

Short-term use of megestrol acetate for estrus prevention in cats when surgery is delayed

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Situation: Veterinary staff shortages and limited access to surgery are contributing to significant delays and waitlists to get cats spayed (<u>Guerios et al. 2022</u>). ACC&D believes the oral contraceptive megestrol acetate (MA) may be administered for short durations to "buy time" for some female cats so that they don't become pregnant while waiting to be spayed. This statement relates only to cats. ACC&D will address dogs in a separate resource.

Alternatives to surgery: In most countries no drugs or vaccines are approved to suppress fertility in intact female or male cats ("queens" and "toms," respectively). However, in some countries, the progestin megestrol acetate (MA) is approved for this purpose. In others, it can be prescribed as an off-label compounded oral medication to prevent estrus in queens. This statement provides information to support veterinarians and owners considering use of MA as a stopgap measure to prevent pregnancy in female cats at risk of conceiving while awaiting spay surgery.

Target animals: ACC&D recommends that MA be considered *only* for cats that can be individually treated at prescribed times with an accurate dose, and whose health can be monitored over time. Intact queens weighing approximately 4 lbs. or more can be treated to prevent estrus. Use in pregnant cats has not been studied; however, MA treatment in pregnant dogs can cause masculinization of female fetuses, which is a birth defect (Asa 2018).

MA has been used in free-roaming, sometimes feral, populations of cats. With this population, there is less ability to control how much medication each cat consumes. Moreover, these animals often cannot be closely monitored for adverse effects or treated effectively should health conditions arise. Because of this, ACC&D has historically advised against use of MA in free-roaming cat populations. The COVID-19 pandemic and associated limitations on spay/neuter programs demanded reconsideration and exploration of safer ways to use MA. In situations when spay surgery is not immediately accessible for female free-roaming cats, we advise weighing the risks and benefits of short-term use of a low dose of MA.

Description of the pharmaceutical: MA is a synthetic form of progesterone. It is prescribed in human medicine to treat a variety of conditions (U.S. FDA nd). In animals, it can be used to prevent pregnancy and estrus (heat) cycles in dogs and cats, as well as other mammals. It has also been prescribed to treat certain skin and behavior problems in dogs and cats of both sexes (Plumb 2005). MA has been studied and used for dogs and cats over several decades in numerous countries under different brand names and at varying recommended doses.

In the United States, megestrol acetate (brand names: Ovaban®, Megace®) was approved by the Food and Drug Administration (FDA) in 1975 for the postponement of estrus and alleviation of false pregnancy in female dogs (Plumb 2005). Regulatory approval has not been sought in the U.S. for use in cats, but the drug can be prescribed for them under the FDA's extra-label use guidelines, which include a veterinarian-client-patient relationship as well as other criteria. Research to date strongly suggests that when considering MA to prevent or suppress estrus, the dosage and treatment duration are important to minimize the likelihood of adverse side effects.

Availability: MA is available globally in human medicine. In the U.S., a veterinary prescription is required for MA for animals; to obtain the drug in a dose and format appropriate for cats, a compounding pharmacy might be required. As noted above, MA is not FDA-approved for cats in the U.S. but can be prescribed under extra-label use guidelines. MA has not commonly been used in the U.S. for either cats or dogs, where both rates of surgical neutering and historic concerns about MA's side effects are high. There has, however, been a subculture of individuals microdosing free-roaming cats due to lack of access or affordability of surgery (see http://birthcontrolforcats.com/).

Outside the U.S., MA is approved for suppression of estrus in cats (and/or dogs) in multiple countries, including but not limited to Australia, Austria, Belgium, France, Germany, Italy, Malaysia, Mexico, the Netherlands, New Zealand, Philippines, Portugal, Spain, Switzerland, Ukraine, and the United Kingdom (Romagnoli and Concannon 2003, Romagnoli 2015). In Europe, no product with MA as the active ingredient is approved for canine and/or feline contraception by the European Medicines Agency (EMA), which covers the European Union; rather, it is approved on a country-by-country basis.

Globally, MA is marketed under multiple brand names for use in dogs and/or cats. Brands available as of 2022 in one or more countries include, but are not limited to, Singestar® (König S.A.), Ovarid® (Jurox), Canipil® (biocanina), Estropill® (Merck), Felipil® (biocanina), Megecat® (Vetoquinol S.A), Mégépil chat® (Clemént Thékan) MiniPil®, Nonoestron (Primavet-Sofia Ltd.), Pilucalm® (Novartis), Pillkan® (Ceva), Estropill® (Intervet Productions S.A.), and Ovaban® (Intervet/Schering-Plough Animal Health).

