FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE
10903 New Hampshire Ave, Building 22, Silver Spring, MD 20993

Clinical Review of Prior Approval Supplements/Efficacy

NDAs/Supplement Nos.:	NDA 022304/S-028, NDA 203794/S-013, NDA 200533/S-029
Supporting Document Nos:	828, 112, 913
Drug Names:	Nucynta (tapentadol) tablets, Nucynta (tapentadol) oral solution, Nucynta ER (tapentadol) extended-release tablets
Sponsor:	Collegium Pharmaceutical, Inc.
Type of Submissions:	Prior Approval Supplements - Efficacy
Date of Submissions:	December 15, 2023; with an amendment submitted on January 9, 2024, and a response to an information request submitted on February 9, 2024, to each NDA.
Date of Review:	June 11, 2024
Reviewer:	Lisa Wiltrout, MD
Team Leader:	Nancy Dickinson, PharmD
Division Director:	Rigoberto Roca, MD
Project Manager:	Wanda Nguyen, PharmD

Background

Collegium Pharmaceutical, Inc. (Collegium) submitted three prior approval supplements with an annotated Written Request (WR) and a pediatric exclusivity determination request for tapentadol on December 15, 2023. The supplements did not include any new pediatric data or labeling for review by the Division. Collegium referenced instead to pediatric data included in NDA 022304/S-024 and NDA 203794/S-010, two supplements previously submitted to the Agency for review in October 2022, to fulfill Studies 1-4 in WR Amendment #5, and the pediatric labeling text for Nucynta tablets and Nucynta OS approved on July 3, 2023.

Tapentadol hydrochloride (HCl) is the active pharmaceutical ingredient in all Nucynta products. Tapentadol is a centrally acting, synthetic analgesic agent. Its exact mechanism of action is unknown. Preclinical studies have shown that tapentadol is a mu-opioid receptor agonist and a norepinephrine reuptake inhibitor. Both factors contribute to the analgesic effects of the compound. Tapentadol is a Schedule II controlled substance with a safety profile typical of an opioid. Given its structural similarity to tramadol, tapentadol has pharmacological effects similar to tramadol and, therefore, may increase the risk of seizures in patients with seizure disorders and may cause serotonin syndrome when used concomitantly with serotonergic drugs. Additionally, adverse reactions of hallucination and suicidal ideation have been reported in the post-marketing experience with tapentadol in adults.

Nucynta tablets and Nucynta OS are immediate-release (IR) formulations of tapentadol indicated for the management of moderate to severe acute pain. Nucynta tablets and Nucynta OS are bioequivalent. Nucynta ER tablets are an extended-release (ER) formulation of tapentadol indicated for the management of moderate to severe chronic pain when a daily, around-the-clock, long-term opioid analgesic is needed.

Pediatric Clinical Development Program for Tapentadol

The Sponsor conducted the tapentadol pediatric clinical development program over a period of approximately 15 years with the goal of using data from one program to fulfill not only the pediatric investigation plan requirements for tapentadol as established by the Pediatric Committee of the European Medicines Agency (EU PDCO) but also the Pediatric Research Equity Act (PREA) post-marketing requirements (PMRs) and the WR for NDAs 022304, 203794, and 200533 as issued by the Agency.

The Sponsor conducted three open-label, single-dose, pharmacokinetic (PK) and safety studies (KF5503/59, KF5503/68, and KF5503/72) and one randomized, placebo-controlled, multiple-dose, efficacy, and safety study (KF5503/65) using tapentadol OS in pediatric patients from birth to less than 18 years of age with acute post-operative pain to fulfill PREA PMRs 355-5 and 1937-3 (for NDAs 022304 and 203794, respectively) and Studies 1 through 4 of the WR. The Sponsor did not conduct studies of tapentadol ER because the Agency released PREA PMRs 1815-1 and 1815-2 (for NDA 200533) in March 2023, and issued WR Amendment #5, which no longer requested Study 5, in November 2023. The Agency released PREA PMRs 1815-1 and 1815-2 as the PMR requirements were no longer feasible on the basis that necessary studies were impossible or highly impracticable because an appropriate pediatric population who met the criteria for chronic pain could not be identified.

