# Bridging

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LUCILE VIGOUROUX, MSC

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#### Emerging technologies are giving veterinarians the tools they need to best address dental disease in horses

dult horses possess 36 to 42 teeth in those large, cavernous mouths. Teeth are made of enamel (the outer covering of the tooth) and dentin (mineralized connective tissue)—a unique composition that makes them the strongest substance in the equine body. This toughness, however, doesn't spare the teeth from fractures, infections, or disorders associated with the periodontal ligament that anchors them into the underlying jaws.

If your horse shows signs of dental pain or difficulty chewing his food, it's time to ring your veterinarian for an exam. Practitioners often use radiography to diagnose ailments affecting other parts of your horse's skeletal system (the bones and joints in the legs, for instance), and, likewise, X rays are a popular first step in addressing dental issues. But these days veterinarians have various imaging modalities beyond radiography at their fingertips. Let's look at the progress they've made.

**The Evolution of Diagnostic Imaging in Dentistry** Over the course of his 40-year career in equine dentistry, Robert Baratt, DVM, MS, FAVD, Dipl. AVDC, AVDC/EQ, ( )

#### A COMPARISON OF DIAGNOSTIC MODALITIES IN EQUINE DENTISTRY

DIAGNOSTIC MODALITY	BENEFITS	LIMITATIONS
Radiography (X rays)	<ul> <li>Readily available, quick and easy to use on the farm.</li> <li>Provides basic yet essential information about the health of the teeth and jaws.</li> </ul>	<ul> <li>Practitioners' potential lack of training in obtaining diagnostic dental radiographs.</li> <li>Diagnostic limitations: Sometimes two-dimensional radiographic images are not enough to make accurate diagnoses, requiring a three-dimensional CT or MRI scan.</li> </ul>
Computed tomography (CT scan)	<ul> <li>These three-dimensional images are more precise, detailed, and sensitive than radiographs for diagnosing dental and orofacial disease.</li> <li>Particularly useful for diagnosing apical infection of maxillary cheek teeth, temporomandibular joint disease, and sinus disease.</li> </ul>	<ul> <li>Lack of availability in most practices.</li> <li>Requires general anesthesia in many cases.</li> <li>Cost.</li> </ul>
Nuclear scintigraphy (bone scan)	Provides valuable information about particular areas of inflammation.	Not sufficient on its own—additional imaging (visual examination, radiograph, or CT) is needed to gain detailed information about the teeth involved.
Magnetic resonance imaging (MRI)	Best suited for imaging soft tissues, primarily oral tumors, tooth roots, and ligaments.	MRI is most useful for soft tissue abnormalities. However, dental disease often involves hard tissue (tooth and bone). For this reason MRI is not typically used in dental cases.
Oral endoscopy	Provides excellent images of the entire oral cavity, including the crown and occlusal surface of each tooth, plus gums and soft tissues.	Does not allow practitioners to examine tooth roots. Radiography is still necessary to look for problems below the gumline.

founder of Salem Valley Veterinary Clinic, in Connecticut, has seen and embraced groundbreaking advancements in diagnostic imaging. Today, the modalities and technologies Baratt and his colleagues use are infinitely more elaborate, precise, and user-friendly than those available in the '80s. It's literally a black-and-white difference.

"When I graduated veterinary school in 1981, the tools we used to assess the horse's mouth were limited to a speculum and a penlight," he says. "Radiographic examination was essentially impossible."

"And for practitioners who did have access to radiography before its digital form was widely available, the image quality was minimally diagnostic," adds Leah Limone, DVM, Dipl. AVDC, owner of Northeast Equine Veterinary Dental Services, in Topsfield, Massachusetts. The first significant evolution in equine dentistry diagnostics was the development of portable digital radiography systems by Fuji in 1981. "Nowadays, using digital radiography, we can capture diagnostic images with great detail, which is critical for the successful diagnosis of a wide range of dental conditions," explains Limone.

While the cost of such equipment back then was considerable for the average solo equine practitioner, it nonetheless quickly became the standard of care for both dentistry and lameness evaluations, says Baratt. Veterinarians still use digital radiography in just about any case involving the skeleton, teeth included. A digital radiographic image provides a relatively easy, quick, and cost-effective first glance into the bony structures inside the horse.

