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April 24, 2015

William Dunn, M.D., Director
Division of Neurology Products
Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
White Oak CDER Office Building 22
Silver Spring, MD 20993

Re: Zanaflex Capsules®, 2 mg, 4 mg and 6 mg
NDA 21-447 / 0139
RESPONSE TO PREA NON-COMPLIANCE LETTER

Dear Dr. Dunn,

Zanaflex is a central alpha-2-adrenergic agonist indicated for the management of spasticity in adults. Reference is made to NDA 21-447 for Zanaflex (tizanidine hydrochloride) Capsules, 2 mg, 4 mg, and 6 mg and the August 29, 2002 NDA approval letter to Elan Pharmaceuticals (original NDA holder) outlining the pediatric post-marketing requirements (PMRs) and the pediatric assessment date of December 31, 2005. Reference is also made to the Division of Neurology Products (Division) Deferral Extension Denied letters, of September 19, 2014 and March 3, 2015 and the Division's March 19, 2015 Notification of Non-Compliance with PREA letter.

Acorda Therapeutics, Inc. (Acorda) is providing a written response to the Division's March 19, 2015 Notification of Non-Compliance with PREA letter outlining the good faith efforts and due diligence to complete the original PREA pediatric assessment (studies) that were outlined in the August 29, 2002 NDA approval letter and in the Division's Written Request letter dated December 20, 2012. The chronology of key communications demonstrating the work Acorda completed on the pediatric PMR studies and justification as to why a deferral of the original pediatric assessment date of December 31, 2005 should have been granted are provided below.

After the Agency's initial pediatric program request in the August 29, 2002 NDA approval letter for completion of pediatric studies in patients by December 31, 2005, the NDA 21-447 was transferred from Elan Pharmaceuticals to Acorda on July 21, 2004. From the time of approval until the NDA was transferred to Acorda (a period of approximately 3.5 year), the original NDA holder did not develop any protocols or initiate any studies to satisfy the pediatric PMR assessment and thus, the pediatric assessment date of December 31, 2005 already was impractical for Acorda to meet. However, Acorda initiated and completed a retrospective pediatric safety study AT02-ZC-01 and a pediatric pharmacokinetic (PK) study AT06-ZC-02, and submitted reports of these to NDA 21-447 on April 7, 2008 with the belief that this work satisfied the pediatric PMR in the NDA approval letter. Following submission

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of the study reports, Acorda was notified by the Division, in 2008, that the Zanaflex Capsules pediatric program was now subject to the Pediatric Research Equity Act (PREA), and therefore, additional studies would be required.

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In June 2011, the Division informed Acorda that it would be rescinding the pediatric PMR in the August 29, 2002 NDA approval letter and would be issuing new pediatric PMRs via a Written Request letter. Although the Written Request was not formally issued until December 20, 2012, Acorda began working on the nonclinical requirement identified by the Division in July, 2011 for a juvenile toxicity study and had completed conduct of the study by the time that the formal Written Request letter was received in December 2012.

To provide further context to Acorda's response, reference is made to the Deferral Extension Notice letter dated November 5, 2012 from FDA's Pediatric and Maternal Health Staff, Office of New Drugs, Center for Drug Evaluation and Research branch, that informed Acorda that a deferral extension of the original pediatric assessment date in the NDA approval letter of August 29, 2002 could be requested prior to January 5, 2013. Acorda submitted the Deferral Extension request to NDA 21-447 on January 4, 2013. In response to this request, the Division issued a Deferral Extension Denied letter on September 19, 2014 that stated:

> *"You have not made any good faith attempts to conduct the required studies" and that "you have not provided a rationale or justification regarding why the studies have not been conducted."*

Acorda respectfully disagreed with these statements. Acorda engaged in substantial activities to satisfy the applicable pediatric program requirements, and worked with the Division to ensure that the steps that were taken met its expectations, a brief description of which follows.

