By Jessica Tremayne
Contributing Editor

A recent groundbreaking study of clinical, histological and immunological data of 22 cases of Pemphigus foliaceus, or PF, shows evidence that it can occur as an adverse drug reaction to the canine flea and tick preventive ProMeris.

PF is the most common spontaneously occurring autoimmune skin disease of dogs and typically displays as lesions on the face, nasal planum and ears. The reaction is rare but serious, says the study’s lead author, Thierry Olivry, DrVet, PhD, Dipl. ACVD, of North Carolina State University.

Ultimately, ProMeris Duo (Metaflumizone–amitraz), which is also used for treating demodicosis, will be discontinued. The product, marketed by Pfizer Animal Health, will be available while supplies last or until mid-September. ProMeris Duo is called ProMeris for Dogs in the US. It is a novel topical ectoparasiticide.

“ProMeris was one of the many products that Pfizer brought into its portfolio when we acquired Wyeth/Fort Dodge Animal Health,” says Jim Brick, director and team leader of U.S. marketing for Pfizer Inc.

“We have completed a thorough review and evaluation of the strategic fit into the Pfizer Animal Health portfolio, and have made the decision to discontinue the manufacture and sale of ProMeris flea and tick control for dogs and cats.

“We notified our current customers of this decision in early April and will continue to fill their orders until Sept. 20, 2011, or while supplies last. We look forward to continuing to meet the needs of our customers with our evolving parasiticide portfolio.”

The study that gathered and presented the ProMeris findings was conducted by Dr. Olivry; Ursula Oberkirchner, resident; and pathologist Keith Linder, DVM, PhD, all of North Carolina State University.

Since ProMeris’ introduction to U.S. and European markets in 2007, veterinarians have reported this adverse reaction, but previous case studies failed to use a drug-reaction probability scale and therefore an ADR couldn’t be definitively identified. Olivry says this examination of all parameters studied suggests that this ADR might represent the first instance of contact drug-triggered PF to be published in Veterinary Dermatology. The article was published in the March issue of the journal.

Spontaneously occurring PF, thought to develop through genetic and environmental triggers, has a higher prevalence in chow chows and Akita Inus, whereas ProMeris-triggered PF has a higher occurrence in Labrador retrievers and other large-breed dogs, Olivry says.

The study found that ProMeris Duo-associated PF not only had a reaction to the same drug, but also shared many of the same phenotypes. Lesions in PD-triggered PF were found to be both
localized and at distant locations from the point of application.

“We contacted specialists who had diagnosed these cases in the U.S. and Europe,” Olivry says. “Dogs were selected if they had a history of skin lesions that first arose at the PD application site, but dogs with a known history of autoimmune disease were omitted.” Skin biopsies from said PD-associated lesions had to reveal microscopic characteristics similar to those of PF, which means the presence of superficial keratinocyte acantholysis.

“Referring veterinarians from cases used completed questionnaires providing information on the patient's lesions and drug application history. Within the 22 dogs included in this study, two groups of affected animals were distinguished: dogs with localized signs or those who also exhibited distant skin lesions.”

Olivry’s goal in revealing his study findings is to provide veterinarians with information on the prognosis and management of this disease. In addition to skin lesions, more severe reactions can occur and can be long-lasting.

“Signs of systemic illness were reported in three dogs in the study, and four required immunosuppressive treatment,” Olivry says. “After ADR PD lesions occur and are then treated, they could recur at a later time without reapplying ProMeris Duo.”

Olivry says the study is referenced in Pubmed as: Metaflumizone-amitraz (Promeris)-associated pustular acantholytic dermatitis in 22 dogs: evidence suggests contact drug-triggered pemphigus foliaceus.

An NCSU Case study

Olivry recommends that veterinarians use alternatives to ProMeris in animals known to have autoimmune disease, Labradors and other large-breed dogs, as well as in dogs that previously developed lesions.

“Dogs developed lesions in a draping pattern or along the dorsal side after having ProMeris Duo applied,” Olivry says. “Some dogs showed systemic signs that included lethargy, generalized pain and anorexia. In the case of a 7-year-old (spayed) female Labrador, a two-week history of skin lesions and lameness was presented.

“Ten months prior to referral, the dog’s monthly flea and tick prevention was changed from Frontline to PD. The patient received a total of three PD applications, three and five months separating them. One month after the third application of PD, the owner noticed extensive crusting on the application site between the shoulder blades as well as lameness in the left front leg. The dog was examined by the primary care veterinarian, who suspected a tick-borne disease as the cause of this dog’s lameness. Doxycycline was then prescribed.”