In some countries, MA might only be available in safe and appropriate dosages (i.e., the lower doses that have shown a better safety profile) for cats from veterinary compounding pharmacies. Veterinary products are typically compounded for a specific individual, in this case, cats. In some U.S. states, veterinarians are permitted to order a supply of "office stock" of non-controlled prescription compounded medications from select compounding pharmacies and then use that supply for individual cats, which can greatly reduce cost. An oral liquid suspension of MA can be flavored (chicken, fish, etc.) and provided in a variety of container volumes. Individual doses can be drawn into oral syringes. Although MA is available in other forms, practical considerations suggest MA compounded as a liquid suspension will be easier and more cost-effective to administer to cats.

Based on U.S. research, MA is relatively inexpensive. 503B compounder Stokes Healthcare (serving the U.S.) can ship "office stock" directly to veterinarians if permitted by their state. A 30 mL vial of MA (10 mg/mL) contains 120 doses. The price quoted on April 2, 2020 was USD \$42, or \$0.35 per dose (not including the cost of syringes or a \$9.50 shipping fee for 2-day delivery). Popular U.S. compounding pharmacies Wedgewood and Roadrunner quoted similar prices. Stokes Healthcare quoted a 6-month shelf life on the product, another agency only 90 days. Veterinarians should check with their preferred compounding pharmacy for details pertaining to their situation and location.

Dosage suggestions: A 2015 review of decades of research divided dosing into low, intermediate, and high levels. It reported that for cats not showing estrus ("heat") signs, 2.5 mg weekly (~0.625 mg/kg/week for a 4kg/8.8lb cat) for up to 30 weeks "can be considered relatively safe" (Romagnoli 2015). This would be considered a low dose and is also the suggested regimen in product inserts in most European countries. There are less data on a simultaneously safe and effective oral dose in cats showing signs of heat. A dose of 5mg/cat daily for three days, followed by the 2.5mg/cat dose weekly, was found to postpone heat for 10 weeks with relatively minor side effects (Romagnoli 2015). However, additional studies would be needed to deem it "safe." It is possible that the lower dose of 2.5mg weekly could also work for cats in heat (Romagnoli 2015).

Community cat caregivers have reported treating groups of cats with MA. Doing so risks some cats being overdosed, and others underdosed. MA has been micro-dosed at 0.1 to 0.2 mg/kg per cat each week via food, and there are anecdotal reports of reduced pregnancies (Greenberg et al. 2013). However, no peer-reviewed data exist for this dosing regimen.

Efficacy: The literature suggests that in cats, the contraceptive effect takes place quickly (Romagnoli 2015). It should be assumed that once a queen stops taking the medication, she will come into heat.

Safety: Potential adverse side effects in cats are more likely at higher doses and/or longer duration of treatment (Greenberg et al. 2013, Romagnoli 2015). Potential side effects include diabetes mellitus, pyometra, adrenal gland suppression (Addison's disease), mammary hyperplasia, and mammary cancer (Romagnoli and Concannon 2003,

Greenberg et al. 2013, Romagnoli 2015). Some side effects may resolve once the cat stops the medication. Side effects, particularly lasting ones, are associated with higher doses of MA (Romagnoli 2015). Regarding human safety, due to risk of birth defects, pregnant women should wear disposable gloves when handling MA and avoid inhaling dust from split or crushed tablets; immediately rinse skin or eyes if exposed (Plumb 2005).

Making this recommendation: The Alliance for Contraception in Cats & Dogs (ACC&D; www.acc-d.org) is a non-profit organization formed in 2000. Our mission is to advance non-surgical sterilants and contraceptives for cats and dogs and promote their global accessibility. We envision a world in which dog and cat populations are effectively and humanely managed, improving the lives of dogs, cats, and the people who care about them. Each veterinarian and, if applicable, cat owner must weigh the benefit of preventing pregnancy with health risks to the individual cat.

Advising this announcement: The primary content of this document was first released on March 31, 2020, during the early months of the Covid-19 pandemic when spay/neuter options were severely curtailed. The decision to provide advice on this contraceptive, not well-known in the U.S., was made in consultation with ACC&D Board members and Scientific Advisors Cheri Asa, PhD; Julie Levy, DVM, PhD, DACVIM; Linda Rhodes, VMD, PhD; and Michelle Kutzler, MBA, DVM, PhD, DACT (biographies on the ACC&D website).

ACC&D consulted with the American College of Theriogenologists (ACT) prior to developing the original resource document. ACT (2021) since released a statement that MA "may be available to veterinarians for treatment of individually owned cats, but only within the strict confines of a veterinarian-client-patient relationship, including a veterinary prescription." ACT discourages MA for feral cats, citing potential for inaccurate dosing, consumption by non-target species or pregnant cats, and potential health risks. It does not specifically address *short-term* use of MA to feral cats awaiting spay/neuter surgery, which is the restricted use delineated in this ACC&D resource.

References and recommended reading

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- U.S. Food and Drug Administration. Megace® (megestrol acetate, USP) Oral Suspension. Product label data. https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020264s017lbl.pdf.

More information, including practical resources, are available on ACC&D's website at https://www.acc-d.org/products/megestrol-acetate.