#### **New Standards of Care**

Times have surely changed: Once revolutionary, digital radiography is now considered "basic" and, in many cases, limiting compared to newer, more high-tech three-dimensional imaging modalities. "The increasing availability of computed tomography (CT) scans, for instance, has greatly enhanced our ability to diagnose dental and sinus pathology (disease or damage)," says Baratt. "In the future we will continue to see increased access to standing CT for horses, eliminating the risk of general anesthesia associated with obtaining a CT scan of a 1,200-pound animal."

Modalities such as radiography and CT generate images that provide valuable information to the practitioner, but sometimes getting answers straight from the horse's mouth is the way to go. That's where oral endoscopy comes in. Put simply, oral endoscopy involves guiding a rigid laparoscope and camera into the depths of the horse's oral cavity to record real-time video and capture still images. "This is a diagnostic tool that all practitioners should invest in," says Baratt, who's been a pioneer of oral endoscopy research in horses. "The ability to closely examine each tooth and point out the pathology in real time to the owner is invaluable."

#### Advanced Imaging Makes Procedures Safer

Imaging is about more than just diagnosing problems—it also helps practitioners treat said problems safely and effectively. "Digital dental radiographs and, in complex cases, CT imaging are imperative in planning for tooth extractions," says Limone. "We need to know the often abnormal anatomy and pathology of the specific tooth we are extracting and also determine how best to extract in the least invasive way to avoid complications." Taking a detailed look at the mouth ahead of an invasive procedure reduces the risk and potential cost associated with a blind approach.

In the same vein, horses undergoing extractions and surgeries have benefited from the precision and safety that come with more sophisticated tools. "Let's circle back to the endoscope, which over the last 10 years has become widely recognized

(Continued on page 22)

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#### **Bridging the Gap**

(Continued from page 18)

not only as an invaluable examination instrument but also as a guiding tool in oral and sinus surgery," says Baratt. Endoscopes essentially act as an extension of surgeons' eyesight, allowing them to precisely see their instruments' positioning relative to lesions of interest.

"Beyond the endoscope, the development of new surgical instruments and techniques now allows equine dentists to perform more oral extractions and fewer repulsions (the latter involving pushing the tooth out via the sinuses using a mallet/dental punch), thereby reducing the incidence of post-extraction complications," Baratt adds. "Last but not least, the improvements of techniques used in standing sedation, notably constant rate infusions (CRI) of sedatives and regional anesthesia, now allow almost all equine dentistry and sinus surgery procedures to be performed standing, without the need for general anesthesia. This is both safer for the horse and more cost-effective for the client."

#### **Diagnostic Imaging's Role in EOTRH**

Neither veterinarians nor scientists can confidently identify the root cause of the intricate condition termed equine odontoclastic tooth resorption and hypercementosis (EOTRH). Horses affected by this unique periodontal disease—usually geldings over the age of 15—spontaneously

#### **Take-Home Message for Veterinarians**

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Due to the oral cavity's proximity to the sinuses, certain cases of dental disease evolve into sinusitis. In a paper published this year, researchers examined data from four studies to determine whether computed tomography (CT) is more accurate than radiography for identifying apical dental pathology in these cases (Gill-Parsons et al., 2022).

In all four studies reviewed, the authors found weak yet statistically significant evidence that CT did indeed identify teeth with apical pathology that radiography had failed to detect. Specifically, the authors concluded that CT is more accurate than radiography for diagnosing equine maxillary apical dental pathology.

That's a start. Going forward, veterinarians must establish clear guidelines on the CT changes associated with apical dental pathology to ensure the accuracy and repeatability of CT-assisted diagnoses. "Loss of the lamina dura, infundibular changes, or pulpal gas as singular findings on CT imaging can be seen in teeth with no underlying histopathological evidence of apical disease and in maxillary teeth imaged in horses without clinical signs of maxillary cheek tooth pathology," the authors wrote. These findings might be useful in furthering earlier and more accurate diagnoses of sinusitis secondary to dental disease.

reabsorb their incisor teeth, which is an extremely painful process.

