



# HEALTH ZONE

## Stem Cells

BY HEATHER SMITH THOMAS / PHOTOS COURTESY OF DR. SCOTT McCLURE

### New Techniques for Harvesting and Administering Stem Cells

**STEM CELL THERAPY** has been utilized in horses to help heal tendon, ligament, and joint injuries for nearly a decade, and new uses for stem cells are continually being explored. At this point there are basically two sources of stem cells for clinical use—from bone marrow and from fat tissue. Allogeneic stem cells—from another (donor) horse—and preserved cells, such as from umbilical cord blood from newborn foals, are not commonly used.

Cells harvested from bone marrow are usually cultured and expanded, putting them back into the horse some weeks later. Cells harvested from fat can be collected and concentrated at a lab and sent back within about 48 hours for quicker administration. Now there is a way to obtain

*(continued on page 114)*



Stem cell therapy can help heal tendon, ligament, and joint injuries



# performance

[per-fawr-muh ns] *noun*

1. The execution of an action.
2. Something accomplished.

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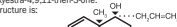
**VETERINARIAN TESTED AND RECOMMENDED**

## Regu-Mate® (altrenogest)

**Solution 0.22% (2.2 mg/mL)**

**CAUTION:** Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION:** Regu-Mate® (altrenogest) Solution 0.22% contains the active synthetic progestin, altrenogest. The chemical name is 17 $\alpha$ -17 $\beta$ -17 $\beta$ -hydroxyestr-4,9,13-trien-3-one. The CAS Registry Number is 850-52-2. The chemical structure is:



Each mL of Regu-Mate® (altrenogest) Solution 0.22% contains 2.2 mg of altrenogest in an oil solution.

**ACTIONS:** Regu-Mate® (altrenogest) Solution 0.22% produces a progestational effect in mares.

**INDICATIONS:** Regu-Mate® (altrenogest) Solution 0.22% is indicated to suppress estrus in mares. Suppression of estrus allows for a predictable occurrence of estrus following drug withdrawal. This facilitates the attainment of regular cyclicity during the transition from winter anestrus to the physiological breeding season. Suppression of estrus will also facilitate management of prolonged estrus conditions. Suppression of estrus may be used to facilitate scheduled breeding during the physiological breeding season.

**CONTRAINDICATIONS:** Regu-Mate® (altrenogest) Solution 0.22% is contraindicated for use in mares having a previous or current history of uterine inflammation (i.e., acute, subacute, or chronic endometritis). Natural or synthetic gestagen therapy may exacerbate existing low-grade or "smoldering" uterine inflammation into a fulminating uterine infection in some instances.

**PRECAUTIONS:** Various synthetic progestins, including altrenogest, when administered to rats during the embryonic stage of pregnancy at doses manyfold greater than the recommended equine dose caused fetal anomalies, specifically masculinization of the female genitalia.

**DOSEAGE AND ADMINISTRATION:** While wearing protective gloves, remove shipping cap and seal; replace with enclosed plastic dispensing cap. Remove cover from bottle dispensing tip and connect user lock syringe (without needle). Draw out appropriate volume of Regu-Mate solution. (Note: Do not remove syringe while bottle is inverted as spillage may result.) Detach syringe and administer solution orally at the rate of 1 mL per 110 pounds body weight (0.044 mg/kg) once daily for 15 consecutive days. Administer solution directly on the base of the mare's tongue or on the mare's usual grain ration. Replace cover on bottle dispensing tip to prevent leakage. Excessive use of a syringe may cause the syringe to stick; therefore, replace syringe as necessary.

**WHICH MARES WILL RESPOND TO REGU-MATE® (altrenogest) SOLUTION 0.22%:** Extensive clinical trials have demonstrated that estrus will be suppressed in approximately 95% of the mares within three days; however, the post-treatment response depended on the level of ovarian activity when treatment was initiated. Estrus in mares exhibiting regular estrus cycles during the breeding season will be suppressed during treatment; these mares return to estrus four to five days following treatment and continue to cycle normally. Mares in winter anestrus with small follicles continued in anestrus and failed to exhibit normal estrus following withdrawal.

