ACC&D
Alliance for Contraception in CATS & DOGS

ESTERILSOL™

August 2011

Product Profile and Position Paper

Esterilsol™ (or its predecessor Neutersol®) is a chemical sterilant for male dogs. The active ingredient is zinc gluconate neutralized by arginine. Esterilsol causes permanent infertility in one treatment.

ESTERILSOL™

CHEMICAL STERILANT FOR MALE DOGS

INTRODUCTION

This product profile and position paper was created from a review of both published and unpublished literature, promotional information, and input from experienced users and representatives of the relevant organizations. ACC&D did not conduct the clinical research on its own; the data quoted were obtained from the cited sources.

This formulation of the chemical compound of zinc gluconate neutralized by arginine was developed to chemically sterilize male dogs. Esterilsol is the current name and Ark Sciences is the technology owner; the formulation was initially introduced in the U.S. under the name Neutersol by Pet Healthcare International. Esterilsol is derived from natural ingredients: zinc, glucose and arginine. It causes permanent infertility in a single treatment. This technology leaves adult dogs with their testicles and their male appearance. It is especially desirable to dog owners who are opposed to castration. This approach may also save time and money compared to surgical castration, and may be useful where surgery is particularly difficult or dangerous to provide. (Sedation is still recommended, but full anesthesia is not necessary, and there is no incision.)

MECHANISM OF ACTION

Esterilsol is administered by a single injection to each testicle with a fine-gauge needle (28 gauge). Esterilsol works by causing atrophy of the epididymis, seminiferous tubules, and prostate resulting in permanent sterility in 99.6% of dogs. As spermatogenesis in seminiferous tubules slows, the reduced feedback to Leydig cells results in lowered testosterone production. As with any medical intervention, effectiveness depends upon proper administration.

STATUS OF NEUTERSOL

This technology is approved by the U.S. Food and Drug Administration (FDA) for permanent sterilization of male dogs from 3 to 10 months of age. While it was available in the U.S. under the name Neutersol it was used off-label in dogs over 10 months of age. Neutersol was developed by Pet Healthcare International, Inc., and introduced in the U.S. in 2003 by Addison Laboratories. When it was introduced, Neutersol was welcomed with enthusiasm by some organizations and veterinarians, while others had a negative response. (A full discussion of the initial reception of Neutersol in the U.S is beyond the scope of this publication; those interested in this topic are welcome to contact ACC&D at info@acc-d.org.) In 2005, production and distribution were discontinued after a business divorce between Pet Healthcare and Addison Laboratories. Plans to reintroduce Neutersol through another marketing company in 2009 were cancelled for undisclosed business reasons. Pet Healthcare International no longer has any rights to this technology. Ark Sciences, LLC, currently owns all Neutersol rights and intellectual property. They have announced plans for a U.S. launch under the product's new name, Esterilsol in early 2012, focusing initially on the nonprofit sector.

STATUS OF ESTERILSOL

Ark Sciences introduced Esterilsol in Mexico in 2008 and began selling the product to private practice veterinarians, government programs, and non-governmental organizations (NGOs). In 2010 Esterilsol received regulatory approval in Bolivia, Panama, and Colombia. (In Colombia it is approved for use in cats as well as dogs.) In Mexico, Colombia, Bolivia, and Panama, Esterilsol is approved for use in dogs three months and older. It has been available in both 2ml and 20ml vials in those countries. (In the U.S., regulatory approval was sought only for the 2ml vials.) Ark Sciences has announced plans to extend distribution to approximately twenty other countries, primarily in Latin America, and to reintroduce their technology in the U.S. in early 2012. Esterilsol is currently available with special permission for limited use in some countries in which it is not approved by regulatory agencies.

ACC&D has supported several Esterilsol field projects and studies. The purpose of the grants has been to help organizations extend reach of their population control programs and to gather data to increase learning about field use of the product. More information on our grant-supported programs is available at www.acc-d.org/EsterilsolGrants.

In Mexico, Esterilsol is distributed by Ark Sciences Mexico. In Colombia, Esterilsol is distributed by Gabrica S.A. In Panama, Esterilsol is distributed by Suplidora Internacional. In Bolivia, Esterilsol is distributed by Mathiesen Group.