Secondary bacterial infections are common, likewise resulting in painful periodontal disease. Hypercementosis excessive deposition of cementum (another mineralized connective tissue similar to bone) on the tooth roots—might or might not accompany tooth resorption and occasionally occurs alone. "Hypercementosis can result in significant gingival (gum) recession and tooth extrusion (displacement out of its socket), but I do not believe it is a significant contributor to oral pain in the absence of secondary bacterial infection," says Baratt. There is currently no treatment for EOTRH, which is a progressive disease; extraction of the incisors is the only permanent solution.

With EOTRH, diagnostic imaging is especially invaluable. "The earliest manifestation of this disease is usually radiographic evidence of replacement resorption of the roots," says Baratt. "At that stage the disease is not yet accompanied by clinical signs of periodontal disease or

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#### Bridging the Gap

#### (Continued from page 22)

oral pain. Frequently, the lateral (third) incisors are the first teeth affected."

Equine odontoclastic tooth resorption and hypercementosis can compromise the oral cavity in several ways. Those secondary bacterial infections can result in the aforementioned inflammatory tooth resorption, alveolar bone infection, and typical clinical signs of periodontal disease: gingivitis, gingival recession, tooth extrusion, and gingival and/or mucosal fistulation (formation of an abnormal pathway between the alveolar bone and the oral cavity). "This stage of the disease results in oral pain," Baratt says.

Therefore, the goal is to intervene before that pain develops.

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The painful progressive course of this disease and an increase in its incidence create the need for improved early diagnosis. "Unfortunately, early radiographic diagnosis of EOTRH does not affect our ability to prevent the inevitable," Baratt says. "There is no known treatment (aside from tooth extraction) at this time."

#### **Take-Home Message**

Now more than ever, vets have the tools to make prompt, precise decisions about your horse's oral health and provide the safest and most effective care possible. The days of peering into the dark oral cavity with a mere flashlight have been replaced by well-lit oral endoscopy exams. Crisp, high-resolution digital radiographic images have kicked fuzzy early computed radiography to the curb. "We can now make accurate diagnoses utilizing oral examinations in combination with advanced imaging modalities," says Limone. "Most conditions can be diagnosed on the farm, which is both efficient and cost-effective, and then a plan can be made for treatment and long-term management." 📣

#### EQUISUL-SDT

(Sulfadiazine/Trimethoprim) Oral Suspension

For use in horses only

Approved by FDA under NADA # 141-360

#### CAUTION

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

#### DESCRIPTION

EQUISUL-SDT is a broad-spectrum antimicrobial from the potentiated sufforamide class of chemotherapeutic agents. These two drugs block different sequential steps in the biosynthesis of nucleic acids. Sulfadiazine inhibits bacterial synthesis of dihydrofolic acid by competing with bacterial synthesis of dihydrofolic acid by competing with para-amirobencio acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by reversiby inhibiting dihydrofolate reductase. The effect of the dual action is to reduce the minimum inhibitory concentration of each agent (synergism) and to convert a bacteriostatic acidor to a bacteriotication is the non-proprietary name for 4-amino-N-2-primidinybenzenesulfonamide. Trimethoprim is the non-proprietary name for 5-{(3,4,5-trimethoxyphenyl)methyl]-2.4-primidinediamine.

Figure 1. Structure of sulfadiazine



ch mL of EQUISUL-SDT contains ingredients (333 mg sulfa an aqueous suspension.

INDICATION EQUISUL-SDT is indicated for the treatment of lower respiratory tract infections in horses caused by susceptible strains of Streptococcus equi subsp. zooepidemicus.

#### DOSAGE AND ADMINISTRATION

Shake well before use dminister EOUISUL -SDT o

ally at the dosage of 24 mg Administer EQUISUL-SD1 orany at the dosage or 24 r combined active ingredients per kilogram body weight (10.9 mg/lb) whice daily for 10 days. EQUISUL-SDT can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb) body weight.

