NDA 022304
NDA 200533
NDA 203794

WRITTEN REQUEST – AMENDMENT #5

Collegium Pharmaceutical Inc.
100 Technology Center Drive, Suite 300
Stoughton, MA 02072

Attention: Heta Mehta
Manager, Regulatory Affairs

Dear Heta Mehta:

Please refer to your correspondence dated July 6, 2023, requesting changes to FDA's July 8, 2013, amended August 14, 2014, June 22, 2015, July 10, 2019, and December 2, 2021, Written Request for pediatric studies for Nucynta (tapentadol).

We have reviewed your proposed changes and are amending the Written Request. All other terms stated in our Written Request issued on July 8, 2013, and as amended on August 14, 2014, June 22, 2015, July 10, 2019, and December 2, 2021, remain the same. Refer to the attached document which shows the changes from the previous Written Request (text added is underlined, text deleted is ~~strikethrough~~).

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated July 8, 2013, as amended by this letter and by previous amendments dated August 14, 2014, June 22, 2015, July 10, 2019, and December 2, 2021, must be submitted to the Agency on or before March 31, 2024, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a new drug application (NDA) or as a supplement to your approved NDA(s) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When requesting pediatric exclusivity based on reports submitted, clearly mark your submission **"PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies

conducted in response to this Written Request. These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website.[1]

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, call Jaimin Patel, Regulatory Project Manager, at (301) 796-0412).

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Copy of Written Request which shows the changes from the previous Written Request.
- Complete Copy of Written Request as Amended.

[1] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

NDA 022304
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WRITTEN REQUEST – AMENDMENT #~~4~~5

Collegium Pharmaceutical Inc.
100 Technology Center Drive, Suite 300
Stoughton, MA 02072

Attention: Heta Mehta
Manager, Regulatory Affairs

Dear ~~Ms.~~Heta Mehta:

Reference is made to your December 20, 2012, Proposed Pediatric Study Request for Nucynta (tapentadol) ~~immediate release tablets and oral solution and for Nucynta ER (tapentadol) extended release tablets~~. Tapentadol is a mu-opioid receptor agonist that also has norepinephrine reuptake inhibitor activity and is listed under Schedule II of the Controlled Substance Act.

These studies investigate the potential use of tapentadol in the treatment of pediatric patients from birth (i.e., neonates) to less than 17 years of age for the management of moderate to severe acute pain and 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.

Although the exact incidence of pain syndromes in the pediatric population is unknown, it is well documented that pediatric patients experience both acute and chronic pain. Accordingly, there is a need for pain medications that can be used to safely and effectively manage pain in this patient population. Tapentadol was first approved for the US market in 2008. The safety and efficacy of tapentadol for the treatment of acute and chronic pain in adults has been well established. There are currently three approved formulations of tapentadol (i.e., immediate-release [IR] tablets, extended-release [ER] tablets, and oral solution [OS]), all of which may potentially benefit pediatric patients with moderate-to-severe acute or chronic pain. While pediatric information on tapentadol is needed, we have determined, as of March 2023, that pediatric studies of Nucynta (tapentadol) extended-release tablets for the chronic pain indication are no longer feasible on the basis that necessary studies are impossible or highly impracticable because an appropriate pediatric population who meet the criteria for chronic pain cannot be identified.

To obtain needed pediatric information on tapentadol, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug

Administration Amendments Act of 2007, that you submit information from the studies described below.

Nonclinical studies:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

The following studies are required using an age-appropriate formulation (i.e., intravenous, oral solution, or oral solid, as appropriate) to obtain the necessary information on the use of tapentadol for the management of acute pain ~~and chronic pain~~ in the pediatric population:

Study 1: Open-label, pharmacokinetics (PK) and safety study or studies of an age-appropriate immediate-release 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 immediate-release 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 immediate-release 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 immediate-release 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

~~**Study 5:** Randomized, double blind, adequately controlled, multiple dose, parallel arm, PK, efficacy, 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, or 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 if there are adequate data from study 4 to support extrapolation of efficacy for the ER formulation in ages 7 to <17.~~

