ABSTRACTS

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THE DEVELOPMENT AND USE OF DESLORELIN IMPLANTS TO SUPPRESS FERTILITY – A SYNOPSIS AND FURTHER ADVANCES

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A new long acting form of the GnRH agonist deslorelin was described to this conference in Norway in 2000 and updated in Brazil in 2004. Since then development progress has been steady with the 6 month version, containing 4.7mg deslorelin (Suprelorin 6\(^®\); S6) recently approved for sale in Europe. In Australia and New Zealand S6 has been available since 2005 and the longer acting Suprelorin 12\(^®\) (S12), the 12 month version, containing 9.4mg deslorelin and approved in Australia for 18 months. Both configurations have been used successfully to label, and in various off label indications, and research and development is being undertaken to add to the number of approvals and to extend the indications for the drug. A series of trials were undertaken in more than 270 dogs for single dose use or repeated use of deslorelin for the contraception of dogs. Doses ranged from 3 to 12 mg per animal per dose and the same dose has been repeated up to six times in 10 dogs. These studies have been presented previously (1, 2) as have studies with bitches involving 145 animals (1, 3). Other indications have also been examined including delaying puberty and treating hormone dependant diseases including BPH and anal adenomas. Urinary incontinence, discussed elsewhere at this conference has also been treated by deslorelin (4) and other GnRH agonists. The drug has also been used widely in contraception of wildlife and exotic species worldwide and the treatment of adrenal cortical disease in ferrets.

This paper will provide a synopsis of the research and development undertaken to achieve the registered claims of the technology and will examine research data and observations obtained in the development of further indications. Drug safety information including data collected from laboratory and field studies and from over three years commercial use will be reported.

New Studies for Extended claim Approval

Suprelorin 12\(^®\)

The S12 product formulation was developed to act for at least 12 months and was relatively unchanged from the successful S6 product and manufactured using the same components. As with the development of S6, content was kept constant to avoid having a technology based on several different formulations. Twenty five male dogs of mixed breeds and ranging from 7.8 to 32.7 kg were used in a dose finding and proof of concept trial previously reported (2). Subsequently 35 male dogs ranging in age from approximately 17 months to 5-7 years and weight from 7.8 to 32.6kg were used in pivotal studies, conducted under GCP guidelines, to confirm the dose selected from previously tested doses. The animals were divided into 3 treatment groups of 10 and 1 placebo group of 5. Dogs in each treatment group were implanted subcutaneously with one of three independently manufactured batches, each implant containing 9.4mg deslorelin. This resulted in an individual dose of deslorelin ranging from 0.29 to 1.22mg/kg. Twice daily health checks were made and weighing, blood sampling for testosterone measurement were made twice in the first month, monthly to week 44, then fortnightly to week 60 then monthly thereafter. The main criterion of fertility was based on testosterone levels being <1ng/ml for >12 months, however scrotal circumference was also measured as a non-invasive method of monitoring activity of the drug. Dogs were withdrawn from the trial when plasma testosterone reached >1 ng/mL. Plasma testosterone was undetectable by week 8 in all except 2 treated dogs, one of which reached zero at week 12 and the other rose markedly after treatment then dropped to zero at week 16. No treatment-related
reactions or adverse symptoms were observed. At least 12 months suppression of plasma testosterone was demonstrated by all except 2 treated dogs, one of which was lost to the study on day 68 due to snake bite. Another dog showed rapid and complete suppression from Weeks 2 to 20 but recovered by week 24. Surgical exploration for the implant site at the time of withdrawal failed to locate the implant, and it is speculated that the implant was lost from this dog. Minimum and maximum individual duration of efficacy was 56 and 132 weeks respectively with a mean of 89 weeks.

References