Ark Sciences has moved production to an FDA-approved manufacturing facility in the U.S. and will be distributing only the 2ml vials. Ark Sciences reports that the average dose used is 1ml per dog, and that each vial can be expected to treat two dogs on average. The cost of Esterilsol varies by country and cost is likely to be different for private practice veterinarians than for government agencies and NGOs. The U.S. pricing structure for nonprofits has been announced: through 2012, Ark Sciences has committed to offer all nonprofits a price of $10 per vial (anticipated to be $5 per dog) if the company receives orders for 500,000 vials by January 31st, 2012. For lower total quantities purchased, the price will adjust on a sliding scale to a maximum of $30 per vial (approximately $15 per dog) for total orders under 50,000.

USE AND EFFECTIVENESS

Esterilsol is administered via an injection to each testicle with a 28 gauge needle. Dosage is determined by measuring each testicle with a caliper provided with the product. The correct dose is indicated on the caliper and is based on the maximum width of each testicle. Sedation is not required but is commonly used in Esterilsol administration to ensure that the dog holds still during the injection. (Anesthesia is not necessary. Reversible sedation is commonly used so that dogs are awake and alert in as little as 15-20 minutes after the Esterilsol injection.) Ark Sciences recommends that practitioners use sedation for at least the first ten dogs they inject and for any dogs that are difficult to handle. Most programs with which ACC&D is familiar routinely sedate dogs prior to Esterilsol injection. The process of measuring the testicles to determine dose, preparing the injections, and administering the injections into each testicle takes approximately five minutes for an experienced practitioner.

Following proper administration protocol is critical to reduce the risk of injection site reactions (see “Complications” below).

In pivotal clinical studies presented to the U.S. Food and Drug Administration (FDA), this formulation was found to cause permanent sterility in 99.6% of treated dogs. Pre-pubescent males never become fertile; it may take up to 30 days after treatment for sterility to be achieved in post-pubescent males. Ark Sciences recommends use of a non-steroidal anti-inflammatory drug (NSAID) to prevent discomfort which may be caused by post-injection swelling, which is the most common side effect. Most programs with which ACC&D is familiar report consistently using NSAIDs.

Upon hearing that administration is through an intratesticular injection, many people express concern about pain caused by the injection itself. However, in studies reviewed and accepted by the FDA (in which sedation was not used), only 2.5%

of dogs showed discomfort by moving or vocalizing. The other 97.5% did not show any reaction to the injection.

Following injection, the testicles atrophy over a period of time ranging from weeks to months, resulting in a reduction in testicular size and changes in shape or texture. These changes may or may not be symmetrical.

Esterilsol does not reduce testosterone to the same degree as castration does, and its effects on hormone-dependent diseases and behaviors have not been established. In one study reviewed and accepted by the FDA, treated pups showed a decrease in serum testosterone levels of 41-52%. (This can be compared with a 95% reduction in castrated pups.) The limited impact on testosterone production is considered a drawback by some pet owners. However, this is a desirable characteristic in areas where pet owners refuse sterilization because they do not want their dog to lose his male appearance, because they believe their dog's behavior will change for the worse, or because they want to avoid health problems associated with reduced testosterone levels. It is important to note that testosterone levels range widely among dogs. (One study found that serum testosterone levels ranged from 1 to 10 ng/ml in intact dogs, while castrated dogs had levels below 0.5. Another study found intact dogs with levels as low as 0.05 ng/ml.) In regard to behavior, one should remember that while castration has been promoted as a treatment for behavior problems, testosterone reduction has only been shown to be linked to decreases in indoor urine marking, roaming, sexual mounting, and dog-to-dog aggression around females in estrus, and does not always decrease these behaviors. If sterilization is being considered to address one of these issues in a particular dog, surgical castration may be indicated. Studies report inconsistent findings on how castration status correlates to aggressive behavior toward humans. In 2011 and 2012, Veterinarians Without Borders-Canada is collaborating with dog population control and dog behavior experts to conduct a study comparing the actual observed behavior changes after sterilization in dogs surgically castrated with those sterilized with Esterilsol. ACC&D is supporting this study and will share results as they become available. In regard to health, castrated dogs have been found to have lower risk for some health problems but higher risk for others. There is no conclusive evidence that castrating male dogs makes them healthier overall.

Dogs sterilized with either Esterilsol or surgical castration may continue to engage in mating behavior. Therefore, neither method of sterilization should be expected to prevent the spread of transmissible venereal tumors (TVTs) or other diseases that may be spread through mating behaviors. (Male dogs castrated prior to puberty display significantly less mating behavior than those castrated as adults.)

While it was available in the U.S., this technology was used off-label to sterilize other species including cats, bears, wolves, goats and other livestock. Approval for use in cats has been received in Colombia. Ark Sciences reports that they are seeking regulatory approval for use of Esterilsol in cats in one or more other countries. However, little data on use in cats is publicly available. No published studies establish dosage, safety, or efficacy in other species.