Efficacy in patients birth to <17 years of age cannot be extrapolated because of the inadequate characterization of the mechanism of action for this product in pediatric patients and will be determined by the studies outlined in the Written Request. ~~Clinical studies in patients from birth to <7 years of age who are anticipated to have moderate to severe pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time are not required given the low incidence and prevalence of conditions requiring such therapy in this age group.~~

Pharmacokinetic and safety studies of IR tapentadol must be completed in pediatric patients ages 2 to <17 years before proceeding in pediatric patients ages birth to <2 years in order to better define the pharmacokinetic and safety profiles of tapentadol in pediatric patients and to inform dosing. The pharmacokinetic and safety studies must be completed before the efficacy trials in corresponding age cohorts to inform dosing.

~~The Sponsor will use existing PK and safety results to select tapentadol ER doses for the planned Phase 3 study in pediatric subjects 7 to <17 years of age (Study 5).~~

Protocols for these studies not previously submitted to an IND and initiated prior to the issuance of this Written Request must be submitted to the Agency and agreed upon prior to initiation.

- *Objective of each study:*

  Study 1: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients 6 to <17 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a traditional or population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

  Study 2: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients 2 to <6 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a traditional or population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age

group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

Study 3: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients birth to < 2 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

Study 4: Evaluate the efficacy and safety of an age-appropriate IR formulation of tapentadol after the first dose and during repeated dosing, if needed in patients birth to <17 years of age. The study must be designed as a randomized, double-blind, adequately-controlled, inpatient, superiority study evaluating efficacy and safety following an initial dose and after repeated dosing.

~~**Study 5:** Evaluate the PK, efficacy and safety of an ER formulation of tapentadol in patients 7 to <17 years of age or evaluate the PK and safety of an ER formulation of tapentadol in patients 7 to <17 years of age. If the study is evaluating efficacy, the study must be designed as a randomized, double-blind, adequately-controlled, superiority study to assess efficacy and safety. Pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a population pharmacokinetic approach to confirm the simulation results for the ER formulation of tapentadol in patients 7 to <17 years of age. If the study is not evaluating efficacy, the study may be uncontrolled and open label.~~

The data from the relevant studies must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of this analysis are to provide supportive evidence of effectiveness and to support the dosing recommendations.

- *Patients to be studied:*

  - *Age group in which studies will be performed:*

    Study 1: Patients from 6 to <17 years of age. Patients must be grouped at baseline into age ranges such as 6 years to <12 years and 12 years to <17 years.

Study 2: Patients from 2 to <6 years of age.

Study 3: Patients from birth to <2 years of age. Patients must be grouped at baseline into age ranges such as birth to <30 days, one month to <6 months, and 6 months to <2 years.

Study 4: Patients from birth to <17 years of age. Randomization will be stratified by age at baseline into age ranges such as birth to <30 days, one month to <6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, and 12 years to <17 years.

~~**Study 5:** Patients from 7 to <17 years of age. Randomization will be stratified by age at baseline into age ranges such as 7 to <12 years and 12 to <17 years.~~

- *Number of patients to be studied:*

  The total safety database for the tapentadol pediatric program (Studies 1-~~4~~5) must equal or exceed ~~300~~ 200 patients in order to adequately assess safety, including:

  - At least 100 pediatric patients exposed to multiple doses of the tapentadol immediate-release formulation with at least 25 patients exposed for at least 48 hours, for the acute pain indication

  - ~~At least 100 pediatric patients exposed to tapentadol extended release formulation for a minimum of 10 days; including at least 50 pediatric patients exposed to tapentadol extended release formulation for at least 2 weeks.~~

  Studies 1, 2, and 3: Studies must include an adequate number of patients to characterize the key pharmacokinetic parameters of tapentadol and tapentadol-O glucuronide to inform the selection of a therapeutic dose for the age ranges studied, taking into account inter-subject variability. For evaluation of the pharmacokinetics, the study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for tapentadol in each pediatric sub- group with at least 80% power, and patients should be approximately evenly distributed over the entire age

range in each age group. Pediatric patients should be approximately evenly distributed between genders.

