Addendum to the FDA Briefing Document

Anesthetic and Analgesic Drug Products Advisory Committee Meeting

October 11, 2018

This addendum contains additional information relevant to the October 11, 2018, Anesthetic and Analgesic Drug Products Advisory Committee Meeting. At this meeting, the committee will discuss oliceridine 1 milligram/milliliter injection, submitted by Trevena, Inc., for the management of moderate-to-severe acute pain in adult patients for whom an intravenous opioid is warranted.

In the FDA briefing document, there is a review of QT/QTc interval prolongation considerations. It is noted that the Applicant performed an additional ion channel evaluation of the two major human metabolites that were under review by the Agency. This addendum reviews the additional reports submitted by the Applicant to support the assessment of proarrhythmic risk of oliceridine, which contained additional preclinical information (results of the assessment of oliceridine and major metabolites on hERG, $Ca_V1.2$ and $Na_V1.5$) and clinical information (assessment of changes in QTcF, QTcI and J-T_{peak}c). FDA agrees with the Applicant that the additional preclinical data collected for the two major metabolites support that the metabolites do not inhibit hERG or $Ca_V1.2$. However, any potential effects of oliceridine on the late $Na_V1.5$ current are unlikely to impact the QTc observations. This is because oliceridine is rapidly cleared. Moreover, the submitted results for the QTc and J-T_{peak}c interval are not consistent with the drug being a mixed ion channel blocker as the changes in J-T_{peak}c tracks with QTc changes. The information provided suggests that the mechanism behind the delayed and dose-proportional QTc prolongation is not explained by direct inhibition of the hERG potassium channel by oliceridine or any of its major metabolites. Due to the uncertainty about the mechanism causing the observed QTc prolongation it is not possible to predict the QTc prolongation with the currently proposed dosing paradigm, which results in exposures of the major metabolites that exceeds the exposures following the highest dose in the thorough QT study (~2.4-fold for M22 and ~2.8-fold for TRV9198662).