

Review Memo Veterinary Services, December 5, 2013 - Ruconest

DATE: December 5, 2013
FROM: John Dennis, DVM, MS, DACLAM, Director of DVS
THROUGH: Carolyn Wilson, PhD, Associate Director for Research, CBER
SUBJECT: Review Memo for Recombinant C1 Esterase Inhibitor (C1EINH, Ruconest®)

STN 125495\0\3

RECOMMENDATION

Approval

CONCLUSION

A genetically engineered rabbit line has been developed to excrete in its milk the recombinant human blood protein C1EINH. Isolation and maintenance of the rabbit colony, breeding strategy, -----(b)(4)-----, milk collection and processing, animal health and product quality assurance are well-described in the submission. Early steps of product development and manufacturing are consistent with currently recognized best practices, based on details provided in the submission.

BACKGROUND

Hereditary angioedema is a serious inherited disorder caused by functional deficiency of C1INH activity. Loss of regulation provided by this plasma protein results in acute angioedema attacks in which other vasoactive peptides increase vascular permeability causing severe swelling of various tissues, including the airways. For the product being reviewed, the active ingredient is produced in the milk of genetically-modified rabbits, maintained as a closed colony in -----(b)(4)---. Rabbits are managed to allow (b)(4) milk production and collection, and the product in the -----(b)(4)----- milk is purified, and lyophilized. There are three other recently-FDA-approved, synthetic products available for acute treatment of this same condition. Advantages of the post-translation processing of the generated human protein in the rabbit mammary gland could allow this product to have unique and advantageous activity compared to alternatives.

Transgenic rabbits have been developed to a limited extent as models for a few human disease conditions and for only one other known pharmaceutical product.

REVIEW

Animal-related procedures, colony maintenance, and skimming of milk take place at -----(b)(4)-----.

----- (b)(4) -----

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----- (b)(4) -----

Diagnostic Tests for these agents are included in ----(b)(4)---- screenings (all negative)

Milking procedures involving (b)(4) are described, as well as strategies to maximize milk yields, including (b)(4). Milk is not collected from animals with observed health problems or weight loss, and no medicinal treatments (b)(4) are given to rabbits. Husbandry, nutrition, animal medical care and animal welfare are consistent with current standards, as a justification for (b)(4) housing of animals could be made, if requested.

Risk of contamination of the purified product is minimized by

1. Control of animal facilities and animal husbandry
2. Animal health monitoring and diagnostics
3. Screening of skimmed milk intermediate for adventitious viral contaminants, and
4. Viral clearance by the purification process.

The -----(b)(4)----- assay is sensitive to a wide number of rabbit and human viruses, including (b)(4) relevant zoonotic agents identified through risk analysis (including -----(b)(4)-----).