



IND 058362
NDA 022450

WRITTEN REQUEST – AMENDMENT # 3

Mallinckrodt, Inc.
Suite 200
12481 High Bluff Drive
San Diego, CA 92130

Attention: Jason Mercer, PhD, RAC
Manager Regulatory Affairs

Dear Dr. Mercer:

Please refer to your correspondence dated and received December 5, 2014, submitted to NDA 022450, requesting changes to our August 24, 2007, Written Request for pediatric studies for acetaminophen.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on August 24, 2007, and as amended on December 20, 2010, and December 8, 2011, remain the same. (Text added is underlined. Text deleted is ~~strikethrough~~.)

Within the section titled: *Number of patients and age groups in which the study will be performed:*

The study must include a sufficient number of patients to produce a sample size adequately powered for detecting treatment differences based on estimates of the effect size of the primary efficacy endpoint. The number of patients must be approximately evenly distributed between genders, approximately evenly distributed across the age ranges, and reasonably distributed within the age ranges. These groups have been determined by assessment of differences in developmental physiology. A minimum of ~~12~~ 9 patients are required per active dose group for traditional pharmacokinetic analysis in each of the age groups indicated below. This number of patients should be adjusted appropriately when considering population PK analysis by sparse sampling approach:

- Birth (28 weeks to < 40 weeks gestational age) to < 28 days chronological age
- 29 days to < 6 months
- 6 months to < 12 months
- 12 months to < 24 months

PK data from this study can be combined with PK data from your completed studies in infants and neonates for the population PK analysis.

Within the section titled: *Timeframe for submitting reports of the studies:*

Reports of the above studies must be submitted to the Agency on or before ~~August 31, 2015~~ May 1, 2016. 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.

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 August 24, 2007, as amended by this letter and by previous amendments dated December 20, 2010, and December 8, 2011, must be submitted to the Agency on or before May 1, 2016, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved new drug application (NDA) with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via fax (240-276-9327) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773.

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.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

- 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.

- Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that acetaminophen 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 study(ies).
- 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 within 210 days of submission of your study report(s). 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 at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872>.

- If your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you may be required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on these requirements and the submission of this information can be found at www.ClinicalTrials.gov.

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If you have any questions, call Spiros Nicols, PharmD, MBA, Regulatory Health Project Manager, at (240) 402-5899.

Sincerely,

{See appended electronic signature page}

Curtis J. Rosebraugh, MD, MPH
Director
Office of Drug Evaluation II
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

Complete Copy of Written Request as Amended

GENERAL REQUIREMENTS

Characterize the efficacy of IV APAP and the APAP plasma concentrations and pain relationship for IV APAP for the indication of the management of pain following multiple doses in different pediatric age groups by evaluating the efficacy of the short-term use of IV acetaminophen in pediatric patients requiring IV analgesics. Because the PK/PD relationship for APAP and analgesia is not well characterized, the studies must be adequate and well-controlled; specifically, the studies must be conducted with a double-blind design with an appropriate comparator in patients who require treatment for pain and who are expected to require IV therapy for the duration of the study. To maximize the trial success, you are strongly encouraged to perform clinical trial simulations to substantiate the choice of the trial design. Prior exposure and pain relief data from adult studies, literature, and any available pediatric studies should be employed for this purpose. The assessment of efficacy should be the primary objective of the study, and the assessment of the PK/PD relationship the secondary objective.

EFFICACY STUDY

Type of study:

The study will be designed as a randomized, double-blind, adequately-controlled, parallel, multiple-dose, superiority trial to obtain both efficacy data and data on the PK/PD relationship with regard to IV APAP treatment in pediatric patients with pain who are expected to require IV therapy for the duration of the trial due to their underlying medical condition. A rationale for the choice of doses and the proposed trial design must be provided in the submitted protocol. We encourage you to base these on information obtained from clinical trial simulations. The choice of dose(s) may also be guided by prior PK studies, literature, or current medical practice.

Number of patients and age groups in which the study will be performed:

The study must include a sufficient number of patients to produce a sample size adequately powered for detecting treatment differences based on estimates of the effect size of the primary efficacy endpoint. The number of patients must be approximately evenly distributed between genders, approximately evenly distributed across the age ranges, and reasonably distributed within the age ranges. These groups have been determined by assessment of differences in developmental physiology. A minimum of 9 patients are required per active dose group for traditional pharmacokinetic analysis in each of the age groups indicated below. This number of patients should be adjusted appropriately when considering population PK analysis by sparse sampling approach:

- Birth (28 weeks to < 40 weeks gestational age) to < 28 days chronological age
- 29 days to < 6 months
- 6 months to < 12 months
- 12 months to < 24 months

PK data from this study can be combined with PK data from your completed studies in infants and neonates for the population PK analysis.

