Iwilfin™ (eflornithine) – New orphan drug approval

- On December 13, 2023, the FDA announced the approval of US WorldMeds' Iwilfin (eflornithine), to reduce the risk of relapse in adult and pediatric patients with high-risk neuroblastoma (HRNB) who have demonstrated at least a partial response to prior multiagent, multimodality therapy including anti-GD2 immunotherapy.

- Iwilfin is the first FDA approved therapy intended to reduce the risk of relapse in pediatric patients with HRNB.

- Iwilfin is an irreversible inhibitor of the enzyme ornithine decarboxylase.

- The efficacy of Iwilfin was established in an externally controlled trial comparing outcomes from Study 3b (investigational arm) and Study ANBL0032 (clinical trial-derived external control arm). Study 3b was an open label, non-randomized trial with two cohorts. A total of 105 eligible patients with HRNB from one cohort (Stratum 1) received eflornithine. Study 3b was prospectively designed to compare outcomes to the historical benchmark event free survival (EFS) rate from Study ANBL0032 reported in published literature.

    - The external control arm was derived from 1,241 patients on the experimental arm of Study ANBL0032, an open-label, randomized trial of dinutuximab, granulocyte-macrophage colony-stimulating factor, interleukin-2, and cis-retinoic acid compared to cis-retinoic acid alone in pediatric patients with HRNB.
    - Patients who met the criteria for the comparative analysis of Study 3b and ANBL0032, with complete data for specified clinical covariates, were matched using propensity scores; the matched efficacy populations for the primary analysis included 90 patients treated with Iwilfin and 270 control patients from Study ANBL0032.
    - The major efficacy outcome measure was event free survival (EFS), defined as disease progression, relapse, secondary cancer, or death due to any cause. An additional efficacy outcome measure was overall survival (OS), defined as death due to any cause.

- In the protocol-specified primary analysis, the EFS hazard ratio (HR) was 0.48 (95% CI: 0.27, 0.85) and OS HR was 0.32 (95% CI: 0.15, 0.70). Given the uncertainty in treatment effect estimation associated with the externally controlled study design, supplementary analyses in subpopulations or using alternative statistical methods were performed. In these analyses, the EFS HR ranged from 0.43 (95% CI: 0.23, 0.79) to 0.59 (95% CI: 0.28, 1.27), and the OS HR ranged from 0.29 (95% CI: 0.11, 0.72) to 0.45 (95% CI: 0.21, 0.98).

- Warnings and precautions for Iwilfin include myelosuppression; hepatotoxicity; hearing loss; and embryofetal toxicity.

- The most common adverse reactions (≥ 5%) with Iwilfin use were hearing loss, otitis media, pyrexia, pneumonia, and diarrhea. The most common grade 3 or 4 laboratory abnormalities (≥ 2%) were increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), decreased neutrophil count, and decreased hemoglobin.

- The recommended oral dose of Iwilfin is based on body surface area (BSA).

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BSA (m^2)	Dosage
> 1.5	768 mg (four tablets) orally twice a day
0.75 to 1.5	576 mg (three tablets) orally twice a day
0.5 to < 0.75	384 mg (two tablets) orally twice a day
0.25 to < 0.5	192 mg (one tablet) orally twice a day

- US WorldMeds plans to launch Iwilfin in the coming weeks. Iwilfin will be available as a 192 mg tablet.