As with surgically spayed female dogs, visual confirmation of sterility may be difficult in Esterilsol-treated dogs. Although the testicles do atrophy over time, the decrease in size is variable. Palpation of the testicles will reveal an abnormal texture resulting from scar tissue. To identify dogs as having been sterilized with Esterilsol, a microchip may be used; some microchip companies will include information on neuter status in a dog's record if this information is provided when pet owners register their pet's microchip. Some programs have used tattoos indicating sterilization status on the inside of the ear, inner thigh, or scrotal area.

COMPLICATIONS

During FDA-required Target Animal Safety Work, this technology caused no deaths and was determined to be safe. One of its greatest appeals is that it does not require general anesthesia or a surgical incision, completely removing the risk factors (the most serious of which is death) associated with them. (One U.S. study of anesthesia-related deaths found the risk of death for dogs to be one in 1,849.) However, any medical intervention presents risks.

Complications reported with Esterilsol use include—but are not limited to—the following:

- **Testicular swelling and pain.** Mild testicular swelling is to be expected and peaks 3-7 days post-injection. Dogs are expected to have mild to moderate pain in the week following injection, peaking on days 2-3. Ark Sciences recommends use of a non-steroidal anti-inflammatory drug (NSAID) to address post-injection discomfort. Follow-up consultation with the administering veterinarian or another veterinarian familiar with Esterilsol is indicated for dogs displaying severe swelling.
- **Vomiting**. In one study, 12 out of 270 dogs (4.4%) vomited one to four times within four hours post-injection. Ark Sciences notes that vomiting is more likely to occur if xylazine is used as a sedative. Fasting for 12 hours before the injection is recommended to decrease the chance of vomiting.
- **Injection site reactions**. In some cases, adverse reactions may occur at the injection site. Reactions range from scaly scrotal skin to ulceration and (rarely) tissue necrosis requiring surgical castration and scrotal ablation (surgical removal of the scrotal tissue). Adverse reactions are believed to be primarily due to imprecise injection technique (see the Esterilsol Training Manual for instructions). Straying from administration protocol in one or more of the following ways may also lead to adverse reactions:
  -Treating dogs which cannot be supervised and managed in accordance with the recommendations in the Client Info Sheet (read on below for further explanation of recommendations)
  -Drawing product from vial more than 6 hours after the vial seal was first punctured
  -Using a needle that is larger than 28 gauge
  -Use of expired product
  Following injection technique and all administration protocol precisely is critical to prevent adverse reactions.

  The rate of injection-site reactions requiring follow-up treatment ranged from 0.7% to 3.9% in several early studies. Incidence decreased substantially as better practices (including administering a light sedative to ensure that the dogs held still during injection and using separate 28-gauge needles for drawing up and injecting the solution) were developed after the initial introduction. Data available from a sampling of a Mexico field trial of 10,000 dogs showed an average complication rate of 1.2%. A 2010 project in Peru treated 249 dogs and reported three adverse reactions (1.2%). However, two small 2010 projects in Colombia and the Dominican Republic reported higher rates of injection site reactions. (The number of dogs in these two projects was too small for a percentage of reactions to be statistically reliable.) It is critical that organizations using Esterilsol follow the administration protocol carefully; administration error is believed to be the cause of most adverse reactions.

  It is important that dogs have appropriate after-care at home with access to a veterinarian if any problems arise. Ark Sciences' Esterilsol Client Information Sheet recommends that dogs' exercise be limited to leash walks for several days, that dogs be prevented from biting or chewing at the scrotum, and that they not be kept on hard or wet surfaces. Dog owners are asked to contact the administering veterinarian if they see "any redness, discharge, or broken skin in the scrotal area". Dogs sedated for the injection are less able to regulate their body temperature and should be kept in a comfortable environment (usually inside) for the first night after treatment. Because of the need to control and monitor dogs post-injection, use on dogs that do not have owners or caregivers that can and will comply with guidelines may result in more frequent and more severe adverse reactions.

  Esterilsol does not contain any preservatives. At this time, Ark Sciences recommends that when a multi-dose vial is used any unused product should be discarded within six hours after the first puncture of the vial to prevent potential product contamination.

  It is possible that environment, individual animal physiology and health status, and/or other factors might also influence the rate of adverse reactions.
- **Long-term effects.** In the past decade (and on a more limited basis for the past several decades), thousands of male dogs have been successfully neutered with this approach with no indication of any long-term detrimental effects.

- **Other side effects.** These include other local reactions as well as neutrophilia, anorexia, diarrhea and leukocytosis. Package insert should be referenced for details.