Relevant Regulatory History

NDAs 022304, 203794, and 200533 changed ownership multiple times between 2008 and 2024; consequently, the Division had a considerable amount of correspondence with several different Sponsors over the years. Key aspects of the regulatory history as it pertains to the approval of each NDA, the deferred pediatric studies issued as PMRs under PREA for each NDA, the WR and the WR amendments issued for tapentadol, and the studies conducted to fulfill the PREA PMRs and the WR are summarized below.

NDA Approval and PREA PMR Issuance Dates

On November 20, 2008, the Agency approved Nucynta tablets (NDA 022304) for use in adults with the indication for the relief of moderate to severe acute pain. At the time of the approval of Nucynta tablets, the Agency deferred the submission of pediatric studies in ages birth to less than 17 years of age until June 30, 2016, to allow for accumulation of additional safety information from both the nonclinical juvenile program and the adult post-marketing database before initiating investigations in pediatric patients. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 355-1: Treatment of moderate to severe acute pain in pediatric patients ages ≥6 years to ≤17 years.

- PMR 355-2: Treatment of moderate to severe acute pain in pediatric patients ages birth to <5 years*.

*There is a typographical error in the approval letter. The correct age group for PMR 355-2 is birth to ≤6 years.

On August 25, 2011, the Agency approved Nucynta ER tablets (NDA 200533) with the indication for the management of moderate to severe chronic pain in adults when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. The Agency waived the pediatric study requirement for pediatric patients less than 7 years of age because the product did not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this age group and was not likely to be used in a substantial number of pediatric patients in this age group. The Agency deferred pediatric studies for ages 7 to less than 17 years because the product was ready for approval for use in adults and the pediatric study had not been completed. The deferred pediatric study issued as a PMR under PREA was as follows:

- PMR 1815-1: A PK, efficacy, and safety study of Nucynta ER for the management of chronic pain in pediatric patients ages 7 to <17 years.

On October 15, 2012, the Agency approved Nucynta oral solution (OS) (NDA 203794) with the indication for the management of moderate to severe acute pain in adults. At the time of the approval of Nucynta OS, the Agency deferred pediatric studies in ages birth to less than 17 years because the product was ready for approval for use in adults and the pediatric studies had not been completed. The Agency acknowledged that a pediatric program to fulfill the PREA requirements for Nucynta tablets (NDA 022304) was ongoing and those studies were intended to also fulfill the PREA requirements for Nucynta OS because the two products are bioequivalent. The deferred pediatric studies issued as PMRs under PREA were as follows:

- PMR 1937-1: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to <17 years.
- PMR 1937-2: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe pain in pediatric patients birth to 5 years.

PREA PMR Release and Reissuance Dates for NDAs 022304 and 203794

On July 10, 2013, the Division released PMRs 355-1 and 355-2 for NDA 022304 and issued new PMRs based on the Agency's issuance of a WR and the Sponsor's request to extend their pediatric study deadlines. The reissued PMRs were as follows:

- PMR 355-3: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages 6 to <17 years.
- PMR 355-4: A PK, efficacy, and safety study of Nucynta for the management of moderate to severe acute pain in pediatric patients ages birth to 5 years.

On June 23, 2015, the Division released PMRs 355-3 and 355-4 for NDA 022304 and PMRs 1937-1 and 1937-2 for NDA 203794 and issued new PMRs based on the Sponsor's revised pediatric study plan and to align with WR Amendment #2. The reissued PMRs were as follows:

- PMR 355-5 (NDA 022304): PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.

- PMR 1937-3 (NDA 203794): PK, efficacy, and safety study or studies of Nucynta for the management of moderate to severe pain in pediatric patients ages birth to less than 17 years.

PREA PMR Issuance and Release Dates for NDA 200533

On July 3, 2019, the Agency issued a new PMR for NDA 200533 based on data provided by the Sponsor in support of potentially extrapolating the efficacy of tapentadol ER in the pediatric population from efficacy data of tapentadol IR in Study KF5503/65 and conducting only a PK and safety study of Nucynta ER. PMR 1815-2 was as follows:

- PMR 1815-2: An open-label, PK and safety study or studies of an extended-release formulation of tapentadol in patients 7 to <17 years of age who are anticipated to have pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

On March 1, 2023, the Agency released PREA PMRs 1815-1 and 1815-2 for NDA 200533 as the PMR requirements were no longer feasible on the basis that necessary studies were impossible or highly impracticable because an appropriate pediatric population who met the criteria for chronic pain could not be identified.

