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Docket Name: Request for Nominations: List of Bulk Drug Substances That May be Used by an Outsourcing Facility to Compound Drugs for Use in Animals

Dipyrone (metamizole) and Treatment of Shar-Pei Fever

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I am writing to nominate dipyrone (metamizole) to be considered for the Federal Drug Administration's Appendix A list of bulk drug substances that may be compounded for veterinary office stock.

I am a published veterinary clinician researcher[1] studying Shar-Pei Autoinflammatory Disease and treating Shar-Pei Fever[2] [3] since the late 1980s.[4] [5] [6]

The drug is currently used in Chinese Shar-Pei and Chinese Shar-Pei mixed breed dogs suffering from Shar-Pei Fever, a subset of Shar-Pei Autoinflammatory Disease.

I have recommended the use of dipyrone for treating severe acute fever in this disorder for over 20 years and have extensive experience with the use of the drug in hundreds of these patients.

As I wrote in our 2011 PLoS Genetics paper, acute fever events in Shar-Pei respond rapidly to dipyrone, a potent antipyretic and analgesic pyrazolone, which has been demonstrated to inhibit IL-1β induced fever by blocking the activation of caspase-1 by the inflammasome.[7] [8] [9]

In the early 1990s, Familial Shar-Pei Fever (FSF) was introduced as a term to identify a condition observed in some Shar-Pei that included renal amyloidosis and recurrent fever of unknown origin, both known to occur in humans affected with familial Mediterranean fever, an inherited condition. Subsequent research into the causes of FSF revealed that FSF was one of several manifestations of a recently identified overarching inherited disease state in Shar-Pei called *Shar-Pei autoinflammatory disease* (SPAID). FSF is one of several possible phenotypic signs of SPAID, as is renal (or systemic) amyloidosis, which can manifest independently from Shar-Pei Fever.

A mutation and copy number variation of a regulatory element upstream to the gene for hyaluronan synthase 2 and subsequent overexpression of hyaluronan has been linked to the Shar-Pei's breed-specific wrinkled, thickened skin and also to SPAID.

Autoinflammatory disease stems from dysregulation of the innate immune system and is characterized by systemic and persistent inflammation. Low molecular weight hyaluronan fragments can both activate and prime the NALP3 inflammasome, a multi-protein complex that leads to the release of IL-1β, a potent activator of systemic inflammation and fever. Various underlying abnormalities in inflammasome function and control of IL-1β release are common to autoinflammatory disorders like FMF in humans. SPAID is the first naturally occurring autoinflammatory disease to be described in animals.[10]

Shar-Pei may have abnormal initiation and also amplification of inflammation as a result of their genetic CNV mutation. This may result in chronic elevations of inflammatory cytokines in the bloodstream (e.g. IL-6, IL-8)). They may over-react to infection and damage. Increased number of mutated copies (higher CNV) has been shown to be associated with increased risk for SPAID (including FSF and amyloidosis). Hyaluronan is a dynamic molecule that is endogenously degraded and turned over rapidly: in hours, days, or weeks depending on its location in the body. It is transported primarily via the lymphatic system to the liver. The breakdown of a Shar-Pei's excessive HA into fragments for routine metabolism may also contribute to autoinflammation and randomly triggered fever events.

Hyaluronan is unique in that its low molecular weight fragments can both activate and prime the inflammasome, a cytosolic multi-protein platform in mast cells, monocytes/macrophages, leading to the release of IL-1β, one of the major drivers of fever and inflammation. [11]

Shar-Pei with FSF may have one or more bouts of unexplained fever, usually 103-107°F (39.4-41.7°C) but rare cases may go higher. Fever greater than 106°F is a medical emergency and veterinary treatment for the hyperthermia is advised for these dogs. I have seen many Shar-Pei experience fevers that exceed 107°F and several of these patients died (one at 111°F) despite my best efforts before a Shar-Pei owner from Southern California contacted me in the early 1990s. He described how his Shar-Pei would routinely spike fevers of 108°F before he discovered that over-the-counter dipyrone tablets that he obtained in Mexico would swiftly bring the fever down and the dog out of danger.

Novin® (injectable dipyrone) was still available when I began in practice and I was already familiar with the drug. I found that dipyrone did indeed rapidly reset the hypothalamic thermoregulatory set point in these dogs.