Study~~ies~~ 4 ~~and 5~~: The study must include a sufficient number of enrolled patients to produce a sample size adequately powered for detecting differences based on estimates of the effect size of the primary efficacy outcome. Patients should be approximately evenly distributed over the entire age range in each age group and between genders in each treatment group.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Pharmacokinetic Endpoints:

  Blood samples are to be collected periodically by either a traditional PK or a population PK approach to adequately characterize the PK parameters of tapentadol and tapentadol-O-glucuronide after a single dose. The pharmacokinetic endpoints for Studies 1, 2, and 3 must include the estimated PK parameters to assess systemic exposure of tapentadol and tapentadol-O-glucuronide in patients birth to <17 years of age. The specific PK parameters to be measured must be stated in the protocol and agreed upon with the Agency.

  Efficacy Endpoints:

  For each study, it is essential to identify a single, age-appropriate, primary efficacy outcome reflecting adequacy of analgesia. In patients ages birth to <17 years, clinical efficacy assessments will be made by using validated, age-appropriate instruments and by evaluating analgesic sparing by measuring the amount of supplemental opioid analgesic medication. Inter-rater variability will be evaluated. Evaluation will include assessments by blinded caretakers and assessors. Rationale for the choice of instruments will be provided in the protocol and must be agreed upon by the Agency. The same scales must be used at all sites.

Important secondary endpoints must include:

- Duration of analgesic effect
- Use of rescue medication
- Incidence of inadequate analgesia
- Pain intensity (using an age-appropriate scale) at multiple time points
- Clinician Global Impression of Change (CGIC)
- Patient Global Assessment of Change (PGIC) or similar assessment (as appropriate)

Safety Endpoints:

Safety outcomes must include:

- Incidence of adverse events (AEs), especially AEs of gastrointestinal, respiratory, and central nervous systems, including oversedation
- Clinical laboratory parameters (such as hematology, blood chemistry, and urinalysis)
- Vital signs including respiratory rate, heart rate, and blood pressure
- Oximetry and/or non-invasive carbon dioxide monitoring

All protocols will document any painful interventions that may affect study assessments.

The following AEs must be actively monitored in studies in inpatients: vital sign abnormalities, oxygen desaturation, somnolence, hypoventilation, and hypotension using standard of care monitoring.

All AEs must be monitored until symptom resolution or until the condition stabilizes.

- *Known drug safety concerns and monitoring:*

  Many of the expected AEs (e.g., respiratory depression, hypotension, CNS depression) are similar to that observed with other opioids. The protocols must include monitoring for the following opioid-class AEs at a minimum:

  - Respiratory depression
  - Hypotension
  - Appropriate clinical laboratory assessments

In addition to opioid-class AEs, tapentadol has been reported to be associated with seizure, serotonin syndrome, and suicidality based on the postmarketing safety experience in adults. Those serious adverse events appear to be confounded by drug-drug and/or drug-disease interactions (DDIs) as these serious AEs were not noted in the safety database of the three approved NDAs (potential DDIs were excluded in all trials).

The protocols must include provisions for actively monitoring the following AEs in addition to the AEs typical of the opioid class:

- Suicidality for subjects ages 6 years and above in Study 4 (acute pain efficacy trial) ~~and Study 5 (chronic pain efficacy trial)~~
- Seizure and serotonin syndrome for all age groups in all <u>four</u> ~~five~~ studies

The protocols must include provisions for capturing the following AEs for all studies when spontaneously reported: suicidality, seizure, and serotonin syndrome.

The protocols must include provisions for AE monitoring until symptom resolution or until the condition stabilizes.