EQUISUL-SDT in containers of 280 mL and 560 mL with draw-off caps: Remove cap. Peel off white foil backed bottle seal and replace cap. Peel off outer cap seal exposing (hole) opening. Push an oral tip syringe into the cap opening. Inver and draw out appropriate volume of EQUISUL-SDT solution (Note: Do not remove syringe while the bottle is inverted as (Note: Do not remove syringe while the bottle is inverted as possible spillage may result.) Detach syringe and administer canaly at the dosage of 24 mg combined active ingredients per kilogram body weight (10.9 mg/h) wice daily for 10 days. ECUISUL-SDF can be administered by volume at 2.7 mL per 45.4 kg (2.7 mL/100 lb) body weight.

#### CONTRAINDICATIONS

DT is contraindicated in horses with a known Ifadiazine, sulfonamide class antimicrobials, allergy to sulfac

WARNING Do not use in horses intended for human consumption. HUMAN WARNINGS

Not for use in humans. For use in animals only. Keep this and all drugs out of the reach of children. Consult a physician in the case of accidental human exposure.

Antimicrobial drugs, including sulfonamides, can cause mild to severe allergic reactions in some individuals. oid direct contact of the product with the skin, eyes, buth, and clothing. Persons with a known sensitivity

to sulfonamides or trimethoprim should avoid exposure to this product. If an allergic reaction occurs (e.g., skin rash, hives, difficulty breathing, facial swelling) seek medical attention.

#### PRECAUTIONS

Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of development of drug-resistant animal pathogens.

The administration of antimicrobials, including sulfadiazine and trimethoppin, to horses under conditions of stress may be associated with acute diarrhea that can be fatal. If acute diarrhea or persistent changes in fecal consistency are observed, additional doses of EQUISUL-SDT should not be administered and appropriate therapy should be initiated

administered and appropriate therapy should be imitated. The safe use of EQUISUL-SDT has not been evaluated in breeding, pregnant, or lactating horses. Potentiated sutfoamides should only be used in pregnant or lactating mares when the benefits to the mare justify the risks to the fetus. Use of potentiated sutformides during pregnancy has been associated with an increased risk of congenital abnormalities that may be related to foldat deficiency. In humans, sutformatices pass through the placenta, are excreted in mill, and may cause thyperbilinubinemia-induce neurotoxicity in nursing neonates.

Decreased hematopoetic activity and blood dyscrasias have been associated with the use of elevated doses and/ or prolonged administration of potentiated suffonamides. EQUISUL-SDT should be discontinued if prolonged clotting times, or decreased platelet, white blood cell or red blood cell counts are observed

Sulfonamides should be used with caution in horses with impaired hepatic function. Although rare, sulfonamide use has been associated with fulminant hepatic necrosis in humans.

Neurologic abnormalities have been reported in several species following administration of potentiated sulfonamides. In horses, potentiated sulfonamides have been associated with gait alterations and behavior changes that resolved after discontinuation of the drug.

The safe use of EQUISUL-SDT has not been evaluated in horses less than 1 year of age.

ADVERSE REACTIONS Adverse reactions reported during a field study of 270 hors of various breeds, ranging from 1 to 25 years of age, which had been treated with either EQUISUL-SDT (n = 122) or with a saline control (n = 88) are summarized in Table of with a saline control (n = 88) are summarized in Table 1. At least one episode of loose stool of varying severity wa observed in 69 of 182 (38%) of the EQUISUL-SD1-treate horses, and 29 of 88 (33%) saline control horses. Of thos animals experiencing loose stool, 2 of 182 (1.1%) of the animals experiencing loose stool, 2 of 182 (1.1%) of the EQUISUL-SDT-treated horses and 0 of 88 (0%) placebo-treated horses were removed from the study due to diarthe (defined as at least one episode of watery stool). Both case of diarthea in this study were self-limiting and resolved without treatment within 5–10 days after discontinuation of EQUISUL-SDT.