One of Olivry’s concerns with lesions occurring after ProMeris application is that primary care practitioners may not be able to identify or connect the product as a cause of the lesions and misdiagnose the patient, as in the case of the 7-year-old female Labrador.

“Skin biopsies were taken from interscapular crusts and histopathology revealed an acantholytic
dermatosis of unknown origin in the female Labrador,” Olivry says. “The patient’s health worsened dramatically over the following days. The dog appeared in pain, she showed lameness of the left front paw and skin lesions had progressed. The veterinarian prescribed prednisone (1 mg/kg twice daily) and tramadol, while a fentanyl patch was applied and doxycycline was continued. “Only minimal improvement of the lameness and skin lesions was seen with this regimen, and the patient was referred to North Carolina State University. Skin cytology was performed on pus obtained from a crusted lesion in the shoulder, and microscopic examination revealed neutrophils and acantholytic keratinocytes suggestive of PF. Serum was collected for detection of circulating antikeratinocyte autoantibody by indirect immunofluorescence (IF) in our laboratory.”

Based on the strong suspicion of the diagnosis of ProMeris-triggered pemphigus foliaceus (PTPF), Olivry says the dosage of prednisolone was increased to 1.5 mg/kg twice daily, and tramadol was to be given as needed to relieve pain. “On histopathology, the presence of a superficial epidermal neutrophilic pustular dermatitis with keratinocyte acantholysis was confirmed, and bacteria or dermatophytes were not seen in the stratum corneum by special stains,” Olivry says. “Direct IF performed on paraffin-embedded skin sections revealed the intercellular deposition of IgG and IgM in both lesional and perilesional epidermis. Circulating antikeratinocyte autoantibodies were not detected at 1:20 serum dilution.”

Olivry and his team concluded this case with a diagnosis of PTPF. “The dog returned for a re-evaluation visit the following week,” Olivry says. “At that time, skin lesions had improved, as there was only minor crusting left in the interscapular region and pinnae. The dog no longer exhibited signs of lameness, and tramadol was discontinued. The dose of prednisolone was tapered progressively over the following 11 days. The disease has remained in remission without any relapse for more than two years.”

**Efficacy**

Before ProMeris became available for veterinary purchase and distribution, studies evaluating its safety and efficacy reported the development of skin lesions at the site of drug application in some treated animals, Olivry says. In one clinical trial enrolling dogs with flea or tick infestation, six of 293 subjects (2 percent) exhibited skin hyperpigmentation, hair matting or scales at application sites. In another experimental study of dogs infested with either fleas or ticks, one dog treated with ProMeris developed dorsal skin lesions that required treatment with an anti-inflammatory drug for seven days. “Specific information on the frequency of these severe adverse drug reactions isn’t available, but it is important that veterinarians are aware of the product’s potential to cause the patient harm,” Olivry says. “Caution needs to be exercised if a vet decides to use this drug.”
Diagnosing and Treating PTPF

(Editor’s note: The information in this story was taken directly from Oberkirchner U, Linder KE, Olivry T. Promeris-triggered pemphigus foliaceus in two dogs: case reports and recommendations for diagnosis and treatment. Veterinary Medicine, submitted March 2011. Not yet published).

How to diagnose generalized PTPF

• History of ProMeris application. This may have begun months before the onset of clinical signs.
• Development of skin lesions (e.g. crusting, alopecia, erythema) at the site of PD application.
• Later development of skin lesions at sites distant from the PD application area.
• Systemic signs (lethargy, fever, pain, anorexia, lameness) may be present in most dogs.
• Perform cytological examination of visible pus and look for acantholytic epidermal cells typical of pemphigus foliaceus (PF).
• Take several biopsies from recent skin lesions, preferably from intact pustules, and submit them for routine histopathology. Microscopic lesions are identical to those of typical autoimmune PF.

How to treat generalized PTPF

• Do not reapply PD.
• Use a mid-potency topical glucocorticoid at the site of skin lesions if feasible.
• Use oral glucocorticoids at immunosuppressive dosages (e.g. prednisone or similar, 2-4 mg/kg/day)
• If signs do not undergo clinical remission within one month, or if they recur after dose tapering, add another immunosuppressive drug such as azathioprine (2 mg/kg/day) or cyclosporine (7-10 mg/kg/day)
• Treat until clinical remission of lesions and taper drug doses progressively until withdrawal, if at all possible.
• Prognosis is generally good. Most dogs with generalized PTPF are likely to achieve complete disease remission and complete drug withdrawal. Oral immunosuppression may be prolonged in some patients.