Division Director Memo
Division of Clinical Evaluation and Pharmacology/Toxicology
Office of Tissues and Advanced Therapies

APPLICATION:	BLA 125703	**TRADE NAME:**	TECARTUS
APPLICANT/SPONSOR:	Kite Pharma, Inc.	**ESTABLISHED NAME:**	brexucabtagene autoleucel
SUBMISSION DATE	12/11/19		
PDUFA DATE	8/11/20	**PRODUCT CLASS:**	CD19-directed, genetically modified, autologous T cell immunotherapy
REVIEW DATE:	7/23/20	**ROUTE:**	Intravenous infusion

INDICATION: Treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL)

Review Team (for specified disciplines)

Clinical: Drs. Megan Zimmerman, Helkha Peredo-Pinto (under OCE oversight) **Statistical:** Dr. Xue Lin; **Pharm/Tox**: Dr. Gaya Hettiarachchi; **Clin Pharm**: Dr. Xiaofei Wang; **CMC**: Drs. Graeme Price, Jakob Reiser, Tal Salz

REVIEW SUMMARY:

Kite Pharma, Inc. submitted this Biologics License Application for licensure of brexucabtagene autoleucel (TECARTUS) for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (r/r MCL).

The primary evidence of safety and efficacy comes from Study KTE-102-C19 (ZUMA-2), a Phase 2, single-arm, open-label, multicenter, study that evaluated the safety and efficacy of brexucabtagene autoleucel in adults, 18 years of age and older, with r/r MCL, who were previously treated with bendamustine or an anthracycline, an anti-CD-20 antibody and a Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib and/or acalabrutnib). The primary efficacy analysis evaluated the proportion of subjects with an objective response rate (ORR), defined as subjects with either a complete response (CR) or a partial response (PR) as assessed by an independent review committee (IRC). The primary analysis was based on the inferential analysis set (IAS), comprised of the first 60 subjects treated with brexucabtagene autoleucel at a target dose of 2×10^6 anti-CD19 CAR T cells/kg. FDA clinical reviewers' re-adjudication of response rates excluded 8 subjects. The FDA re-adjudicated ORR (52 subjects) was 86.7% (95% CI: 75.4, 94.1) and CR was 61.7% (95% CI: 48.2%, 73.9%). Median duration of response (DOR) for the IAS was 240 days. The safety analysis set included 82 subjects, with adverse events of special interest, cytokine release syndrome and neurotoxicity, reported in 91% and 80% of subjects, respectively.

Although ZUMA-2 demonstrated a quite favorable ORR and CR, two issues with respect to efficacy were identified by the review team: 1) follow-up of subjects was insufficient to allow for an adequate assessment of DOR to support traditional approval and 2) the proposed indication is broader than the population studied in ZUMA-2, which did not include any subjects who were BTK treatment naïve, a population that is encompassed in the proposed broader indication. Accelerated approval is supported based on intermediate clinical endpoints of ORR and preliminary DOR that are likely to predict longer term clinical benefit, with confirmatory post-marketing clinical studies to adequately assess DOR and evaluate safety and efficacy in BTK naïve patients.

Please see primary reviews from the clinical and statistical reviewers for details of the review. I concur with the review team's recommendation of Accelerated Approval with a Risk Mitigation and Evaluation Strategy (REMS) and conclude that the Applicant has provided substantial evidence of effectiveness and safety from an adequate and well controlled study supported by appropriate animal data to support Accelerated Approval for the proposed indication, and that the benefit/risk profile is favorable with implementation of a REMS for the serious life-threatening risks of CRS and neurotoxicity.

RECOMMENDED REGULATORY ACTION:

ACCELERATED APPROVAL

Tejashri Purohit-Sheth, M.D.
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