- *Extraordinary results:*

  In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Tapentadol IR

Dosage form	Tablets	Oral solution	Injectable
Route of administration	Oral	Oral	Intravenous

Regimen	Single and multiple dose

~~Tapentadol ER~~

~~**Dosage form**~~	~~Tablets~~
~~**Route of administration**~~	~~Oral~~
~~**Regimen**~~	~~Multiple dose~~

Use an age-appropriate formulation in the studies described above. An age-appropriate formulation may involve changes in dosing strength and/or presentation. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested

studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by- step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

  The efficacy study~~ies~~ will be designed to provide at least 80% power to detect a clinically meaningful difference, at the conventional significance level of 0.05. A clinically meaningful effect size will be pre-specified and justified in the protocol, and must be discussed with and agreed upon by the FDA prior to initiating the study. The overall two-sided Type I error must be controlled at 5%. A detailed statistical analysis plan is required and must be submitted prior to the start of the study.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that tapentadol is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must

submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website[1] ~~at~~ ~~http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf~~ and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*[2]. ~~at~~ ~~http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf~~.

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before March 31, 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the studies, but have not submitted

[1] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[2] https://www.fda.gov/media/135373/download

the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA(s) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When requesting pediatric exclusivity based on reports submitted ~~submitting the reports~~, please clearly mark your submission "**~~SUBMISSION OF PEDIATRIC STUDY REPORTS -~~ PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North IV, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);

2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);

3. the action taken (i.e. approval, complete response); or

4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA

website[3]. ~~at~~
~~http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872~~

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

If you have any questions, call Jaimin Patel, Regulatory Health Project Manager, at (301) 796-0412.

~~Sincerely,~~

~~*{See appended electronic signature page}*~~

~~Billy Dunn, MD~~
~~Director~~
~~Office of Neuroscience~~
~~Office of New Drugs~~
~~Center for Drug Evaluation and Research~~

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

[3] https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

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WRITTEN REQUEST – AMENDMENT #5

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Stoughton, MA 02072

Attention: Heta Mehta
Manager, Regulatory Affairs

Dear Heta Mehta:

Reference is made to your December 20, 2012, Proposed Pediatric Study Request for Nucynta (tapentadol). Tapentadol is a mu-opioid receptor agonist that also has norepinephrine reuptake inhibitor activity and is listed under Schedule II of the Controlled Substance Act.

These studies investigate the potential use of tapentadol in the treatment of pediatric patients from birth (i.e., neonates) to less than 17 years of age for the management of moderate to severe acute pain and 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.

Although the exact incidence of pain syndromes in the pediatric population is unknown, it is well documented that pediatric patients experience both acute and chronic pain. Accordingly, there is a need for pain medications that can be used to safely and effectively manage pain in this patient population. Tapentadol was first approved for the US market in 2008. The safety and efficacy of tapentadol for the treatment of acute and chronic pain in adults has been well established. There are currently three approved formulations of tapentadol (i.e., immediate-release [IR] tablets, extended-release [ER] tablets, and oral solution [OS]), all of which may potentially benefit pediatric patients with moderate-to-severe acute or chronic pain. While pediatric information on tapentadol is needed, we have determined, as of March 2023, that pediatric studies of Nucynta (tapentadol) extended-release tablets for the chronic pain indication are no longer feasible on the basis that necessary studies are impossible or highly impracticable because an appropriate pediatric population who meet the criteria for chronic pain cannot be identified.

To obtain needed pediatric information on tapentadol, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies

described below.

Nonclinical studies:
Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

Clinical studies:

The following studies are required using an age-appropriate formulation (i.e., intravenous, oral solution, or oral solid, as appropriate) to obtain the necessary information on the use of tapentadol for the management of acute pain in the pediatric population:

Study 1: Open-label, pharmacokinetics (PK) and safety study or studies of an age-appropriate immediate-release 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 immediate-release 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 immediate-release 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 immediate-release 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

Efficacy in patients birth to <17 years of age cannot be extrapolated because of the inadequate characterization of the mechanism of action for this product in pediatric patients and will be determined by the studies outlined in the Written Request.

Pharmacokinetic and safety studies of IR tapentadol must be completed in pediatric patients ages 2 to <17 years before proceeding in pediatric patients ages birth to <2 years in order to better define the pharmacokinetic and safety profiles of tapentadol in pediatric patients and to inform dosing. The pharmacokinetic and safety studies must be completed before the efficacy trials in corresponding age cohorts to inform dosing.