CONCLUSION

Esterilsol is a safe, effective method for sterilizing male dogs without surgery. Though sedation is most often indicated and administration protocol requires precision and care, Esterilsol may offer savings in cost, time and facility requirements. It is most desirable to, and appropriate for, population control programs which are challenged to provide surgery at sufficient levels and/or which serve communities that are averse to castration. It is safest for use in dogs with owners or caregivers that can monitor dogs in the days following treatment. The technology currently has regulatory approval in the U.S., Mexico, Colombia, Panama, and Bolivia and it is currently commercially available in Mexico, Colombia, and Bolivia. It is expected to be commercially available in the U.S. again in early 2012 and in Panama in the near future. Ark Sciences has announced plans to introduce Esterilsol in approximately twenty additional countries.

RECOMMENDATIONS AND DISCUSSION

ACC&D believes that Esterilsol can be a meaningful tool for organizations to reach further in their sterilization programs. In particular, we believe this approach may benefit organizations that are unable to provide surgery at needed levels, or that are unable to sterilize male dogs because the dog owners do not wish to have their dogs castrated. Esterilsol may also offer significant cost benefits over surgical castration. Space and time for recovering dogs from anesthesia is a limiting factor for many sterilization programs. The much shorter recovery time required for Esterilsol-treated dogs may provide a significant advantage to such programs, allowing them to sterilize more male and/or female dogs.

ACC&D recognizes that sterilizing males alone may have little or no impact on population size unless a very high rate is achieved. Female reproduction must be controlled to achieve population stability or reduction. However, birth control is part of a comprehensive approach to managing dog populations and improving the welfare of animals in any community. We understand that population control programs around the world provide sterilization for both females and males as part of their work teaching responsible pet ownership and improving the health of animals in the communities they serve. It is also important to note that there is very little understanding of the population dynamics of free-roaming dogs and cats (more data is available on wildlife populations, but this may or may not apply to dogs and cats), so the impact of sterilizing males has not been conclusively established.

Esterilsol may provide less of a benefit over surgical castration for cats than for dogs because castrating cats is a relatively quick and simple procedure. Additionally, testosterone-mediated behaviors in cats seem to pose more of a nuisance and safety risk in cats than in dogs (e.g. reduction in urine marking and fighting with other cats). The impact of Esterilsol in testosterone levels in cats has not been established.

ACC&D realizes that administration protocol and injection technique are critical to reduce the incidence of injection site reactions. Even small errors in injection technique may result in much higher rates of reactions. We urge all practitioners to pursue hands-on training in injection technique from an Ark Sciences-approved trainer and to follow administration protocol exactly. Systems should also be put in place to help dog owners/caregivers provide after-care for treated dogs and to receive immediate follow-up care for any adverse reactions that occur. Minor reactions can become severe reactions if prompt care is not sought or received. Dog owners should adhere to all follow-up care instructions carefully and contact their veterinarian with any questions or concerns. Use in dogs that do not have owners or caregivers who can provide the recommended monitoring and care post-treatment (as may be the case for unowned or loosely-owned dogs) may result in a higher rate of and more severe adverse reactions. Organizations that are able to follow up directly with dogs in their home (or, for unowned dogs, their home territory) for several days post-injection may be able to use Esterilsol on these dogs more safely.

Most pet owners, veterinarians, and animal welfare organizations are accustomed to the risks and benefits of surgical sterilization. While many are enthusiastic about the concept of alternative non-surgical methods of sterilization, we've learned that specific new approaches can be met with caution and some skepticism. ACC&D feels strongly that any new sterilization method should be introduced with careful thought and adequate resources for education so that potential users can determine the best use of new non-surgical methods.

As with any medical intervention, ACC&D encourages all pet owners, veterinarians, and organizations to consider the associated risks and benefits and to engage in open discussion with other stakeholders (i.e. family members, practice partners, organizational staff/volunteers) about potential use. When treating un-owned or loosely owned free roaming dog populations (as part of "TNR" or "ABC" programs), both surgery and Esterilsol treatment present some risks for the individual animal, especially when dogs are released soon after the procedure with limited or no supervision. Organizations need to weigh the risks and benefits for both individual animals and the population as a whole.

Additional information and Esterilsol training materials are available at www.acc-d.org/Esterilsol. Information on Esterilsol-related programs ACC&D has supported, please visit www.acc-d.org/EsterilsolGrants. We also welcome interested parties to contact us at info@acc-d.org. Information can also be found at www.arksciences.com (Ark Sciences can be contacted through their website).

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