My November 13, 1995 monograph, "Familial Shar-Pei Fever and Familial Amyloidosis of Chinese Shar-Pei Dogs: A Recently Described Syndrome of Dysregulation", that I wrote to advise veterinary practitioners who treated Shar-Pei afflicted with FSF, included the following paragraphs:

1. FEVER.

If fever does not exceed 106° F, specific treatment to lower body temperature is not critical. Body temperature will usually return to normal in 24-36 hours in most FSF patients regardless of treatment. However, temperatures of 108-112°F can occur. Obviously, reducing core body temperature in these patients is important. Treat these patients for hyperthermia in addition to the suggestions below. Because of the

possibility of malignant hyperthermia, clients with Shar-Pei with this disorder should be instructed to have a rectal thermometer on hand and be prepared to check the dog's temperature at home if needed.

Patients with extremely high fevers due to FSF often also require dipyrone administration. This drug reduces the elevated body temperature and diminishes pain and inflammation in patients experiencing clinical attacks. It is speculated that the drug works by interfering with neutrophil chemotaxis and/or inhibition of PGE_2 synthesis by stimulated neutrophils. A dose of 250-500mg (0.5-1.0 ml of 50%) Dipyrone Injectable subcutaneously usually lowers the temperature within 1-1.5 hrs. If no improvement is seen, the dose can be repeated up to the manufacturer's recommended dosage of 11mg/kg IM, SC or IV q8h. One injection is usually sufficient, though. <<As of 2/96, the FDA has started to discontinue the sale of Dipyrone to veterinarians because of use/abuse in food animals. This will seriously hamper the treatment of FSF episodes in Shar-Pei and practitioners are urged to write and ask them to reconsider.>> Most patients on colchicine (see below) have a reduced frequency of fevers, but a few do not and may require continued intermittent treatment for fever events.

I was incorrect about dipyrone's mechanism of action (MOA) then but it would be more than 10 years before the underlying pathogenesis of the autoinflammatory disorder in Shar-Pei would begin to be unraveled. Subsequent research into dipyrone's MOA has shown it has complex systemic effects. Members of the faculty of Veterinary Medicine in Olsztyn, Poland published an excellent 2014 review of the current knowledge of the pharmacological characteristics of dipyrone in people and animals but unfortunately omitted the emerging data about dipyrone's effects inhibiting IL-1β.[12] They do excerpt however that "metamizole can block both PG (prostaglandin)-dependent and PG-independent pathways of fever induced by LPS, which suggests that this drug has a profile of antipyretic action distinctly different form that of other COX inhibitors, which could be advantageous in treating fever." [13] Shar-Pei autoinflammatory fever follows PG-independent pathways involving IL-1β, IL-8 and IL-6, explaining why COX inhibitors have lesser effects on downstream inflammatory pathways.

We continued to obtain dipyrone compounded from bulk drug after the December 6, 1995 FDA-CVM Update that described why extra-label use of dipyrone was not permitted in food animals and Novin® and other injectable dipyrone products were subsequently taken off the market in the U.S. and not available to equine or small animal practitioners for use in non-food animals. Dipyrone was the only drug that would reduce the life-threatening, often recurrent, fevers in many Shar-Pei patients. Without dipyrone, therapy of acute high fever was less likely to be successful, treatment was prolonged by as much as days without resolution of the fever and financial costs were dramatically higher to the owners.

The United States has banned the use of dipyrone in humans and prohibited its use in food animals. Dipyrone is widely administered as an antipyretic drug in Europe, Asia, Africa and South America. Its clinical usage in human medicine is prohibited here due to the association with agranulocytosis. The frequency of the latter syndrome, a deficiency of innate immunity, is 3-19 per million among human

patients given dipyrone. Shar-Pei suffer from abnormally increased innate immunity activity. The pro-apoptotic effects on myelocytes are usually seen at high, prolonged doses in geriatric people but immune-allergic reactions may be seen in some humans without prior exposure. Injectable dipyrone is rarely given more than once or twice during an event and there is no reason to give doses beyond standard recommendations to achieve desired results in Shar-Pei. The use of the drug remains controversial worldwide. It is available over-the-counter as a common headache therapy in some countries like Israel, Brazil and Mexico, available only by prescription in others (e.g. Germany) and completely banned in Sweden and the United States, among others.

The 2010 North American Companion Animal Formulary reported the canine dosage to be 25-100mg/kg IV, SC, PO, IM q8-24h. Most Shar-Pei weigh approximately 20 kg. 25mg/kg X 20kg = 500mg. Dipyrone is most commonly compounded into a 50% solution for injection of 500mg/ml. Most Shar-Pei respond to a total of 250-500 mg dipyrone administered subcutaneously, a very low dose.