#### Table 1. Number of Horses with Adverse Reactions During the Field Study with EQUISUL-SDT

Adverse Reactions	Equisul-SDT (n=182)	Saline control (n=88)
Loose stool (including diarrhea)	69 (38%)	29 (33%)
Colic	3 (1.6%)	2 (2.2%)
Diarrhea	2 (1.1%)	0 (0%)

To report suspected adverse events, for technical assistance or to obtain a copy of the SDS, contact Aurora Pharmaceutical, Inc. at 1-888-215-1256 or www.aurorapharmaceutical.com. For additional infor oout adverse drug experience reporting for ar , contact FDA at 1-888-FDA-VETS or online at

#### CLINICAL PHARMACOLOGY

Following oral administration, EQUISUL-SDT is rapidly absorbed and widely distributed throughout body tissues Sulfadiazine levels are usually highest in the kidney, while the tissue concentration in other tissues is only slightly lowe than plasma concentrations. Concentrations of trimethoprin are usually higher in the lungs, kidney, and liver than in the blood. Sulfadiazine and trimethoprim are both eliminated

primarily by renal excretion, both by glomerular filtration and tubular secretion. Urine concentrations of both sulfadiazine uousiar secrevon. Urine concentrations of both sulfadiazine and trimethopping are several-fold higher than blood concentrations.<sup>1</sup> Sulfadiazine and trimethoprim are 20% and 35% bound to plasma protein, respectively. Administration of sulfadiazine and trimethoprim with food has no apparent

effect on the absorption of sulfadiazine but the absorption of trimethoprim is decreased.

Based on a study in fed horses, trimethoprim concentrations following repeat oral administration of 24 mg/kg EQUISUL-SE to 6 horses reached peak concentration in 0.5 to 12.0 hours The median plasma elimination half-life was 3 hours, with a range of 2.31 to 4.96 hours. Peak sulfadiazine concentration were reached within 1.0 to 12.0 hours in the same study. The median plasma elimination half-life for sulfadiazine was The median plasme elimination half-life for sulfadiazine was approximately 7.80 hours, with a range of 6.78 to 10.39 hours. Only minor accumulation of both drugs was observed following repeat onal administration of EOUISUL-SOT and both drugs reached steady state by day 3. Sulfadiazine and timethoprim key steady state parameters associated with administration in 6 fed horses over a period of 7 days are administration in 6 fed horses over a period of 7 days are administration in found in Table 2

Table 2. Median (Range) of sulfadiazine and trimethoprim pharmacokinetics parameters following repeat dosing of 24 mg/kg bid EQUISUL-SDT for 7 days to six horses in fed condition

Drug	Sulfadiazine	Trimethoprim
Tmax (hr)	4.75 (1.00–12.00)	8.50 (0.50–12.00)
Cmax	17.63	0.78
(µg/mL)	(10.10–31.15)	(0.60–1.14)
AUC 0–12 (last dose)	159.35	5.47
(hr*µg/mL)	(73.90–282.54)	(3.31–10.91)
T 1/2	7.80	3.00
(hr)	(6.78–10.39)	(2.31–4.96)

MICROBIOLOGY EQUISUL-SDT is the combination of the sulfonamide sulfa-diazine and trimethoprim. These two drugs block sequential steps in nucleic acids biosynthesis. Sulfadiazine inhibits bacterial synthesis of dihydrolici acid by competing with para-aminobenzoic acid Trimethoprim blocks the production of tetrahydrolici acid from dihydrolici acid by reversibly inhibiting dihydrofalar feductase. The two drugs aci supercritically reducing the minimum inhibitory concentration sprengistically, reducing the minimum inhibitory concentration of each, while enhancing the bacteriostatic action of each separately to a bactericidal action when combined.

EQUISUL-SDT administered as a combined sulfadia Exological administered as a combined subadiative timethoprim dose of 24 mg/kg body weight twice daily for 7 days provided concentrations of sulfadiazine and trimethoprim with T>MIC90 (%T) values of 100% and 98% respectively. The minimum inhibitory concentration (MIC) values for EQUISUL-SDT against indicated pathogens isol values for EQUISUL-SDT against indicated pathogens side eff from lower respiratory tract infections in horese servolled in a 2010-2011 effectiveness field study are presented in Table 3.4 MI/OS were determined in accordance with the Clinical and Laboratory Standards Institute (CLSI) Approvec Standard M31-A3 using a broth microdilution system and 3° lysed horse blood.