WR Issuance Date

In December 2012, the Sponsor resubmitted a Proposed Pediatric Study Request (PPSR) for tapentadol to NDAs 022304, 203794, and 200533. The studies contained in the PPSR were intended to fulfill the PREA PMRs for the three approved tapentadol products and serve as a proposal for the studies that would be contained in a WR for the active moiety, tapentadol, for pediatric exclusivity under the Best Pharmaceuticals for Children Act (BPCA).

On July 8, 2013, the Agency issued a formal WR to obtain needed information on the use of tapentadol in pediatric patients from birth (i.e., neonates) to less than 17 years of age for the management of moderate to severe acute pain and pediatric patients from 7 to less than 17 years of age for the management of moderate to severe chronic pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time.

The required clinical studies in the WR were as follows:

- **Study 1:** Open-label, PK and safety study of an age-appropriate IR formulation of tapentadol in patients 2 to <17 years of age with moderate to severe pain, on an age-appropriate pain scale, requiring treatment with an opioid analgesic.
- **Study 2:** Open-label, PK and safety study of an age-appropriate IR formulation of tapentadol in patients birth to <2 years of age with moderate to severe pain, on an age-appropriate pain scale, requiring treatment with an opioid analgesic.
- **Study 3:** Randomized, double-blind, adequately controlled, multiple-dose, efficacy and safety study of an age-appropriate IR formulation of tapentadol in patients birth to <17 years of age with moderate to severe acute pain, on an age-appropriate pain scale, requiring treatment with an opioid analgesic.

- **Study 4:** Open-label, PK and safety study of an ER formulation of tapentadol in patients 7 to <17 years of age with moderate to severe pain, on an age-appropriate pain scale, requiring a continuous, around-the-clock opioid analgesic for an extended period of time.
- **Study 5:** Randomized, double-blind, adequately controlled, multiple-dose, parallel-arm efficacy and safety study of an ER formulation of tapentadol in patients 7 to <17 years of age with moderate to severe pain, on and age-appropriate pain scale, requiring a continuous, around-the-clock opioid analgesic for an extended period of time.

WR Amendment Issuance Dates

On August 14, 2014, the Agency issued WR Amendment #1 with revisions to the design and conduct of Studies 1 through 5.

On June 22, 2015, the Agency issued WR Amendment #2 with revisions to the description of the appropriate study population in Study 5 and the clinical efficacy assessments required in Studies 4 and 5.

On July 10, 2019, the Agency issued WR Amendment #3 with a revision to the design of Study 5 to align with the issuance of PMR 1815-2 for NDA 200533.

On December 2, 2021, the Agency issued WR Amendment #4 with a revision to the safety database for Study 5 and extension of the timeframe for submission of study reports from on or before December 21, 2021, to on or before March 31, 2024.

On November 3, 2023, the Agency issued WR Amendment #5 in which the request for pediatric information on the ER formulation of tapentadol in patients ages 7 to less than 17 years (i.e., Study 5) was removed to align with the release of PMRs 1815-1 and 1815-2 for NDA 200533 on March 1, 2023.

The required clinical studies in WR Amendment #5 were as follows:

- **Study 1:** Open-label, pharmacokinetics (PK) and safety study or studies of an age-appropriate IR formulation of tapentadol in patients 6 to <17 years of age who are anticipated to have moderate to severe pain, requiring treatment with an opioid analgesic.
- **Study 2:** Open-label, PK and safety study or studies of an age-appropriate IR formulation of tapentadol in patients 2 to <6 years of age who are anticipated to have moderate to severe pain, requiring treatment with an opioid analgesic.
- **Study 3:** Open-label, PK and safety study or studies of an age-appropriate IR formulation of tapentadol in patients birth to <2 years of age who are anticipated to have moderate to severe pain, requiring treatment with an opioid analgesic.
- **Study 4:** Randomized, double-blind, adequately controlled, multiple-dose, efficacy and safety study or studies of an age-appropriate IR formulation of tapentadol in patients birth to <17 years of age who are anticipated to have moderate to severe acute pain, requiring treatment with an opioid analgesic.