Analgin 30%, an injectable solution of 300 mg/ml metamizole (dipyrone), is registered internationally for use as a veterinary product. Their label recommends 100-200 mg/kg as a dosage for dogs and cats.

Novin® and other commercially prepared injectable dipyrone products had a label describing correct dosage use in dogs and cats for many, many years. I was unable to locate any reports of adverse reaction, particularly agranulocytosis, in non-human species.

I have not had any adverse reactions in my patients or reported to me through members of the Shar-Pei community except possible subsequent gastric ulcers, something sometimes seen after FSF fever regardless of what, if any, treatment has been used. It has been very safe. My only concern with the drug is that if the fever is due to an underlying infection, appropriate antibiotic therapy may be delayed and the immune reaction inappropriately suppressed if dipyrone alone is administered in these cases. I am very selective in what clients/patients receive a prescription for dipyrone and they are carefully educated in when/how to give the injection and to contact us immediately. The drug is most needed in the hospital situation for emergency fever. It needs to be already on the shelf so that it can be administered immediately. It is not a drug that can wait for arrival from a compounding pharmacist next week.

Colchicine, the drug most commonly used for prophylaxis, is not a substitute for dipyrone in most FSF patients with a history of very high fever. Many of the dogs with fever exceeding 106 are already on colchicine, either compounded or through Takeda's Patient Assistance Program for Shar-Pei Fever. Dipyrone is the life-saving rescue drug and without any similar replacement.

In humans with Familial Mediterranean Fever or other autoinflammatory diseases whose symptoms are not controlled by colchicine, another option is available that cannot be used by dogs. Anakinra (Kineret®), an IL-1 receptor antagonist, has been a game-changer in human autoinflammatory disease. The anakinra molecule is a recombinant, non-glycosylated version of human (species-specific) IL-1RA and is also prohibitively expensive. It is not an option for these dogs.

Mild fever events are often treated with prescription oral meloxicam, aspirin or other NSAIDs to reduce inflammation and provide pain relief. These drugs are ineffective antipyretics in the face of high fever in this disorder and more aggressive measures including IV fluid therapy and colonic enemas are sometimes needed if dipyrone is not available. Shar-Pei Fever can be fatal and dipyrone needs to be readily available for emergency treatment. I strongly believe it should be on the shelf of every emergency hospital and wherever Shar-Pei patients are routinely seen.

Other supporting papers that review the veterinary use of dipyrone in dogs have been published in the last 5 years. In one, dosages of 15, 25 and 35mg/kg dipyrone were administered IV to dogs for post-ovariohysterectomy analgesia and compared to placebo. The authors' objectives included observing for adverse effects that could be associated with administration and the only one observed was vomiting in the first 6 post-op hours. There were no changes in laboratory parameters. A dose of 25-35mg/kg was most effective.[14] Dipyrone was also studied as part of therapy along with tramadol +/- other NSAIDs for severe chronic pain treatment in 69 dogs with cancer. No adverse events (including no agranulocytosis) were recorded in this population of mostly 10-14 year old dogs with cancer.[15] Another study of tramadol alone or in combination with meloxicam or dipyrone in dogs undergoing mastectomy showed little to no benefit of adding meloxicam or dipyrone to tramadol for multimodal pain control.[16] They reported no adverse events. Dipyrone and meloxicam or the combination of both on hemostasis in conscious dogs was examined.[17] Dipyrone inhibited platelet aggregation for up to 3 hours without impacting the viscoelastic properties of the blood clot nor increasing risk of bleeding.

In summary, Dipyrone is not a drug for prophylaxis in SPAID. Dipyrone is used in emergent situations where the fever is spiking rapidly, is already approaching or exceeding 106°F or in patients with a history of fever over 106°F in the past. In the latter group, the drug is administered as soon as fever or prodromal signs typical for the patient are detected. Dipyrone is an injectable medication compounded from bulk drug and must be on-hand when it is needed because the dog is suffering and its life is in serious danger. Approximately 24% of Shar-Pei will experience at least one fever event during its lifetime. Many Shar-Pei with fevers can be managed with aspirin or other NSAIDs.

My concern is for the subset that have rapidly developing hyperthermia due to priming and activation of the inflammasome leading to IL-1β release and whose fevers can exceed 106°F degrees in less than one hour from onset. Dipyrone is an IL-1β blocker that blocks the pathway much earlier in the inflammatory cascade than NSAIDs and has been much more effective and reliable in resolving the high fever. It will often drop a Shar-Pei's temperature one or two degrees within an hour if administered early enough in the cascade. It can save their life.

Yours Truly,

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