Mallinckrodt Pharmaceuticals

15 July 2016

Sharon Hertz, M.D.
Director, Division of Anesthesia, Analgesia, and Addiction Products
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

**RE: NDA 204,031; SN 0042**
**RESPONSE TO PREA NON-COMPLIANCE LETTER**
**DEFERRAL EXTENSION REQUESTED**

**Attention: Swati Patwardhan, Regulatory Project Manager**

Dear Dr. Hertz:

On April 25, 2016 the Agency issued a Notification of Non-Compliance with PREA Letter pertaining to PMR 2131-1. The letter noted that the final study report for MNK15000300 was not submitted by March 31, 2016 as required under the PMR.

Mallinckrodt is actively recruiting clinical investigators and patients for study MNK15000300 titled "*A Phase 4, Open-Label Study of the Pharmacokinetics and Safety of XARTEMIS® XR (7.5 mg Oxycodone Hydrochloride/325 mg Acetaminophen) in Postsurgical Adolescent Subjects (Ages 12 to 17) with Moderate to Severe Acute Pain*." This study is intended to fulfill PMR 2131-1. The protocol for Study MNK15000300 was included as part of the initial Pediatric Study Plan (iPSP) submitted with the Xartemis XR NDA and FDA provided comments and agreement on the study design prior to study start.

Mallinckrodt has experienced challenges in recruitment of clinical investigators for this study that have caused a significant delay in the conduct of the study. Despite considerable efforts to recruit qualified and experienced clinical investigators, a significant portion (~93%) of the investigators contacted has either declined to participate or have not responded. Several investigators provided specific reasons for declining the study. While some investigators declined for reasons related to staff capacity or available patient population, a high number of investigators declined for reasons related to the study design including the number of blood draws, inclusion/exclusion criteria, "difficult study design", and length of hospital stay. The latter set of reasons is addressable through modification of the study design. Therefore, Mallinckrodt is proposing to amend the study protocol in order to address these concerns and encourage more investigators to participate in the study. These changes will increase the likelihood of successfully completing the study while maintaining the quality of data obtained. In parallel with this submission, Mallinckrodt is submitting a draft protocol amendment to the Xartemis XR IND (104,702) for Agency review and comment. It is Mallinckrodt's intention to reach agreement with the Agency on a modified study design that will be acceptable to clinical investigators and provide the information needed to fulfill PMR 2131-1.

Mallinckrodt is fully committed to completion of the postmarketing requirements for Xartemis XR. Due to the unanticipated delays caused by difficulty recruiting clinical investigators, Mallinckrodt anticipates submission of the final study report by (b) (4) Section 1.9.2 of this submission includes a deferral extension request for pediatric studies with Xartemis XR to take into account the anticipated completion date for study MNK15000300 (b) (4)
(b) (4)

This submission is submitted in electronic format as eCTD SN 0042 via the Electronic Submissions Gateway. The submission has been checked and found free from virus infection using Trend Micro™ OfficeScan™ v10.6. For technical information related to this submission, please contact Juanito Baladad, Manager, Regulatory Operations, at 314-654-6107.

If you have any questions or need additional information, please contact me by telephone at 919-469-3574 ext 53511 or by email at jason.mercer@mallinckrodt.com. You may also contact Jennifer Weidman, Senior Director, Regulatory Affairs, at 919-469-3574 ext 53515 or by email at Jennifer.weidman@mallinckrodt.com.

Sincerely,

Jason Mercer, PhD, RAC
Manager, Regulatory Affairs

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page