

THE FASCINATING STORY OF PERCORTEN®-V *(desoxycorticosterone pivalate, or DOCP) INJECTABLE SUSPENSION*

DOCP: Developed to save human lives

Addison's disease (hypoadrenocorticism) is a relatively uncommon condition, first described in 1885 by Dr. Thomas Addison, the "Father of Endocrinology." Although Addison's disease is not well known, some very well-known people have suffered from it. Undoubtedly, the most famous was President John F. Kennedy.

In patients with Addison's disease, the adrenal glands do not function properly and the body is unable to produce normal amounts of certain hormones – the mineralocorticoids and glucocorticoids. The disease can be fatal if not treated. During President Kennedy's lifetime, the only known treatment was a medication called desoxycorticosterone pivalate (DOCP, trade name PERCORTEN®). President Kennedy's life depended on injections of this product every 25 days.

In the late 1960's, an oral drug was developed for Addison's disease in humans and doctors stopped prescribing DOCP injections. Over the next 20 years, sales fell so low that the manufacturer, Ciba-Geigy, decided to discontinue it. When the company notified their distributors of this decision, they suddenly heard an uproar from veterinarians who had been using the product to treat *dogs* with Addison's disease! The veterinarians reported that the results were exceptional and that dogs' lives would be at risk if the product were to be discontinued. This was all new information to Ciba-Geigy. At that time, they had no idea that the product was being used to treat dogs.

Ironically, the canine form of Addison's disease touched another First Family: President Reagan's daughter had a dog that suffered from it, and was being treated with regular injections. The presidential family also expressed concern when notified that the supply of DOCP could be discontinued.

An act of compassion

The FDA had no studies on the safety or effectiveness of DOCP in dogs and therefore could not allow it to be labeled and sold as a canine medication. However, the FDA knew that, without it, the dogs that had been using it could die. In order to supply those dogs, the FDA asked Ciba-Geigy Animal Health (now Novartis) – a company that had no products for dogs at the time – to conduct a research trial in which the drug could be made available to select patients. Ciba-Geigy applied for an "Investigational New Animal Drug" (INAD) status and was granted permission for a "compassionate use" only status, allowing them to provide it to those that needed it. The people at Ciba-Geigy Animal Health understood the very limited market potential for the product. But, knowing the life-saving nature of the medication, they felt there was only one choice—they had to do it.

At the outset of the trials, Ciba-Geigy gathered all the available DOCP from their facilities worldwide, and shipped it to their researchers in Greensboro, North Carolina. At that time (1989) the whole world's entire supply of DOCP was kept in a small container secured at their distribution facility.

Research phase

For nine years, Ciba-Geigy / Novartis maintained DOCP in "investigational status" as a not-for-profit research drug, studying more than 1,000 clinical cases. Scientists learned a great deal about canine Addison's disease. Among other things, they observed that it is more prevalent

among females than males, and is seen most frequently among mixed breeds, Poodles, Labrador Retrievers, Great Danes, West Highland Terriers and Rottweilers**.

In 1998, the FDA granted Novartis marketing approval, allowing them to manufacture, sell and distribute DOCP under the brand name PERCORTEN-V* (the "V" indicates "veterinary"). It is the only drug approved for the treatment of canine Addison's disease but, because the disease is diagnosed infrequently (1-3 cases per 1000 dogs**), the demand for PERCORTEN-V is small.

It has been demonstrated that PERCORTEN-V is well tolerated with a low incidence of side effects. In a small percentage of dogs, depression, excessive thirst and urination, digestive, skin and coat changes, weakness, and injection site reactions (pain, abscesses) may occur. Some of these effects may resolve with adjustments in dose or interval of PERCORTEN-V or concomitant glucocorticoid administration. It should not be used in pregnant dogs or dogs that are suffering from congestive heart disease.

A complex manufacturing process

PERCORTEN-V is difficult and costly to manufacture. It begins with a hormone, extracted from natural sources, and modified through a complex chemical process. Quality control on pharmaceutical hormones is always critical, because hormones have such a profound effect on the body. Every production lot must be rigorously tested to meet strict standards, with almost no tolerance for error, as variances may require an entire lot to be destroyed.

Production of PERCORTEN-V is a challenging process. Novartis has worked with several different production facilities in its efforts to manufacture the product more efficiently. In addition, because Addison's disease affects a relatively small number of dogs, only a small amount of PERCORTEN-V is needed each year. This low volume, together with the high production costs, results in a high cost per unit. PERCORTEN-V accounts for a small percentage of total sales and profits for Novartis Animal Health. However, despite this, Novartis is committed to maintaining the supply of this drug for those dogs that depend on it.

A delicate balance

The outward signs of canine Addison's disease - vomiting, diarrhea, excessive thirst, loss of appetite, and depression - are so common among dogs that they might signal a whole host of other canine diseases. An astute veterinarian who suspects Addison's disease will perform blood tests in order to make a definitive diagnosis.

By law, PERCORTEN-V may be used only by or on the order of a licensed veterinarian. This is extremely important for the well being of the dog. The chemical balance affected by the disease is so delicate that Addisonian patients must be carefully monitored on an ongoing basis. A veterinarian may sometimes see the need to adjust the dosage of PERCORTEN-V, followed by a physical exam and laboratory tests to see how the dog is responding.

For additional product information, please see attached product insert.

The happy ending to the story is that with regular medication, diligent monitoring, and ongoing veterinary care, dogs with Addison's disease can live a long, happy, active life.

*NADA #141-029, Approved by the FDA

** Data on file, Novartis Animal Health

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