Protocols for these studies not previously submitted to an IND and initiated prior to the issuance of this Written Request must be submitted to the Agency and agreed upon prior to initiation.

- *Objective of each study:*

Study 1: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients 6 to <17 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a traditional or population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

Study 2: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients 2 to <6 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a traditional or population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

Study 3: Characterize the PK and safety of an age-appropriate IR formulation of tapentadol after a single dose in patients birth to < 2 years of age. The pharmacokinetics of tapentadol and tapentadol-O-glucuronide must be characterized using a population pharmacokinetic approach. Use available PK data for tapentadol in adults or the older pediatric age group to help select the study dose and PK sampling time. Information derived will help establish a dosing regimen in pediatric patients in this age group.

Study 4: Evaluate the efficacy and safety of an age-appropriate IR formulation of tapentadol after the first dose and during repeated dosing, if needed in patients birth to <17 years of age. The study must be designed as a randomized, double-blind, adequately-controlled, inpatient, superiority study evaluating efficacy and safety following an initial dose and after repeated dosing.

The data from the relevant studies must be combined to develop exposure-response for safety and effectiveness endpoints. The goals of this analysis are to provide

supportive evidence of effectiveness and to support the dosing recommendations.

- *Patients to be studied:*

  - *Age group in which studies will be performed:*

    Study 1: Patients from 6 to <17 years of age. Patients must be grouped at baseline into age ranges such as 6 years to <12 years and 12 years to <17 years.

    Study 2: Patients from 2 to <6 years of age.

    Study 3: Patients from birth to <2 years of age. Patients must be grouped at baseline into age ranges such as birth to <30 days, one month to <6 months, and 6 months to <2 years.

    Study 4: Patients from birth to <17 years of age. Randomization will be stratified by age at baseline into age ranges such as birth to <30 days, one month to <6 months, 6 months to <2 years, 2 years to <6 years, 6 years to <12 years, and 12 years to <17 years.

  - *Number of patients to be studied:*

    The total safety database for the tapentadol pediatric program (Studies 1-4~~5~~) must equal or exceed 200 patients in order to adequately assess safety, including:

    - At least 100 pediatric patients exposed to multiple doses of the tapentadol immediate-release formulation with at least 25 patients exposed for at least 48 hours, for the acute pain indication

    Studies 1, 2, and 3: Studies must include an adequate number of patients to characterize the key pharmacokinetic parameters of tapentadol and tapentadol-O glucuronide to inform the selection of a therapeutic dose for the age ranges studied, taking into account inter-subject variability. For evaluation of the pharmacokinetics, the study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for tapentadol in each pediatric sub- group with at least 80% power, and patients should be

approximately evenly distributed over the entire age range in each age group. Pediatric patients should be approximately evenly distributed between genders.

Study 4: The study must include a sufficient number of enrolled patients to produce a sample size adequately powered for detecting differences based on estimates of the effect size of the primary efficacy outcome. Patients should be approximately evenly distributed over the entire age range in each age group and between genders in each treatment group.

- *Representation of Ethnic and Racial Minorities:* The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*

  Pharmacokinetic Endpoints:

  Blood samples are to be collected periodically by either a traditional PK or a population PK approach to adequately characterize the PK parameters of tapentadol and tapentadol-O-glucuronide after a single dose. The pharmacokinetic endpoints for Studies 1, 2, and 3 must include the estimated PK parameters to assess systemic exposure of tapentadol and tapentadol-O-glucuronide in patients birth to <17 years of age. The specific PK parameters to be measured must be stated in the protocol and agreed upon with the Agency.

  Efficacy Endpoints:

  For each study, it is essential to identify a single, age-appropriate, primary efficacy outcome reflecting adequacy of analgesia. In patients ages birth to <17 years, clinical efficacy assessments will be made by using validated, age-appropriate instruments and by evaluating analgesic sparing by measuring the amount of supplemental opioid analgesic medication. Inter-rater variability will be evaluated. Evaluation will include assessments by blinded caretakers and assessors. Rationale for the choice of instruments will be provided in the protocol and must be agreed upon by the Agency. The same scales must be used at all sites.

