

Aglepristone

- **(a-gle-pris-tone)**
- ***Alizin®*, *Alizine®***
- **Injectable Progesterone Blocker**

PRESCRIBER HIGHLIGHTS

- Injectable progesterone blocker indicated for pregnancy termination in bitches; may also be of benefit in inducing parturition or in treating pyometra complex in dogs & progesterone-dependent mammary hyperplasia in cats.
- Not currently available in USA; marketed for use in dogs in Europe, South America, etc.
- Localized injection site reactions are the most commonly noted adverse effect; other adverse effects reported in >5% of patients include: anorexia (25%), excitation (23%), depression (21%), & diarrhea (13%).

USES/INDICATIONS

Aglepristone is labeled (in the U.K. and elsewhere) for pregnancy termination in bitches up to 45 days after mating.

In dogs, aglepristone may prove useful in inducing parturition or treating pyometra complex (often in combination with a prostaglandin F analog such as cloprostenol).

In cats, it may be of benefit for pregnancy termination (one study documented 87% efficacy when administered at the recommended dog dose at day 25) or in treating mammary hyperplasias or pyometras.

PHARMACOLOGY/ACTIONS

Aglepristone is a synthetic steroid that binds to the progesterone (P4) receptors thereby preventing biological effects from progesterone. In dogs, it has an affinity for uterine progesterone receptors approximately 3X that of progesterone. In queens, affinity is approximately 9X greater than the endogenous hormone. As progesterone is necessary for maintaining pregnancy, pregnancy can be terminated or parturition induced. Abortion occurs within 7 days of administration.

Benign feline mammary hyperplasias (fibroadenomatous hyperplasia; FAHs) are usually under the influence of progesterone and aglepristone can be used to medically treat this condition.

Aglepristone has been shown to have inhibitory effects on progesterone-receptor positive canine mammary carcinoma cells (Guil-Luna et al. 2011).

When used for treating pyometra in dogs, aglepristone can cause opening of the cervix and resumption of miometrial contractility.

Within 24 hours of administration, aglepristone does not appreciably affect circulating plasma levels of progesterone, cortisol, prostaglandins or oxytocin. Plasma levels of prolactin are increased within 12 hours when used in dogs during mid-pregnancy which is probably the cause of mammary gland congestion often seen in these dogs.

Aglepristone also binds to glucocorticoid receptors but has no glucocorticoid activity; it can prevent endogenous or exogenously administered glucocorticoids from binding and acting at these sites.

PHARMACOKINETICS

In dogs, after injecting two doses of 10 mg/kg 24 hours apart, peak serum levels occur about 2.5 days later and mean residence time is about 6 days. The majority (90%) of the drug is excreted via the feces.

CONTRAINDICATIONS/PRECAUTIONS/WARNINGS

Aglepristone is contraindicated in patients who have documented hypersensitivity to it and during pregnancy, unless used for pregnancy termination or inducing parturition.

When being considered for use in treating pyometra in bitches, peritonitis must be ruled out before using.

Because of its antagonistic effects on glucocorticoid receptors, the drug should not be used in patients with hypoadrenocorticism or in dogs with a genetic predisposition to hypoadrenocorticism.

The manufacturer does not recommend using the product in patients in poor health, with diabetes, or with impaired hepatic or renal function, as there is no data documenting its safety with these conditions.

ADVERSE EFFECTS

As the product is in an oil-alcohol base, localized pain and inflammatory reactions (edema, skin thickening, ulceration, and localized lymph node enlargement) can be noted at the injection site. Resolution of pain generally occurs shortly after injection; other injection site reactions usually resolve within 2-4 weeks. The manufacturer recommends light massage of the injection site after administration. Larger dogs should not receive more than 5 mL at any one subcutaneous injection site. One source states that severe injection reactions can be avoided if the drug is administered into the scruff of the neck.

Systemic adverse effects reported from field trials include: anorexia (25%), excitation (23%), depression (21%), vomiting (2%), diarrhea (13%) and uterine infections (3.4%). Transient changes in hematologic (RBC, WBC indices) or biochemical (BUN, creatinine, chloride, potassium, sodium, liver enzymes) laboratory parameters were seen in <5% of dogs treated.

When used for pregnancy termination, a brown mucoid vaginal discharge can be seen approximately 24 hours before fetal expulsion. This discharge can persist for an additional 3-5 days. If used in bitches after the 20th day of gestation, abortion may be accompanied with other signs associated with parturition (e.g., inappetence, restlessness, mammary congestion).

Bitches may return to estrus in as little as 45 days after pregnancy termination.

REPRODUCTIVE/NURSING SAFETY

Unless used for pregnancy termination or at term to induce parturition, aglepristone is contraindicated during pregnancy.

One study (Baan et al. 2005) using aglepristone to induce parturition (day 58) demonstrated no significant differences in weight gain between those puppies in the treatment group versus the control group suggesting that aglepristone did not have effect on milk production of treated bitches.

OVERDOSAGE/ACUTE TOXICITY

When administered at 3X (30mg/kg) recommended doses, bitches demonstrated no untoward systemic effects. Localized reactions were noted at the injection site, presumably due to the larger volumes injected.

DRUG INTERACTIONS

No documented drug interactions were noted. Theoretically, the following interactions may occur with aglepristone:

- **Progestins(natural** or synthetic): Could reduce the efficacy of aglepristone.
- **Glucocorticoids**: Aglepristone could reduce the efficacy of glucocorticoid treatment.
- **Ketoconazole, Itraconazole, Erythromycin**: The manufacturer states that although there is no data, these drugs may interact with aglepristone.

