

Supervisory Memorandum

Date: 11/25/2019

From: Ilan Irony, M.D.

To: BLA 125685 (original submission) file

Re: Enzyvant's RETHYMIC (allogeneic cultured post-natal thymus tissue)

This memorandum complements the clinical review. We acknowledge Dr. Winson Tang's contribution to the review and the review memo. Dr. Tang departed FDA before he was able to sign his review, and the document was finalized and signed by Dr. Elizabeth Hart, acting team leader and by myself.

I emphasize here the clinical review team's conclusion that their recommendation for approval is based on a favorable benefit risk profile for RETHYMIC. The benefit of this product is based on substantial evidence of effectiveness gathered from 7 main studies and supported by 3 expanded access-treated subjects. Although these studies were designed and conducted as single arm studies without randomization to a concurrent control group, the applicant provided to the BLA historical comparator mortality data from patients with complete DiGeorge Anomaly; these control data are also consistent with more recent external control data, based on literature publications. The data show a large effect size on survival, with 75% (95% confidence interval [0.65,0.83] survival rate in RETHYMIC treated subjects at 2 years against a background of almost universal mortality by 2 years of age in the same population. This is strong evidence that RETHYMIC, and not bias or natural phenotypic variability, is the responsible for the T cell reconstitution and survival.