Protocol Submission Dates for Studies Conducted to Fulfill the PREA PMRs and the WR

In May 2010, the Sponsor submitted a protocol for Study KF5503/59, a single-dose PK study of tapentadol OS in pediatric patients 6 to less than 18 years of age, to IND 108134. In June 2010, the Division placed Study KF5503/59 on full clinical hold because of safety concerns about an

unexpectedly large number of reports of CNS disorders, such as seizure, serotonin syndrome, and hallucinations, in the post-marketing experience with tapentadol IR in adults. In March 2011, after the Agency completed a post-marketing safety evaluation of Nucynta tablets, the Division removed Study KF5503/59 from full clinical hold and allowed the study to proceed with protocol revisions to address safety concerns of seizure, suicidal ideation, and serotonin syndrome associated with use of Nucynta.

In August 2012, Grünenthal GmbH, the marketing holder of Palexia IR and ER (the European equivalent of Nucynta IR and ER tablets), submitted a protocol for Study KF5503/68, a single-dose PK study of tapentadol OS in pediatric patients 2 to less than 18 years of age, to IND 116020. The Division reviewed the protocol and allowed the study to proceed.

In October 2013, the Sponsor, in conjunction with Grünenthal, submitted a protocol for Study KF5503/65, a placebo-controlled, efficacy and safety study of tapentadol OS in pediatric patients from birth to less than 18 years of age, to INDs 108134 and 116020. The Sponsor proposed staggered enrollment with pediatric patients ages 6 to less than 18 years enrolled first, followed by pediatric patients ages 2 to less than 6 years, and then patients ages birth to less than 2 years after PK and safety data were obtained. The Division reviewed the protocol and allowed the study to proceed.

In May 2014, the Sponsor, in conjunction with Grünenthal, submitted a protocol for Study KF5503/72, an open-label, PK and safety study in pediatric patients from birth to less than 2 years of age, to INDs 108134 and 116020. The Division reviewed the protocol and allowed the study to proceed.

Supplemental NDA Submission Dates for Studies Conducted to Fulfill the PREA PMRs and Partially Fulfill the WR

On December 20, 2021, Collegium submitted two supplements (NDA 022304/S-024 and NDA 203794/S-010) with pediatric data from studies KF5503/59, KF5503/68, KF5503/72, and KF5503/65 to support extending the indication for Nucynta IR tablets and Nucynta OS to pediatric patients 2 years and older. Upon review of the supplements for filing, the Division determined that the supplements were not sufficiently complete to permit a substantive review because of clinical and statistical deficiencies.

On February 18, 2022, the Division issued a Refuse to File letter for NDA 022304/S-024 and NDA 203794/S-010 with the following clinical and statistical deficiencies:

1. You have not submitted any electronic datasets for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.
2. You have not submitted any of the raw data needed to derive the primary and secondary efficacy endpoints for Study KF5503/65 in Module 5.
3. You have not submitted Case Report Forms for serious adverse events and discontinuations due to treatment-emergent adverse events for studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 5.
4. You have not submitted financial disclosure information for any of the investigators in studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 in Module 1.

5. You have not submitted a rationale for assuming the applicability of foreign data to the U.S. population for studies KF5503/59, KF5503/65, and KF5503/72.

On October 3, 2022, Collegium resubmitted NDA 022304/S-024 and NDA 203794/S-010 with pediatric data from studies KF5503/59, KF5503/68, KF5503/72, and KF5503/65 to support extending the indication for Nucynta IR tablets and Nucynta OS to pediatric patients (b)(4) years and older. Collegium did not request pediatric exclusivity determination at this time because the data included in the supplements only partially fulfilled the WR. Collegium had not yet conducted any studies of tapentadol ER in pediatric patients ages 7 to less than 17 years with chronic pain.

On July 3, 2023, the Division approved NDA 022304/S-024 and NDA 203794/S-010. The Division concluded that the PK, efficacy, and safety data included in the supplements supported the approval of Nucynta tablets in pediatric patients aged 6 years and older with a body weight of at least 40 kg and Nucynta OS in pediatric patients aged 6 years and older with a body weight of at least 16 kg. The Agency also concluded that PMRs 1937-3 and 355-5 were fulfilled because the Sponsor submitted data from studies conducted in pediatric patients from birth to 17 years of age with acute pain.