Important secondary endpoints must include:

- Duration of analgesic effect
- Use of rescue medication
- Incidence of inadequate analgesia
- Pain intensity (using an age-appropriate scale) at multiple time points
- Clinician Global Impression of Change (CGIC)
- Patient Global Assessment of Change (PGIC) or similar assessment (as appropriate)

Safety Endpoints:

Safety outcomes must include:

- Incidence of adverse events (AEs), especially AEs of gastrointestinal, respiratory, and central nervous systems, including oversedation
- Clinical laboratory parameters (such as hematology, blood chemistry, and urinalysis)
- Vital signs including respiratory rate, heart rate, and blood pressure
- Oximetry and/or non-invasive carbon dioxide monitoring

All protocols will document any painful interventions that may affect study assessments.

The following AEs must be actively monitored in studies in inpatients: vital sign abnormalities, oxygen desaturation, somnolence, hypoventilation, and hypotension using standard of care monitoring.

All AEs must be monitored until symptom resolution or until the condition stabilizes.

- *Known drug safety concerns and monitoring:*

  Many of the expected AEs (e.g., respiratory depression, hypotension, CNS depression) are similar to that observed with other opioids. The protocols must include monitoring for the following opioid-class AEs at a minimum:

  - Respiratory depression
  - Hypotension

- Appropriate clinical laboratory assessments

In addition to opioid-class AEs, tapentadol has been reported to be associated with seizure, serotonin syndrome, and suicidality based on the postmarketing safety experience in adults. Those serious adverse events appear to be confounded by drug-drug and/or drug-disease interactions (DDIs) as these serious AEs were not noted in the safety database of the three approved NDAs (potential DDIs were excluded in all trials).

The protocols must include provisions for actively monitoring the following AEs in addition to the AEs typical of the opioid class:

- Suicidality for subjects ages 6 years and above in Study 4 (acute pain efficacy trial)

- Seizure and serotonin syndrome for all age groups in all four studies

The protocols must include provisions for capturing the following AEs for all studies when spontaneously reported: suicidality, seizure, and serotonin syndrome.

The protocols must include provisions for AE monitoring until symptom resolution or until the condition stabilizes.

- *Extraordinary results:*

  In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*

  Tapentadol IR

Dosage form	Tablets	Oral solution	Injectable

Route of administration	Oral	Oral	Intravenous
Regimen	Single and multiple dose		

Use an age-appropriate formulation in the studies described above. An age-appropriate formulation may involve changes in dosing strength and/or presentation. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

3) you have not marketed the formulation within one year after the Agency publishes such notice,

the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by- step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and

as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of studies and statistical assessments:*

  The efficacy study~~ies~~ will be designed to provide at least 80% power to detect a clinically meaningful difference, at the conventional significance level of 0.05. A clinically meaningful effect size will be pre-specified and justified in the protocol, and must be discussed with and agreed upon by the FDA prior to initiating the study. The overall two-sided Type I error must be controlled at 5%. A detailed statistical analysis plan is required and must be submitted prior to the start of the study.

- *Labeling that may result from the studies*: You must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that tapentadol is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the

reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website[1] and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*[2].

- *Timeframe for submitting reports of the studies:* Reports of the above studies must be submitted to the Agency on or before March 31, 2024. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the studies. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the studies, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a new drug application (NDA) or as a

[1] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[2] https://www.fda.gov/media/135373/download

supplement to your approved NDA(s) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When requesting pediatric exclusivity based on reports submitted, please clearly mark your submission "**PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North IV, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);

2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);

3. the action taken (i.e. approval, complete response); or

4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website[3].

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

[3] https://www.fda.gov/drugs/development-resources/reviews-pediatric-studies-conducted-under-bpca-and-prea-2012-present

If you have any questions, call Jaimin Patel, Regulatory Health Project Manager, at (301) 796-0412.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

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/

PETER P STEIN
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