Representation of ethnic and racial minorities:

The study 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.

Inclusion criteria:

Pediatric inpatients with pain who are expected to require IV therapy for the duration of the trial due to their underlying medical condition and for whom there is consent of the parent or guardian.

Blood sampling:

A sufficient number of blood samples must be drawn in order to capture the acetaminophen PK profile in each patient. The total volume of blood drawn and the PK methods to be employed in the data analysis must be determined *a priori* and stated in the protocol. It is acceptable to use a population pharmacokinetic approach with sparse sampling; however, blood samples must be dispersed throughout the profile to ensure proper parameter estimation. The proposed design must ensure precise estimates of the mean clearance and volume of distribution (central).

Plasma and urine concentrations of acetaminophen must be determined in a pre-specified number of patients.

Study endpoints:

1. Pharmacokinetics

Descriptive statistics must be derived employing traditional or population PK methods for PK parameters of acetaminophen, such as clearance, volume of distribution, elimination $T_{1/2}$, C_{max} , AUC.

The PK of acetaminophen in pediatric subjects should be qualitatively compared to the adult PK data from ongoing or completed adult PK trials using IV acetaminophen. This is to qualitatively compare the exposures shown to be effective and safe in adults.

The relationship of exposure (infusion rate/dose/AUC/ C_{max}) must be explored with regard to:

- pharmacodynamic endpoints, such as analgesic effects, time to use of rescue medication, amount of rescue medication, and
- safety endpoints, such as major adverse events and most frequent adverse events (see below).

The plasma levels of acetaminophen must be reported.

2. Efficacy

Analgesic effects (including analgesic duration) must be studied. It is essential to identify a single primary efficacy outcome reflecting adequacy of analgesia. Clinical assessments will be made using validated, age-appropriate instruments. Inter-rater variability will be evaluated. Evaluation will include assessment by blinded caretakers and assessors. Rationale for choice of scale will be provided in the protocol and must be agreed upon by the Division of Anesthesia, Analgesia and Addiction Products. The same scale must be used at all sites. Clinical assessments must be made at appropriate intervals in relation to the PK sampling, to the extent possible, to provide understanding of the concentration-response relationship.

Secondary efficacy parameters will include duration of analgesic effect and rescue medication which will be pre-specified and should be reflective of standard of care.

3. Safety

- Incidence of adverse events
- Vital signs
- Laboratory testing to include pertinent tests of hepatic function such as transaminase levels

Extraordinary results:

In the course of conducting this study, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a similar 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:

Dosage form: acetaminophen injection

Route of administration: intravenous

Regimen: Single and/or multiple dose. Dose ranging is encouraged. The dosing regimen will not exceed 15 mg/kg or 1 gm per dose. The total daily dose will not exceed 4 grams per 70 kg (normalized for pediatric patients of lower weight).

Use an age-appropriate formulation in the study described above. 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.

Drug-specific safety concerns:

Liver function will be assessed during the studies and in selected patients at short-term follow-up. Those patients manifesting hepatotoxicity will be followed until resolution of the hepatotoxicity (a level below ULN) or until a new stable baseline is established. Elevations in transaminases will trigger further evaluation of hepatic function, specifically coagulation studies.

Statistical information, including power of study and statistical assessments:

Efficacy studies will be powered (at least 80%). The sample size for the treatment arms will be determined based on the estimates of the effect size for the primary efficacy endpoint to show statistically significant and clinically meaningful treatment differences. 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 study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that acetaminophen 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 study(ies). 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 study(ies).

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 study(ies) 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 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 available 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 May 1, 2016. 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 study(ies). 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 study(ies), 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.

If you wish to discuss any amendments to this Written Request, the proposed changes and the reasons for the proposed changes must be submitted 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.

Reports of the studies should be submitted as a supplement to your approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, 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, via fax (301-594-0183) or messenger, to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

Please note that, as detailed below, and in accordance with the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, certain additional requirements now apply to this Written Request. These additional requirements are as follows:

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 - 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);
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 - the exclusivity determination (i.e., granted or denied).

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SPIROS NICOLS
03/30/2015