Pediatric Exclusivity Determination Request Submission Date

On December 15, 2023, after the Agency's issuance of WR Amendment #5 on November 3, 2023, Collegium submitted three supplements (NDA 022304/S-028, NDA 203794/S-013, and NDA 200533/S-029) with an annotated WR and a pediatric exclusivity determination request for tapentadol.

Other Important Correspondence

On October 18, 2012, the Division and the Sponsor held a meeting to discuss the ongoing pediatric clinical programs for Nucynta IR and ER tablets. The Division stated that the Sponsor could submit a PPSR for tapentadol that included their plans for studies in the pediatric age range. The Division also stated that studies conducted under PREA could be included in a WR; however, studies in pediatric patients that were completed and submitted to the Agency prior to issuance of a WR could not be used to fulfill the requirements of the WR.

In November 2013, the Sponsor informed the Division of their plan to use data from Study KF5503/68 (being conducted by Grünenthal under IND 116020) to fulfill PREA and WR requirements and asked the Division how this should be handled from an administrative perspective. The Sponsor also asked the Division whether the partial completion of Study KF5503/59, and the initiation of Study KF5503/68, prior to the issuance of the WR, and prior to the Sponsor's agreement with the WR, would affect their ability to obtain pediatric exclusivity. On November 15, 2013, the Division responded to the Sponsor's administrative inquiries in an email communication. The Division recommended the Sponsor either establish cross-reference to Grünenthal's IND 116020, or submit the protocol, and eventually the study report, for Study KF5503/68 to both IND 108134 and IND 116020 as a joint study. The Division also stated that the statuses of Study KF5503/59 and Study KF5503/68 as already initiated prior to the issuance of the WR would not impact the potential for pediatric exclusivity because the studies were far from complete, and no data had yet been submitted to the Agency.

In September 2018, the Sponsor submitted a rationale for including 17-year-olds in the pediatric population being evaluated for the US FDA primary and secondary endpoints in Study KF5503/65. The Sponsor also submitted an amended statistical analysis plan to address concerns about potential bias with the analysis of pediatric patients from birth to less than 2 years old separate from the analysis of pediatric patients 2 to less than 18 years old.

In December 2018, the Division issued an advice letter in response to the Sponsor's September submission stating that the rationale to include patients 17 years of age in the efficacy analysis in Study KF5503/65 and use this data to fulfill the WR appeared reasonable. The Division also concluded that the method to address the introduction of potential bias to the analysis of the birth to less than 2 years age group also appeared acceptable.

Division's Review of the Annotated WR and Recommendation Regarding the Pediatric Exclusivity Determination Request

The Division generally agreed with the Sponsor's responses in the annotated WR. The Division noted that studies KF5503/59, KF5503/65, and KF5503/68 deviated slightly from the age requirements in the WR (birth to less than 17 years of age) because these studies included pediatric patients who were 17 years of age to fulfill EU PDCO pediatric investigation plan requirements. Upon review of the regulatory history, the Division confirmed that the Sponsor submitted protocols for all studies conducted and that the protocols were agreed upon by the Division before initiation of the studies. The Division also confirmed that the Sponsor and the Division communicated about and agreed to the inclusion of 17-year-olds in the efficacy analyses for Study KF5503/65. The Division concluded that the limited number of 17-year-olds included in studies KF5503/59, KF5503/65, and KF5503/68 did not affect the interpretation of the study results and that studies KF5503/59, KF5503/65, KF5503/68, and KF5503/72 met the terms of the WR; therefore, the Division recommended granting the Sponsor's request for pediatric exclusivity determination for tapentadol. Refer to the tapentadol pediatric exclusivity determination checklist, signed by the Division and Dr. Mary Thanh Hai, and submitted in DARRTS on June 11, 2024, for additional information about the Sponsor's responses and the Division's comments in the annotated WR.

Pediatric Exclusivity Board Meeting

On May 15, 2024, the Pediatric Exclusivity Board met, reviewed the annotated WR with the Division, and concluded that the pediatric data submitted by the Sponsor met the terms of the WR. The Pediatric Exclusivity Board granted the Sponsor's request for pediatric exclusivity for tapentadol. On June 4, 2024, the Division discussed the outcome of the Pediatric Exclusivity Board meeting with the Pediatric Review Committee (PeRC).

Recommended Regulatory Action

The Division recommends approval of these efficacy supplements with no new changes to the labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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