As noted above, on December 20, 2012, the Agency issued a Pediatric Written Request letter for tizanidine hydrochloride capsules outlining the pediatric PMR studies to be conducted;

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Separately from the pediatric request, in February 2011, the FDA advised Acorda that a Tracked Safety Issue had been created in CDER's Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) to provide a comprehensive regulatory history of the potential safety issue of QT prolongation in patients. In addition, in a telephone call on June 14, 2011 and a formal postmarketing requirement (PMR 1808-1) letter received on August 24, 2011, the Division advised that an additional PMR was being implemented for a thorough QTc study for tizanidine. Because of this potential safety concern, Acorda informed the Division in several correspondence that it would be placing any further studies in pediatric patients (and the pediatric PMR studies) on hold until data from the thorough QTc study was available to confirm that there was not a potential safety risk of QT prolongation from use of tizanidine in the pediatric population.

Acorda worked with the Division to reach agreement on a protocol design for the thorough QTc study between September 23, 2011 and March 1, 2013 that included multiple interactions (i.e., emails, written correspondence and phone calls). Acorda began implementation of the thorough QTc study once agreement was reached with the Division, but, due to the length of time that it took to obtain approval to initiate the thorough QT study,

the pediatric clinical PMR study could not begin in the timeline that was initially proposed to FDA via email in July 2011, (b) (4) because, as noted above, Acorda believed that it should not begin any additional clinical studies in a pediatric population until this potential cardiovascular safety issue was better understood.

This issue with study sequencing was described in Acorda's January 4, 2013 Deferral Extension Request letter submitted to NDA 21-447 in sequence 0121 on January 4, 2013. Acorda proposed in this Deferral Extension request to have a final PK/PD protocol to the Agency in February 2015. This date was proposed as it allowed time for the thorough QTc study to be completed (as per PMR 1808-1). As discussed above, in order to avoid possible undue safety risks to pediatric patients Acorda needed to obtain the data from the QTc prolongation study before completing the draft pediatric protocol. Acorda received a Deferral Extension Denied letter from the Division dated September 19, 2014, prior to the submission of the thorough QTc study report. The thorough QTc program spanned a period of approximately 3.5 years beginning with the initial discussions with the Division in June 2011, approximately 15 months to reach agreement on the final protocol and 16 months for study conduct and completion of the of the final QTc study report for ZAN-QT-1006 which was submitted to NDA 21,447 in sequence 0136 on November 24, 2014. This report is under review and as of the date of this letter, comments have not been received from the Division.

In response to the Division's Deferral Extension Denied letter of September 19, 2014, Acorda submitted a Request for Reconsideration of Denial of Deferral Extension letter to NDA 21-447 in sequence 0133 on October 14, 2015. This request included a detailed list of the steps that Acorda has taken towards completion of the pediatric program and the thorough QTc study p were itemized along with revised proposed milestone dates, details of correspondence and activities that justified the revised proposed milestone dates for the pediatric PMRs. The Division then issued another Deferral Extension Denied letter dated March 3, 2015. Based on the two Deferral Extension Denied letters that were received it appeared that the Division did not believe that it was important to complete the thorough QT study prior to exposing pediatric patients to the potential safety issue of QTc prolongation.

Acorda remains puzzled by inconsistent communications from FDA related to the pediatric program requirements and the due dates. The August 29, 2002 approval letter for NDA 21-447 required a pediatric assessment of safety and effectiveness in patients under 16 years old citing a deferral date of December 31, 2005. This commitment was rescinded in June 2011 and supplanted by commitments outlined in the Written Request letter of December 20, 2012. (b) (4) However, the Division's Deferral Extension Denied Letters of September 19, 2014 and March 3, 3015, as well as the Notice of Non-Compliance letter, continue to cite the original deferral date for the pediatric assessments as December 31, 2005, and the original patient population as 0-16 years old. Acorda does not believe that it is in non-compliance (b) (4)

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[redacted]

Acorda remains committed to fulfilling the post-marketing requirements under PREA and to completion of the studies requested by the Division as outlined in the Written Request letter of December 20, 2012. (b) (4) [redacted]

(b) (4) [redacted]. Therefore, separately Acorda is submitting a pediatric waiver request for the balance of the pediatric PMR studies.

If you have any questions or comments concerning this submission, please contact me by telephone (914) 326-5739; cell phone (914) 606-2450; email wpfister@acorda.com; or fax (914) 606-9507.

Sincerely,

William Pfister

William Pfister, Ph.D.
Senior Director Development, Regulatory Affairs

Desk copies (letter): Pediatric and Maternal Health Staff, Office of New Drugs
Taura Holmes, PharmD, Regulatory Project Manager (via e-mail)

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