tympanic membranes has not been evaluated. The integrity of the tympanic membrane should be confirmed before administering the product. Reevaluate the dog if hearing loss or signs of vestibular dysfunction are observed during treatment.

Use of topical otic corticosteroids has been associated with adrenocortical suppression and iatrogenic hyperadrenocorticism in dogs (see **ANIMAL SAFETY**).

Use with caution in dogs with impaired hepatic function (see **ANIMAL SAFETY**).

The safe use of CLARO™ in dogs used for breeding purposes, during pregnancy, or in lactating bitches has not been evaluated.

ADVERSE REACTIONS:

In a field study conducted in the United States (see **EFFECTIVENESS**), there were no directly attributable adverse reactions in 146 dogs administered CLARO™.

To report suspected adverse drug events and/or obtain a copy of the Safety Data Sheet (SDS) or for technical assistance, contact Bayer HealthCare at 1-800-422-9874.

For additional information about adverse drug experience reporting for animal drugs, contact FDA at 1-888-FDA-VETS or online at <http://www.fda.gov/AnimalVeterinary/SafetyHealth>.

PHARMACOLOGY:

CLARO™ Otic Solution is a fixed combination of three active substances: florfenicol (antibacterial), terbinafine (antifungal), and mometasone furoate (steroidal anti-inflammatory). Florfenicol is a bacteriostatic antibiotic which acts by inhibiting protein synthesis. Terbinafine is an antifungal which selectively inhibits the early synthesis of ergosterol. Mometasone furoate is a glucocorticosteroid with anti-inflammatory activity.

MICROBIOLOGY:

The compatibility and additive effect of each of the components in CLARO™ solution was demonstrated in a component effectiveness and non-interference study. An *in vitro* study of organisms collected from clinical cases of otitis externa in dogs enrolled in the clinical effectiveness study determined that florfenicol and terbinafine hydrochloride inhibit the growth of bacteria and yeast commonly associated with otitis externa in dogs. No consistent synergistic or antagonistic effect of the two antimicrobials was demonstrated. The addition of mometasone furoate to the combination did not impair antimicrobial activity of the two clinically significant extent.

In a field study (see **EFFECTIVENESS**), at least 10 isolates from successfully treated cases were obtained for *S. pseudintermedius* and *M. pachydermatis*.

EFFECTIVENESS:

In a well-controlled, double-masked field study, CLARO™ was evaluated against a vehicle control in 221 dogs with otitis externa. One hundred and forty six dogs were treated with CLARO™ and 75 dogs were treated with the vehicle control. All dogs were evaluated for safety. Treatment (1 mL) was administered once on Day 0 to the affected ear(s). Prior to treatment, the ear(s) was cleaned with saline. The dogs were evaluated on Days 0, 7, 14, and 30. Blood work and urinalysis were obtained on Day 0 pre-treatment and Day 30 at study completion. Four clinical signs associated with otitis externa were evaluated: erythema, exudate, swelling, and ulceration. Success was based on clinical improvement at Day 30. Of the 183 dogs included in the effectiveness evaluation, 72.5% of dogs administered CLARO™ solution were successfully treated, compared to 11.1% of the dogs in the vehicle-control group (p=0.0001).

ANIMAL SAFETY:

In a target animal safety study, CLARO™ was administered orally to 12-week-old Beagle puppies (4 dogs/sex/group) at 0X, 1X, 3X, and 5X the recommended dose once every 2 weeks for a total dosing period of 28 days (3 times the treatment duration). No clinically relevant treatment-related findings were noted in hearing tests, body weight, weight gain, or food consumption. CLARO™ administration was associated with post-treatment ear wetness or clear aural exudate, increased absolute neutrophil count, decreased absolute lymphocyte and eosinophil counts, suppression of the adrenal cortical response to ACTH-stimulation, decreased adrenal weight and atrophy of the adrenal cortex, increased liver weight with hepatocellular enlargement/cytoplasmic change, and decreased thymus weight. Other potentially treatment-related effects included mild changes to AST, total protein, inorganic phosphorus, creatinine, and calcium.

STORAGE INFORMATION:

Store between 20°C-25°C (68°F-77°F), excursions permitted 10°C-30°C (59°F-86°F).

HOW SUPPLIED:

CLARO™ solution is supplied in a single-use dropperette in a blister. Each dropperette contains one 1 mL dose.

CLARO™ is available in cartons of two, ten, or twenty dropperettes.

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