Response in mares in the transition phase between winter anestrus and the summer breeding season depended on the degree of follicular activity. Mares with inactive ovaries and small follicles failed to respond with normal cycles post-treatment, whereas a higher proportion of mares with ovarian follicles 20 mm or greater in diameter exhibited normal estrus cycles post-treatment. Regu-Mate® (altrenogest) Solution 0.22% was very effective for suppressing the prolonged estrus behavior frequently observed in mares during the transition period (February, March and April). In addition, a high proportion of these mares responded with regular estrus cycles post-treatment.

**SPECIFIC USES FOR REGU-MATE® (altrenogest) SOLUTION 0.22%:**

### SUPPRESSION OF ESTRUS TO:

1. Facilitate attainment of regular cycles during the transition period from winter anestrus to the physiological breeding season. To facilitate attainment of regular cycles during the transition phase, mares should be examined to determine the degree of ovarian activity. Estrus in mares with inactive ovaries (no follicles greater than 20 mm in diameter) will be suppressed but these mares may not begin regular cycles following treatment. However, mares with active ovaries (follicles greater than 20 mm in diameter) frequently respond with regular post-treatment estrus cycles.

2. Facilitate management of the mare exhibiting prolonged estrus during the transition period. Estrus will be suppressed in mares exhibiting prolonged behavioral estrus either early or late during the transition period. Again, the post-treatment response depends on the level of ovarian activity. The mares with greater ovarian activity initiate regular cycles and conceive sooner than the inactive mares. Regu-Mate® (altrenogest) Solution 0.22% may be administered early in the transition period to suppress estrus in mares with inactive ovaries to aid in the management of these mares or to mares later in the transition period with active ovaries to prepare and schedule the mare for breeding.

3. Permit scheduled breeding of mares during the physiological breeding season. To permit scheduled breeding, mares which are regularly cycling or which have active ovarian function should be given Regu-Mate® (altrenogest) Solution 0.22% daily for 15 consecutive days beginning 20 days before the date of the planned estrus. Ovulation will occur 5 to 7 days following the onset of estrus as expected for nontreated mares. Breeding should follow usual procedures for mares in estrus. Mares may be registered and scheduled either individually or in groups.

**ADDITIONAL INFORMATION:** A 3-year well controlled reproductive safety study was conducted in 21 pregnant mares, and compared with 24 untreated control mares. Treated mares received 2 mL Regu-Mate® (altrenogest) Solution 0.22% (110 lb body weight) (2x dosage recommended for estrus suppression) from day 20 to day 32 of gestation. This study provided the following data:

1. In filly offspring (all ages) of treated mares, crown size was increased.
2. Filly offspring from treated mares had shorter interval from Feb. 1 to first ovulation than fillies from their untreated mare counterparts.
3. There were no significant differences in reproductive performance between treated and untreated animals (mares & their respective offspring) measuring the following parameters:
  - interval from Feb. 1 to first ovulation, in mares only.
  - mean interovulatory interval from first to second cycle and second to third cycle, mares only.
  - follicle size, mares only.
  - at 50 days gestation, pregnancy rate in treated mares was 81.8% (9/11) and untreated mares was 100% (4/4).
  - after 3 cycles, 11/12 treated mares were pregnant (91.7%) and 4/4 untreated mares were pregnant (100%).
  - colt offspring of treated and control mares reached puberty at approximately the same age (82 & 84 weeks respectively).
  - stallion offspring from treated and control mares showed no differences in seminal volume, spermatozoal concentration, spermatozoal motility, and total sperm per ejaculate.
  - stallion offspring from treated and control mares showed no difference in sexual behavior.
  - testicular characteristics (scrotal width, testis weight, parenchymal weight, epididymal weight and height, testicular height, width & length) were the same between stallion offspring of treated and control mares.

### REFERENCES:

1. Shoemaker, C.F., E.L. Squires, and R.K. Shideler. 1989. Safety of Altrenogest in Pregnant Mares and on Health and Development of Offspring. Eq. Vet. Sci. (9); No. 2: 69-72.
2. Squires, E.L., R.K. Shideler, and A.O. McKinnon. 1989. Reproductive Performance of Offspring from Mares Administered Altrenogest During Gestation. Eq. Vet. Sci. (9); No. 2: 73-76.

**WARNING: Do not use in horses intended for food.**

**HUMAN WARNINGS:** Skin contact must be avoided as Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed through unbroken skin. Protective gloves must be worn by all persons handling this product. Pregnant women or women who suspect they are pregnant should not handle Regu-Mate® (altrenogest) Solution 0.22%. Women of child bearing age should exercise extreme caution when handling this product. Accidental absorption could lead to a disruption of the menstrual cycle or prolongation of pregnancy. Direct contact with the skin should therefore be avoided. Accidental spillage on the skin should be washed off immediately with soap and water.

### INFORMATION FOR HANDLERS:

**WARNING:** Regu-Mate® (altrenogest) Solution 0.22% is readily absorbed by the skin. Skin contact must be avoided; protective gloves must be worn when handling this product.

**Effects of Overexposure:** There has been no human use of this specific product. The information contained in this section is extrapolated from data available on other products of the same pharmacological class that have been used in humans. Effects anticipated are due to the progestational activity of altrenogest. Acute effects after a single exposure are possible; however, continued daily exposure has the potential for more untoward effects such as disruption of the menstrual cycle, uterine or abdominal cramping, increased or decreased uterine bleeding, prolongation of pregnancy and headaches. The oil base may also cause complications if swallowed. In addition, the list of people who should not handle this product (see below) is based upon the known effects of progestins used in humans on a chronic basis.

### PEOPLE WHO SHOULD NOT HANDLE THIS PRODUCT:

1. Women who are or suspect they are pregnant.
2. Anyone with thrombocytopenia or thrombotic disorders or with a history of these events.
3. Anyone with cerebral/vascular or coronary artery disease.
4. Women with known or suspected carcinoma of the breast.
5. People with known or suspected estrogen-dependent neoplasia.
6. Women with undiagnosed vaginal bleeding.
7. People with benign or malignant tumors which developed during the use of oral contraceptives or other estrogen-containing products.
8. Anyone with liver dysfunction or disease.

**ACCIDENTAL EXPOSURE:** Altrenogest is readily absorbed from contact with the skin. In addition, this oil based product can penetrate porous gloves. Altrenogest should not penetrate nitrile, rubber, or impervious gloves; however, if there is leakage (i.e., pinholes, spillage, etc.), the contaminated area covered by such occlusive materials may have increased absorption. The following measures are recommended in case of accidental exposure.

**Skin Exposure:** Wash immediately with soap and water.  
**Eye Exposure:** Immediately flush with plenty of water for 15 minutes. Get medical attention.  
**If Swallowed:** Do not induce vomiting. Regu-Mate® (altrenogest) Solution 0.22% contains an oil. Call a physician. Vomiting should be supervised by a physician because of possible pulmonary damage via aspiration of the oil base. If possible, bring the container and labeling to the physician.

**CAUTION:** For oral use in horses only. Keep this and all medication out of the reach of children.

Store at or below 25°C (77°F).

NADA# 331-310. Approved by FDA.

### HOW SUPPLIED:

Regu-Mate® (altrenogest) Solution 0.22% (2.2 mg/mL). Each mL contains 2.2 mg altrenogest in an oil solution. Available in 1000 mL plastic bottles.

\* U.S. Patents 3,453,267; 3,478,067; 3,484,462

### Manufactured by:

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# HEALTH ZONE

## Stem Cells



Fat can be taken from the tail head to be processed and ready to inject in two hours

(continued from page 112)

and use those cells within a much shorter time.

Dr. Scott McClure, associate professor of equine surgery, Iowa State University, is utilizing this new method.

“A research group has simplified the procedure for stem cell processing so that we can obtain them and inject them back into the horse wherever there’s an injury, to stimulate healing,” he said. “Stem cells are present throughout the body and have the ability to perpetuate themselves. They can also divide and differentiate into the appropriate cells for healing bones, tendons, ligaments, or whatever.”

Stem cells can divide and differentiate into the appropriate cells for healing bones, tendons, ligaments, or whatever

It’s helpful to have a population of cells to aid healing wherever there is damaged tissue.

“The body has a way of doing this, to some degree, but not always to an adequate degree to heal the tissue the way we’d like it to heal,” McClure said. “We can add more stem cells to that area to speed optimal healing.

“We can utilize stem cells to treat specific injuries. We use autologous cells—from the patient’s own body. We can harvest cells from bone marrow and send this material to a lab where it is cultured and the number of MSC (mesenchymal stem cells) are expanded to the number that we need. These are sent back for us to place into the injury to be treated,” he said.

(continued on page 116)

# The Science of Trusted

Regu-Mate® (altrenogest) is the name veterinarians and their clients depend on for estrus control (suppression, management).

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Talk to your veterinarian about proper use and safe handling of Regu-Mate®. Avoid skin contact. Always wear protective gloves when administering Regu-Mate®. This product is contraindicated for use in mares with a previous or current history of uterine inflammation. Pregnant women, or women who suspect they are pregnant, should not handle this product. For complete product information, see accompanying product insert.

<sup>1</sup> Data on file, Merck Animal Health

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(continued from page 114)

“The other way is to harvest some adipose (fat) tissue from the patient and send it to the California laboratory (VetStem). They isolate the cells and ship them back within about 48 hours. In the past couple of years, there has been some interest in trying to find a way to harvest and inject these cells the same day, while the patient is still there in the clinic or hospital.

“We could potentially maintain a pool of embryonic stem cells (which are not autogenous) like a drug on the shelf to inject into any patient,” he continued. “Embryonic cells are fairly flexible, but there is always the possibility of reaction (and rejection) by the patient since these are not from the horse’s own body. Another option would be to have fetal blood or umbilical cord MSCs saved for each horse (at birth) to use at a later date, but this is not commonly done.

“So we’ve been looking at possible things we might do to obtain rapidly derived autologous stem cells—looking at what we can take from the horse today and put back into that horse today. We can process those cells while we are doing surgery for instance and put them right into that injury,” McClure said.

This technology has already been used in humans and is now being used in veterinary medicine.

“I can harvest some fat from a horse standing here right now, and in two hours I can have a stromal vascular fraction to inject,” he said. “This is in contrast to what we get when we culture stem cells in a petri dish for a period of time. If we culture the cells, all we have are pure MSC. If I take some adipose tissue and process it right now, however, I have a population of stem cells, a population of fibroblasts and other cells, and some very small embryonic-like cells. It’s actually a mixture of cells; there are stem cells along with some other cells that also aid healing,” he said.

Some of those cells are very beneficial.

“We can have that population of cells available to re-inject within about two hours,” McClure said. “We don’t have to send a sample off to a lab and wait 24 or more hours. We can do it right here on the counter in the clinic or hospital with what we have available now for equipment and technology.

“For instance, I can diagnose a horse with a tendon injury today, liposuction some fat from his tail head or wherever there’s a good source of adipose tissue on that horse, and be ready to inject these cells in two hours. We are still in the early stages of this technology, but we know it works. We’ve done it enough times now, in enough horses, to know it is effective. There are still some questions because we don’t know yet if we are better off to put in five million of the mixed stromal vascular fraction today or 10 million pure cultured cells 2½ weeks later. If we put in 2½ to 5 million today, they are already there and have gone to work,” he said.

“There are many things to evaluate, but it clearly appears that treating horses early with the stromal vascular fraction has clinical benefits. This technology has been used in humans and other veterinary species. It’s unique and simple. With this technique the fat tissue is digested with a group of enzymes and then the cells are concentrated, spun out, rinsed, and re-injected,” explained McClure.

“Many people in medical and engineering fields have worked on this technology to get it to this stage,” he said. “We use a centrifuge-type device that also serves as an incubator. It heats, agitates, spins, and allows us to do this very easily. The research to create this process took a lot of labo-



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ratory steps and has been able to compress them, utilizing a device to make it functional on a countertop in a hospital.”

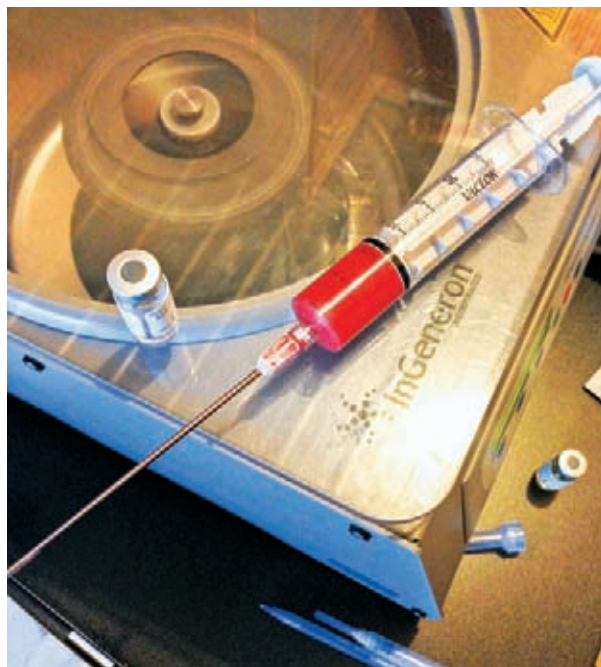
This technology is available now in a growing number of veterinary facilities.

“Some of the advantages are due to the fact that there is a large population of MSC in adipose tissue, and since horses have a large supply of adipose, we have the opportunity to obtain a lot of MSC,” he said. “We are starting with a reasonably large population, to derive our subsequent population of cells.

“I’ve been doing this more than two years, and I feel the advantages are multiple. We are able to treat these cases earlier—on the same day we harvest the cells—and treat more cases. When the decision is made, we can do it effectively and efficiently. We don’t have to be hauling horses back and forth and waiting a number of weeks,” he continued.

“Another beneficial aspect is that the cells are being put back into the horse fresh. In some of the research we’ve done, we found that adipose-derived MSCs that are this fresh divide more rapidly than cells that have been cultured a number of times. Thus, we can utilize cells that have a large colony-forming unit potential.”

There are some phenotypic differences regarding what these MSCs want to do, based on their source.



A centrifuge-type device (above and at left) also serves as an incubator



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“It’s been shown that cells derived from adipose tissue tend to differentiate very well toward becoming bone, versus the cells derived from bone marrow (that are cultured), which differentiate well toward chondrocytes,” McClure said. “In the laboratory, in culture, there are some differences in what these cells want to do,

but in that scenario we are counting on laboratory stimulation; we are putting some things in with these cells to differentiate them. However, if you put them into a certain environment—such as a bone formation—this will influence how well they will take that route.

“We can’t say that the exact same

things occur in the body as occur in the lab,” he explained. “When we inject these cells into a defect in a tendon, that environment will be much more tenogenic (influencing the cells to become tendon tissue) than what we would be able to do in the laboratory. If you inject some cells into a fracture callus in a leg, that would be an environment where they would be much more likely to form bone than they would in the environment of a laboratory dish.

“There are still some areas where people debate what’s best, one way or the other. They can make legitimate arguments on which might be better (cultured cells or fresh ones), but this new technique is an available option,” McClure said.

With new technology, it is nice to be in the forefront, but one has to be cognizant of not making mistakes

This method will probably be used more and more in the future.

“In my experience to date, I’ve found it to be an effective method,” he said. “We’ve treated some tendon and ligament injuries here, and some joints, and this is as effective as any other source of stem cells.”

The first horse McClure treated had a hole in a suspensory ligament branch, and now that horse is back to barrel racing and doing well.

“This horse belonged to a personal friend,” McClure said. “I didn’t know how well this system would work, so I tried it on that horse as an experiment. With new technology like this, it’s nice to be in the forefront and trying it early on, but you also don’t want to be making mistakes. We have to be a bit cautious. The horses I treated early did well, however, and I’ve been pleased with their healing progress, so I am now using this on a growing number of cases.”



A staple closure is performed after bone marrow aspiration

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