LABORATORY CONSIDERATIONS

None were noted.

DOSES

Warning: As accidental injection of this product can induce abortion; it should not be administered or handled by pregnant women. Accidental injection can also cause severe pain, intense swelling and ischemic necrosis that can lead to serious sequelae, including loss of a digit. In cases of accidental injection, prompt medical attention must be sought.

Dogs:

- **To induce parturition:** At day 60 (not before day 58; post-estimated LH surge); (extra-label): 15 mg/kg subcutaneously and another dose 9-24 hours later. Use standard

protocols to assist with birth (including oxytocin to assist in pup expulsion if necessary) or to intervene if parturition does not proceed.

- **To terminate pregnancy (up to day 45)** (extra-label in USA): 10 mg/kg (0.33 mL/kg) subcutaneous injection (into the scruff of the neck) only. Repeat one time, 24 hours after the first injection. A maximum of 5 mL should be injected at any one site. Light massage of the injection site is recommended after administration. (Label information; *Alizin*®—Virbac U.K.)
- **As an adjunct to treating pyometra/metritis (extra-label):**
 - a. **When attempting to preserve fertility (mating should occur in the first or second estrus post-treatment) in bitches up to 5 years old with a lack of detectable ovarian cysts:** Treatment begun at week 2-4 of diestrus with a single SC injection of aglepristone at 10 mg/kg. Doses are repeated at days 2, 7, and 14. During first 7 days, daily injections of amoxicillin/clavulanic acid were also given. (Jurka et al. 2010)
 - b. **For metritis:** 10 mg/kg subcutaneously once daily on days 1, 2 and 8. For open or closed pyometra: aglepristone 10 mg/kg subcutaneously once daily on days 1, 2 and 8 and cloprostenol 1 microgram/kg subcutaneously on days 3 to 7. Bitches with closed pyometra or with elevated temperature or dehydration should also receive intravenous fluids and antibiotics (e.g., amoxicillin/clavulanate at 24 mg/kg/day on days 1-5). If pyometra has not resolved, additional aglepristone doses should be given on days 14 and 28. (Fieni 2006)

Cats:

- **For treating mammary fibroadenomatous hyperplasia** (extra-label): 10 – 15 mg/kg subcutaneously on days 1, 2 and 7. Weekly treatment should be made until resolution of signs and may be required for several weeks. Relapses can occur especially in cats that have been treated with a long-acting progestin (e.g., medroxyprogesterone acetate).
- **To terminate pregnancy (up to day 45);** (extra-label): 10 – 15 mg/kg subcutaneously twice 24 hours apart.

MONITORING

- Clinical efficacy.
- For pregnancy termination: ultrasound 10 days after treatment and at least 30 days after mating.
- Adverse effects (see above).

CLIENT INFORMATION

- Only veterinary professionals should handle and administer this product.
- When used for pregnancy termination in the bitch, clients should understand that aglepristone might only be 95% effective in terminating pregnancy when used between days 26-45.
- A brown mucoid vaginal discharge can be seen approximately 24 hours before fetal expulsion.
- Bitch may exhibit the following after treatment: lack of appetite, excitement, restlessness or depression, vomiting, or diarrhea.
- Clients should be instructed to contact veterinarian if bitch exhibits a purulent or hemorrhagic discharge after treatment or if vaginal discharge persists 3 weeks after treatment.
- When used for pyometra, there is a substantial risk of treatment failure and ovariohysterectomy may be required.

CHEMISTRY/SYNONYMS

Aglepristone is a synthetic steroid. The manufactured injectable dosage form is in a clear, yellow, oily, non-aqueous vehicle that contains arachis oil and ethanol. No additional antimicrobial agent is added to the injection.

Aglepristone may also be known as RU-534, *Alizine*®, or *Alizin*®.

STORAGE/STABILITY

Aglepristone injection should be stored below 25°C and protected from light. The manufacturer recommends using the product within 28 days of withdrawing the first dose.

COMPATIBILITY/COMPOUNDING CONSIDERATIONS

Although no incompatibilities have been reported, due to the product's oil/alcohol vehicle formulation it should not be mixed with any other medication.

DOSAGE FORMS/REGULATORY STATUS

Veterinary-Labeled Products:

Note: Not presently available or approved for use in the USA. In several countries: Aglepristone Injection: 30 mg/mL in 5 mL & 10 mL vials; *Alizine*® or *Alizin*®; (Rx)

Human-Labeled Products: None.

REVISIONS/REFERENCES

Monograph revised/updated August 2013.

Baan, M., et al. (2005). Induction of parturition in the bitch with the progesterone-receptor blocker aglepristone. *Theriogenology* 63(17): 1958-72.

- Fieni, F. (2006). Clinical evaluation of the use of aglepristone, with or without cloprostenol, to treat cystic endometrial hyperplasia-pyometra complex. *Theriogenology* **66**(6-7): 1550-6.
- Guil-Luna, S., et al. (2011). Aglepristone Decreases Proliferation in Progesterone Receptor-Positive Canine Mammary Carcinomas. *Journal of Veterinary Internal Medicine* **25**(3): 518-23.
- Jurka, P., et al. (2010). Age-Related Pregnancy Results and Further Examination of Bitches after Aglepristone Treatment of Pyometra. *Reproduction in Domestic Animals* **45**(3): 525-9.