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RESEARCH**

APPLICATION NUMBER:

204417Orig1s000

NON-CLINICAL REVIEW(S)

January 26, 2015

Review and Evaluation of Pharmacology and Toxicology
Nonclinical NDA Review

NDA: NDA 204-417
Sponsor: Sun Pharma
Received: May 29, 2012
Drug: Levetiracetam Extended-Release Tablets
Indication: Epilepsy

Evaluation:

This application seeks the same indication, dose, route, and duration of administration as those of the reference product, Keppra XR. No nonclinical studies were provided. The excipients in this product have all been used in approved oral drugs at similar levels; all excipients except polyvinyl alcohol fall below the IIG limit for oral administration. While the proposed amount of polyvinyl alcohol per unit dose is within IIG levels, the total daily amount exceeds the IIG levels, so a safety assessment was provided. This information, which includes reports of in vitro and in vivo genotoxicity studies, acute and subchronic (up to 90 days) oral toxicity studies in rats, mice, and dogs, and a two-generation reproductive toxicity study in rats, shows no evidence of genotoxicity and no adverse toxicological or reproductive effects at doses of up to 5000 mg/kg/day (highest dose tested). Polyvinyl alcohol is GRAS for use in dietary supplements with an estimated daily intake of up to 180 mg/day. The FAO/WHO acceptable daily intake (ADI) for polyvinyl alcohol is 50 mg/kg/day (JECFA, 2003). Therefore, there is no safety concern associated with the daily amount in this product (approximately 60 mg/day at the maximum recommended daily dose of 3000 mg/day). The proposed specifications for all impurities are within the ICH limits. As agreed at the pre-NDA meeting, Sun conducted a search of the published literature. No new nonclinical information pertaining to safety was identified. Thus, no changes to the nonclinical sections of the label are planned.

Recommendations:

The application is approvable from a pharm/tox standpoint.

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/s/

J EDWARD FISHER
01/26/2015

LOIS M FREED
01/26/2015