Table 3. Trimethoprim/sulfadiazine minimum inhibitory concentration (MIC) values<sup>8</sup> of isolates recovered from horses with lower respiratory infection caused by *Streptococcus equi* subsp. zooepidemicus treated with EQUISUL-SDT in the U.S. (2010–2011)

Treatment Outcome	Success	Failure
Number of Isolates	65 <sup>c</sup>	46
Time of Sample Collection	Pre- Treatment	Pre- Treatment
MIC 50 <sup>b</sup> (µg/mL)	0.25/4.75	0.25/4.75
MIC 90 <sup>b</sup> (µg/mL)	0.25/4.75	0.25/4.75
MIC Range (ug/mL)	0.12/2.4 to 0.5/9.5	0.12/2.4 to 0.5/9.5

The correlation between in vitro susceptibility data and Clinical effectiveness is unknown.
 The lowest MIC to encompass 50% and 90% of the most susceptible isolates, respectively.
 Cone isolate of S. equi subsp. zooepidemicus was not

tested

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EFFECTIVENESS EFFECTIVENESS A negative control, randomized, masked, field study evaluat-ed the effectiveness of EQUISUL-SDT administered at 24 mg/kg body weight, orally, twice daily for 10 days for the treatment of lower respiratory tract infections in horses caused by 32reptooccuse agui subsp. zoegohemicus. In this study, a total of 182 horses were treated with EQUISUL-SDT, and 88 horses were treated with saline. One hourded seventy-three horses (112 EQUISUL-SDT and 61 saline) were included in the statistical analysis. Therepartic success was characterized by absence of fever and no worsening of clinical since at Day 5 and Day 10, and sinfingant clinical was ciralacuerized by absence of rever and no worsening of clinical signs at Day 5 and Day 10, and significant clinical improvement or resolution of clinical signs of lower respiratory tract infection by Day 17. The observed success rates are 58.9% (66/112) and 14.8% (9/61) for the EQUISUL-SDT and ne-treated groups, respectively

Table 4 summarizes the statistical analysis results on the overall success rate

Table 4. Overall Clinical Effectiveness Results

Equisul-SDT Saline P-value\* east Square Means 61% 13.1% 0.0123 \* P-value and estimated success rates are based on backransformed mean estimates from the statistical analysis.

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NIMAL SAFETY a target animal safety study, EQUISUL-SDT was adminis-red orally to 32 healthy adult horses at 0 (0X), 24 (1X), 22 (3X), or 120 (5X) mg/kg twice daily for 30 days. Loose stool was the most common abnormal observation. Observations of loose stool (pellets with liquid or unformed/ coxpile stool) occurred more often in horese treated with EQUISUL-SDT with the incidence of loose stool increasing a dose related manner. All incidents of loose stool were If-limiting and resolved without treatment.

Horses in all EQUISUL-SOT groups demonstrated statistically significantly higher mean serum creatinine concentrations, and those in the 3X and 5X groups demonstrated statistically significantly higher mean serum albumin concentrations. Statistically higher mean serum plus of the mean serum gamma glutamy transferase (GGT) activity were seen in the 1X and 5X groups. Individual animal creatinine, GGT, and albumin concentrations remained within the reference range. Individual animal elevations in absolute neutrophil counts ranged up to 7.09 x  $10^3$ /mcL (reference range: 1.96-5.31 x  $10^3$ /mcL).

Based upon blood concentrations obtained during the study it was noted that the sulfadiazine and trimethoprim plasma concentrations did not increase in proportion to dose. For sulfadiazine, a 3X and 5X dose resulted in an average exposure of 2.0X and 2.8X the concentrations observed following a 1X dose. For trimethorpim, the corresponding values were 2.5X and 3.5X as compared to the 1X dose. Values were 2.5X and 3.5X as compared to the 1X dose. Furthermore, marked intersubject variability, particularly with sulfadiazine, resulted in substantial overlap of individual subject blood levels across the three dosing groups.

135 mL 280 mL

560 mL 900 mL

[footnote]

#### Kahn CM, Line S, eds. The Merck Veterinary Manua 10th Ed. Merck & Co. 2010.

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STORAGE CONDITIONS Store upright at 59°- 86° F (15°- 30° C), Brief periods up to 104° F (40° C) are permitted. Protect from freezing. EQUISUL-SDT in containers of 280 mL and 560 mL — discard 60 days after removing bottle seal.

### HOW SUPPLIED EQUISUL-SDT is available in the following package sizes: