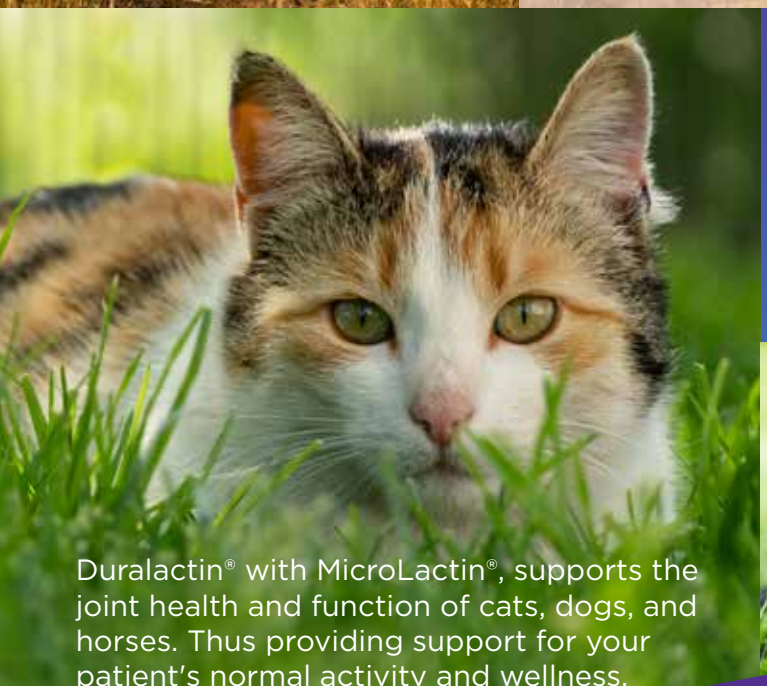
Duralactin®



Technical Monograph

Duralactin® with MicroLactin®, supports the joint health and function of cats, dogs, and horses. Thus providing support for your patient's normal activity and wellness.

PRN® PHARMACAL

Duralactin®

Introduction

Inflammation: A Double-Edged Sword

Acute inflammation protects the body from injury and invading microorganisms. It is a rapid-onset, non-specific defense that responds in a similar fashion to all types of foreign organisms and injuries.

In most cases, acute inflammation resolves quickly after eliminating the inciting cause. However, if inflammation does not subside normally, it may result in chronic inflammation. Chronic inflammation progresses slowly, damages healthy tissues, and may result in permanent tissue damage. For example, osteoarthritis can cause cartilage loss and osteophyte formation, while hepatitis can lead to cirrhosis. These permanent changes cannot be reversed. Inflammation also causes pain and impairs a patient's quality of life. Additionally, localized inflammation can have systemic effects that can affect other organ systems and overall health.

Anti-inflammatory drugs, such as corticosteroids and nonsteroidal anti-inflammatory drugs (NSAIDs), are used by veterinarians to combat the destructive effects of chronic inflammation. However, the risk of side effects associated with these drugs limits their use in some patients and leads the veterinary healthcare team to search for alternatives in the form of nutraceuticals and supplements.

Duralactin® brand products are nutritional supplements aimed at managing inflammation in cats, dogs, and horses, long term. The active ingredient in Duralactin® products is MicroLactin®, which is a specialized milk protein. Specialized milk protein concentrate (SPMC) has been shown to reduce inflammation by inhibiting neutrophil migration. This technical monograph will review the inflammatory process, neutrophil migration, MicroLactin, hyperimmunization, and the published target animal studies in dogs and horses.

Duralactin® (MicroLactin®) Technical Monograph

Contents

The Inflammatory Process[1,2]

Immediately after an injury occurs, local mast cells, neutrophils, and resident macrophages alert the immune system to the presence of damaged cells or foreign organisms. These sentinel cells release cytokines (such as interleukin 1 and interferon α), kinins (such as bradykinin), and vasoactive amines (such as histamine) to trigger the inflammatory process. These and other inflammatory mediators are the chemical communication signals that direct the entire inflammatory process.

Acute inflammation ensues with two phases of inflammation:

1. The vascular stage of inflammation consists of vasodilation and increased vascular permeability.
2. The cellular stage of inflammation involves the migration of leukocytes, predominantly neutrophils, into the affected tissues.

Neutrophils enter inflamed tissues and eliminate foreign organisms via phagocytosis. Additionally, they release toxic substances (e.g., degradative enzymes [elastase and collagenase]), reactive oxygen species, and proinflammatory mediators. The proinflammatory mediators amplify the inflammatory process by stimulating the bone marrow to produce more neutrophils, recruiting circulating neutrophils to the site of inflammation, and helping stimulate the arachidonic acid metabolism cascade. Circulating macrophages then migrate into the tissues to eliminate damaged cells and dying neutrophils and to help heal tissues.

Neutrophil migration[3]

It is imperative that the body regulate the migration of the neutrophils, as this migration requires a series of sequential steps: rolling, integrin activation, firm attachment, transmigration, and chemotaxis.

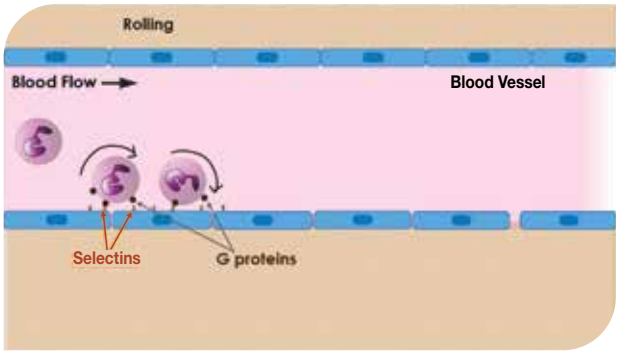


Figure 1 - Rolling

Rolling: Circulating neutrophils come in contact with the blood vessel wall via loose interactions between selectin receptors on endothelial cells and *glycoproteins* on the neutrophil. The force of the *blood flow* breaks the bond just as another forms a little further down the endothelium. The neutrophils form, break, and form new bonds with the *selectin* receptors, it appears to roll along the endothelial surface.

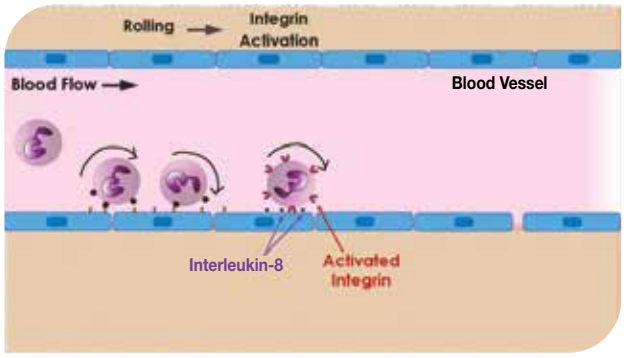


Figure 2 - Integrin activation

Integrin activation: As neutrophils roll along the endothelium, they contact the proinflammatory chemokine called *IL-8*, which is expressed by endothelial cells during times of inflammation. *IL-8* binds to chemokine receptors on neutrophils triggering an intercellular cascade within the neutrophil. Thus the integrin receptor on the surface of the neutrophil is activated.

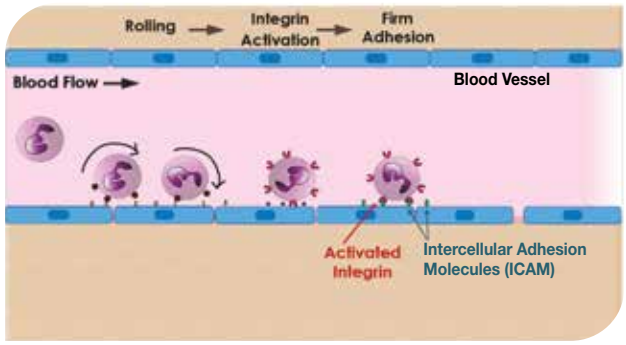


Figure 3 - Firm Adhesion

Firm adhesion: The *activated integrin* receptors on neutrophils bind strongly to *intercellular adhesion molecules (ICAM)* on the endothelial surface. This interaction is stronger than the force of blood flow, and the neutrophil stops rolling and adheres to the endothelial wall.

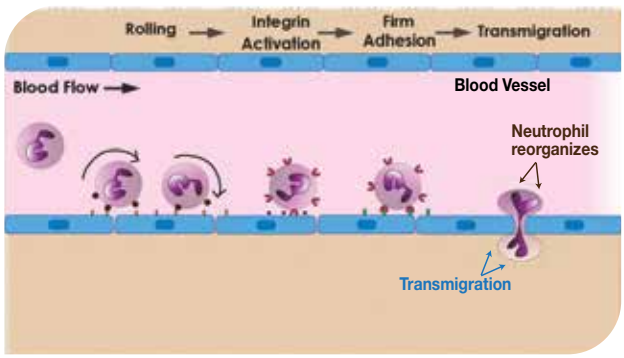


Figure 4 - Transmigration

Transmigration: Once adhered, the neutrophil crawls to the closest endothelial cell border. The neutrophil cytoskeleton reorganizes, dramatically changing shape. A leading edge of the neutrophil inserts itself between two endothelial cells, allowing it to exit the circulation and enter the underlying connective tissue. This process is referred to as transmigration.

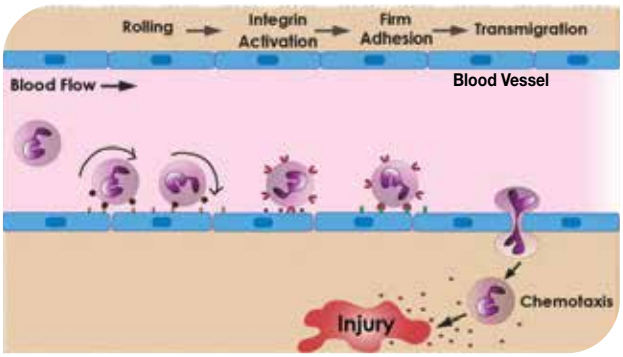


Figure 5 - Chemotaxis

Chemotaxis: Once the neutrophil enters the affected tissue, it follows a gradient of chemokines, molecules from damaged cells and microbial products to the site of inflammation.

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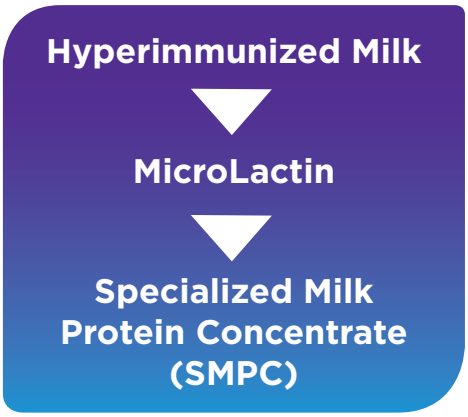
Milk: Defending Against Inflammation

Mother's milk provides infants with complete and balanced nutrition in addition to a number of protective properties. Maternal immunoglobulins defend the young against specific microorganisms. Other components of milk, such as lactoperoxidase and lactoferrin, provide protection against a range of microorganisms. Antioxidants found in milk decrease tissue damage caused by free radicals.[4] Compared to formula-fed human babies, studies have shown that breastfed babies have a decreased risk for digestive illnesses, ear infections, respiratory infections, asthma, allergies, obesity, and childhood leukemia.[5] Importantly, the maternal immunity delivered through milk is necessary for infant survival in many species.[4]

In 1976, researchers discovered that dairy milk contains a natural anti-inflammatory substance during times of infection. This factor is secreted in milk in order to protect calves from tissue damage caused by inflammation triggered by bacterial and viral infections. However, the factor is not present normally in milk, only during times of infection. It was also found that this milk contains an orally active factor—most frequently called *hyperimmune milk factor (HIMF)*—that has been shown to reduce inflammation in a number of species.

MicroLactin®

MicroLactin® is a protein concentrate of HIMF in which the lactose and salts have been reduced. Known as Specialized Milk Protein Concentrate (SMPC), a variety of assays have shown it to retain the biologically active properties of HIMF.[6] MicroLactin is the active ingredient of Duralactin® brand products. The published papers that have examined the use of MicroLactin in managing inflammation in dogs and horses are reviewed in the next section.



MicroLactin is well tolerated in dogs, cats, and horses. Because it is derived from milk, side effects (e.g., gastrointestinal upset) may occur in patients with dairy intolerances.

Target Animal Studies: Canine Efficacy Study[7]

Gingerich DA, Strobel JD. Use of Client-Specific Outcome Measures to Assess Treatment Effects in Geriatric, Arthritic Dogs: Controlled Clinical Evaluation of a Nutraceutical. *Veterinary Therapeutics.* 2003; 4(1): 56-66.

Summary

The efficacy of special milk protein concentrate (SMPC, also known as MicroLactin®) was evaluated in a placebo-controlled, double-blinded, randomized, parallel trial of 50 geriatric, large breed dogs. Overall improvement was seen by owners in 67% of the MicroLactin-treated dogs, whereas only 35% of the owners of dogs in the placebo group reported improvement during the 8-week study period. The treatment group also displayed a greater degree of improvement than the placebo group in regard to orthopedic score ($P < 0.001$) and owner global assessments ($P = 0.004$).

Objective: Evaluate the efficacy of special milk protein concentrate (SMPC, also known as MicroLactin) in geriatric, large-breed dogs with signs of osteoarthritis.

Study Design

Test population: Fifty, client-owned, large-breed dogs ranging from 7 to 12 years of age were randomly assigned to either the treatment or control groups. All participants displayed clinical signs consistent with osteoarthritis. Obese patients or those with underlying disorders that required overlapping treatments (e.g., NSAIDs, steroids, analgesics) were excluded. Five companion-animal practices in the Cincinnati area evaluated the dogs on an outpatient basis.

Treatments: The treatment group received 2 grams of SMPC (MicroLactin) per day, whereas the placebo group received rice flour. The study period lasted 8 weeks after a 1-week placebo run-in period. The capsules and bottles were identical, and veterinarians and owners were blinded to the group assignments.

Evaluations: Owners evaluated their dogs utilizing an overall assessment, a standardized questionnaire, and a case-specific questionnaire. Veterinarians assigned a global assessment score and performed physical exams at 0, 4, and 8 weeks. A complete blood count and standard chemistry profile were performed at the beginning and end of the treatment period. The global assessment score evaluated whether the patient had improved, which ranged from -1 (worse) to 3+ (excellent). The standardized questionnaire form was identical for all patients. The case-specific questionnaire, which is known as "Cincinnati Orthopedic Disability Index" (CODI), identifies the arthritic impairments specific to each patient's clinical signs. Owners completed both questionnaire types biweekly.

Results

Thirty-five dogs (17 in the placebo and 18 in the treatment group) completed the study. Owners reported an overall improvement in 66.7% of the MicroLactin®-treated dogs but in only 35.3% of the placebo-treated dogs. There was also a significant degree of improvement in the MicroLactin-treated group. The owner global assessments and questionnaire scores (both standardized and case-specific) improved significantly in the MicroLactin group over the course of the study ($P < 0.01$). The placebo group did not improve significantly over the course of the study. The owner's overall assessment and the case-specific questionnaire (CODI) scores improved significantly from the placebo group ($P < 0.05$). The physical examination findings of both the treatment and placebo groups improved slightly but significantly. According to published orthopedic standards, MicroLactin had a large effect on the owner overall assessments and on the case-specific questionnaire scores, intermediate effect on veterinarians' overall assessments and standardized test scores, and negligible effect on the physical examination findings. Both the MicroLactin and the placebo were well-tolerated, except that one participant from each group needed to withdraw from the study due to vomiting.

Change in Questionnaire Scores

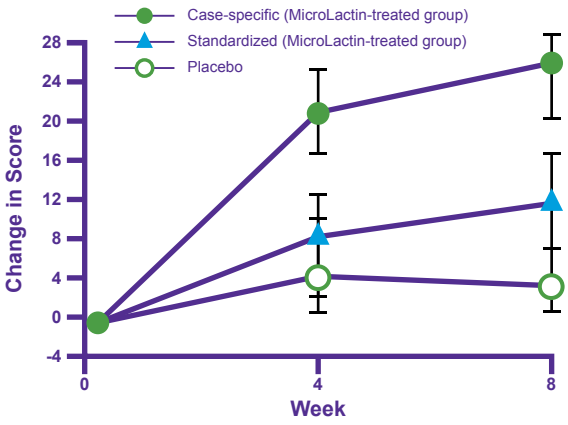


Figure 1: Owner-reported changes (mean +/- SEM) in disability scores of MicroLactin®-treated dogs on the case-specific and standardized questionnaires as compared to the placebo group. Graph borrowed from Gingerich DA, Strobel JD. Use of client-specific outcome measures to assess treatment effects in geriatric, arthritic dogs: controlled clinical evaluation of a nutraceutical. *Veterinary Therapeutics*. 2003; 4(1): 56-66.

Overall Global Response as Seen by Dog Owners and by Veterinarians

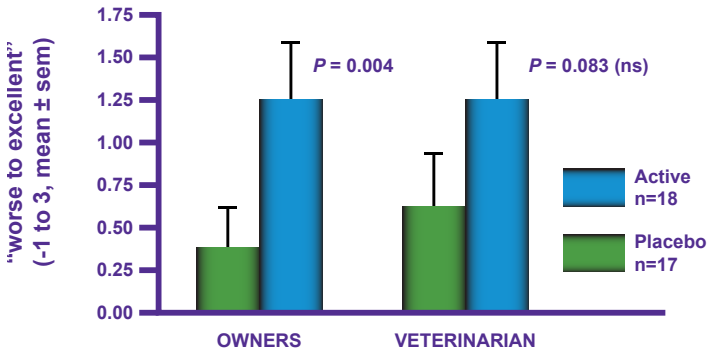


Figure 2: Global assessments of overall response (mean +/- SEM) to MicroLactin compared to the placebo as reported by owners and veterinarians after 8 weeks. The arthritic dogs were scored on a scale from -1 (worse) to 3 (excellent). Graph adapted from Gingerich DA, Strobel JD. Use of client-specific outcome measures to assess treatment effects in geriatric, arthritic dogs: controlled clinical evaluation of a nutraceutical. *Veterinary Therapeutics*. 2003; 4(1): 56-66.

Significance

This placebo-controlled, double-blinded, prospective, randomized study evaluated the efficacy of MicroLactin® by examining the owner's assessment of their dog's clinical improvement. The results suggest that MicroLactin has therapeutic value in dogs with signs of osteoarthritis. It is a well-tolerated alternative for the long-term management of musculoskeletal conditions, especially in geriatric dogs.

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MicroLactin® and Equine Inflammatory Conditions[8]

Bello TR, Allen TA. The Use of MicroLactin for Inflammatory Conditions in Equine Veterinary Practice. *Journal of Equine Veterinary Science.* 2005; 25(9): 380-382.

Summary

A clinical survey was performed of 58 horses that were treated with Duralactin® Equine for a variety of inflammatory conditions. Additional therapies were included as necessary. Improvement was seen in 86% of the cases.

Objective: Utilize MicroLactin® as a therapeutic for a variety of inflammatory conditions in horses. Conditions that show improvement can be further studied in future placebo-controlled studies.

Materials and Methods

Each horse received 1 scoop of Duralactin Equine (7,000 mg MicroLactin) twice daily with food. Additional therapies were prescribed as necessary. The survey includes a large range of breeds and ages (0.75-36 years). There were 20 mares, 36 geldings, and 2 stallions.

Limitations

This study did not have a control or placebo consort. Additionally, it is understood that some of the horses conditions were acute and some may have resolved without intervention.

Results and Discussion

Inflammation was reduced in 86% of the cases (44/51). Seven horses were lost to follow-up. The inflammatory conditions included in the survey are listed in Table 1.

Table 1

Inflammatory Conditions in Equine Survey	
AFFECTED SITE	**CONDITION**
Respiratory tract	Small airway inflammatory syndrome
	Allergic rhinitis
Distal limb	Navicular syndrome
	Laminitis
	Hoof reconstruction
	Fetlock pain with soft tissue trauma
	Hock inflammation with joint trauma
Neurologic system	Equine protozoal myeloencephalitis (EPM)
Subcutaneous tissue	Nonpoisonous snake bite
	Multiple tick bites
	Perivulvar inflammation
	Necrotizing vasculitis
Muscle	Traumatic myositis
	Unbalanced shoes
	Hindquarter pressure in training
Skin	Culicoides-bite hypersensitivity
	Topical groin irritation
	Dermatophilus skin infection
	Fibrous tracts and SQ granulomas
Intestines	Toxic enteritis
	Ingestion of toxic plants
Kidney	Undiagnosed
Head	Lacerations

Significance

This clinical survey shows clinical improvement after the supplementation of MicroLactin® in a variety of equine inflammatory conditions. The results can direct future placebo-controlled trials in these and other inflammatory conditions. MicroLactin can affect inflammation throughout the body.

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Equine Protozoal Myeloencephalitis Study[9]

Bello TR, Allen TM. An Intensive Approach in the Treatment of Clinical Equine Protozoal Myeloencephalitis. *Journal of Equine Veterinary Science.* 2008; 28(8): 479-483.

Summary

Twenty-eight horses affected with neurologic signs due to equine protozoal myeloencephalitis (EPM) were treated with a triple therapy of ponazuril, transfer factor, and MicroLactin®. Ponazuril provided antiparasitic therapy, transfer factor stimulated cell-mediated immunity, and MicroLactin inhibited inflammatory reactions. After treatment, 82% (23/28) of the horses were able to return to work.

Many experts consider EPM as "a serious parasitic disease with neurologic consequences" instead of a "serious neurologic disease caused by a parasite." The study's authors wanted to address the host-parasite immunologic reactions associated with the disease by including ponazuril, transfer factor, and MicroLactin in the treatment protocol. Ponazuril is an antiparasitic. Transfer factor contains dialyzable leukocyte extracts that can transfer and stimulate cell-mediated immunity, which is important in controlling intracellular parasites. MicroLactin protects against destructive inflammatory reactions.

Objective: Utilize a triple therapy of ponazuril, transfer factor, and MicroLactin to combat the parasitic, immunologic, and inflammatory components of equine protozoal myeloencephalitis (EPM) in order rehabilitate equine athletes.

Materials and Methods

Twenty-eight horses with clinical signs of EPM—such as gait abnormalities (stumbling), behavior changes, weakness, and asymmetrical muscle loss—exhibited positive serum immunoblot tests to confirm exposure to *Sarcocystis neurona*. A presumptive diagnosis of EPM was made based on clinical signs, a positive serum *immuoblo*t test, and physical examinations; a confirmatory cerebral spinal fluid analysis was not performed. Nine breeds were represented in the study with ages ranging from 3-20 years. There were 15 geldings and 13 mares.

Transfer factor (750 mg twice daily for 7 days, then once daily for 30 days) was fed for a total of 37 days, while both MicroLactin® (7,000 mg twice daily) and ponazuril (5 mg/kg once daily) were given for 28 days. Five horses were treated with ponazuril and transfer factor, and the remaining 23 were treated with a triple therapy of ponazuril, transfer factor, and MicroLactin. Fifteen horses required an extended course of medication.

Results

After treatment, 82% (23/28) of the horses were able to return to work. Eighteen of these returned to their previous activity or were sold as athletes, while five of these horses remained in physical rehabilitation but were able to do controlled exercise under saddle.

Five acutely affected horses were not helped by the therapy. Two of these horses were deemed unsafe and were euthanized within 60 days. The final three made improvements but remained unsafe to ride and were euthanized within 6-24 months of therapy. A treatment crisis occurred in one horse that received only transfer factor and ponazuril.

Significance

Treatment of EPM with ponazuril alone has an expected improvement rate of 60%, with only 10-20% of horses making a complete recovery.[10] With the addition of transfer factor to promote cell-mediated immunity and MicroLactin to inhibit exuberant inflammation, 82% of horses improved, with 64% making a full recovery. The study's authors "considered transfer factor, MicroLactin, and ponazuril to be equal partners attacking the clinical challenge from different, but specific, directions." Although this study was not placebo-controlled, it suggests an improved treatment response for EPM with the described triple therapy.

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Glossary

Acute inflammation - rapid-onset, non-specific defense that protects the body from invading microorganisms and injury.

Chronic inflammation - inflammation which does not subside normally, progresses slowly, and damages healthy tissues.

Duralactin® - specific product containing MicroLactin® which supports the joint health and function of cats, dogs, and horses.

HIMF - orally active factor called hyperimmune milk factor (from hyperimmunized cow milk) that has been shown to reduce inflammation in a number of species

ICAM - intercellular adhesion molecules

MicroLactin® - a specialized milk protein concentrate in which the lactose and salts have been reduced.

SPMC - specialized milk protein concentrate

Duralactin®

DURALACTIN Canine Chewable Tablets - 60/180 CT
- Contains 1,000 mg MicroLactin
- Palatable vanilla flavored tablet

DURALACTIN Canine Soft Chews - 60/90 CT
- Contains 1,500 mg MicroLactin
- Palatable liver flavored bone-shaped soft chew

DURALACTIN Joint Plus Canine Soft Chews - 60/90 CT
- Contains 1,500 mg MicroLactin
- Contains Glucosamine HCl, MSM, Omega-3 (EPA and DHA) Fatty Acids, Zinc, Manganese and Vitamin E
- Palatable beef flavored bone-shaped soft chew

DURALACTIN Feline Capsules - 60 CT
- Contains 200 mg MicroLactin
- Convenient capsule that can be given alone, with food, or sprinkled over food

DURALACTIN Feline + Fatty Acids Soft Chews - 60 CT
- Contains 300 mg MicroLactin
- Contains Omega-3 (DHA and EPA) and Omega-6 fatty acids
- Palatable fish flavored heart-shaped soft chew

DURALACTIN Feline L-Lysine Paste
- Contains 200 mg MicroLactin per dose
- Contains L-Lysine, Omega-3 and Omega-6 fatty acids
- Available in 32.5 mL syringe
- Palatable liver flavored paste

DURALACTIN EQUINE PELLETS - 1.875 lb. bag
- Contains 7,000 mg MicroLactin per dose
- Give directly or feed with food.

DURALACTIN Equine Joint Plus Pellets - 3.75 lb. bag
- Contains 7,000 mg MicroLactin per dose
- Give directly or with food

This product has not been approved by the FDA nor is it intended to diagnose, treat, cure, or prevent any disease. Should only be used through consultation of a veterinarian and in conjunction with an overall wellness program.

PRN® Pharmacal, an employee-owned company, has been dedicated to developing specialized therapeutics that address the unmet, underserved and overlooked needs of the veterinary medicine community since 1978. Our commitment: quality solutions - as needed, when needed.

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