CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22279Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	May 13, 2015
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	22279
Applicant	Mikart, Inc.
Date of Submission	December 4, 2014
PDUFA Goal Date	June 4, 2015
Proprietary Name / Established (USAN) names	Hycofenix/hydrocodone bitartrate, pseudoephedrine hydrochloride, and guaifenesin oral solution
Dosage forms / Strength	Oral Solution/2.5 mg, 30 mg, and 200 mg, respectively, in each 5 ml
Proposed Indication(s)	For symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold.
Recommended Action:	Approval for adults and adolescents ≥ 18 years of age

1. Introduction

This third complete response submission by the Applicant, received December 4, 2014, is a 505(b)(2) new drug application based on a clinical pharmacology program for a hydrocodone bitartrate, pseudoephedrine, and guaifenesin combination immediate release oral solution for the symptomatic relief of cough, nasal congestion, and to loosen mucus associated with the common cold.

The original NDA, submitted on August 22, 2008, presented a single dose bioavailability study, which was determined to be inadequate to evaluate the bioequivalence (BE), drug-drug interaction, and food effect of the proposed combination product and a complete response action was taken on June 22, 2009. On July 26, 2010, the Applicant filed the first complete response resubmission, which included data from a single-dose BE study and a food effect study. However, an audit conducted by the Agency identified deficiencies relating to (1) documentation irregularities, and (2) integrity of the bioanalytical data generated at the analytical site. Because of these deficiencies, these studies were not acceptable to support this NDA submission and a second complete response action was taken on January 25, 2011. Subsequently, the Applicant re-conducted the clinical pharmacology program consisting of single-dose relative bioavailability and food-effect studies and filed a complete response resubmission received on 7/19/2011, however, upon review bioequivalency criteria were not met for the guaifenesin drug component and a complete response action was taken for NDA 22-424 on September 29, 2011. For this submission, the Applicant submitted a new set of studies in to support the bioequivalence of the guaifenesin component of their proposed product to that of an approved reference guaifenesin product. New bioequivalence studies were not conducted for the hydrocodone or pseudoephedrine components as BE had been previously determined.

Reference ID: 3754888

This CDTL review will provide an overview of the application, with a focus on the newly conducted clinical pharmacology studies submitted to support BE of the guaifenesin component of the hydrocodone/pseudoephedrine/guaifenesin combination product. The PDUFA date for this application is June 4, 2015.

2. Background

The product under development is one of the hydrocodone-containing cough/cold products belonging to a group of previously illegally marketed products. According to the Agency's Federal Register notice [(published on October 1, 2007 [Docket No. 2007N-0353], all manufacturers of hydrocodone-containing products had to stop manufacturing these products by December 31, 2007. The Agency has encouraged manufacturers of these and other unapproved products to submit NDAs to obtain approval for marketing these products in the United States. This application is to market a combination product containing hydrocodone bitartrate, pseudoephedrine, and guaifenesin, as an immediate release oral solution containing 2.5 mg, 30 mg, and 200 mg of hydrocodone, pseudoephedrine, and guaifenesin, per 5 mL respectively. Guaifenesin and pseudoephedrine are a well known expectorant and decongestant products, respectively, found in many cough and cold products and listed in the OTC monograph (21 CFR 341.40). The proposed dosage is two teaspoonfuls (10 mL) every 4 hours, not to exceed 4 doses (40 mL) in 24 hours for adults (b) (4) (b) (4)

The Applicant had a pre-IND meeting on March 26, 2007 with the Division to discuss plans to develop two immediate release oral cough and cold solutions, the current NDA 22-279 and the already mentioned related NDA 22-424 hydrocodone and guaifenesin double combination product. (b) (4) The Applicant planned to conduct all pharmacological studies using the triple combination product in order to obtain data to support both combination products. The Applicant submitted an opening IND on September 25, 2007 for the proposed Hydrocodone, Pseudoephedrine and Guaifenesin triple combination oral solution (IND 76,365). As stated above, the original NDA was submitted on August 22, 2008, and was determined to be inadequate to evaluate the BE, drug-drug interaction, and food effect of the triple combination product and a complete response action was taken on June 22, 2009. Subsequent complete response submissions submitted July 26, 2010, July 19, 2011, failed to support approval due to failure of an inspection at the analytical site and failure to meet bioequivalency criteria for the guaifenesin component.

As the Applicant has not conducted clinical trials to assess the safety and efficacy of their proposed combination product, the development program for this application is based on demonstration of bioequivalence to the reference ingredients of the combination product. Since hydrocodone is not a monograph product, clinical studies would normally be required to support a combination product containing hydrocodone and other active ingredients in order to demonstrate the contribution of each component to the combination product as required by regulation (21CFR 300.50). However, because of the prior regulatory precedent of approving

Tussionex Pennkinetic (the combination of hydrocodone and chlorpheniramine) with clinical pharmacology data only, combination products containing hydrocodone and other monograph active ingredients that are permitted monograph combinations can be developed under a clinical pharmacology program only. Therefore, clinical efficacy and safety studies may not be necessary to support this combination product provided that the applicant carries out a satisfactory clinical pharmacology program. However, lack of such a program (lack of bioequivalence) would not allow the Applicant to rely on the Agency's previous determination of safety and efficacy for the reference products and therefore require the Applicant to support any differences with clinical studies or evaluate and correct the reason(s) for lack of bioequivalence and repeat the bioequivalence studies.

Of note is that Hycodan (ENDO Pharmaceuticals) was the initial hydrocodone reference product as listed in the Orange Book. However, the manufacturer of Hycodan discontinued marketing Hycodan solution. The Applicant subsequently used a generic hydrocodone bitartrate product as the hydrocodone reference product, however, Hycodan is still the reference drug for reliance for safety and efficacy of hydrocodone.

3. CMC/Device

The proposed product is an aqueous oral immediate release solution containing hydrocodone bitartrate 2.5 mg, pseudoephedrine hydrochloride 30 mg, and guaifenesin 200 mg per 5 mL. Inactive ingredients (excipients) include sorbitol, glycerin, polyethylene glycol, methylparaben, propylparaben, citric acid, sodium citrate, saccharin, D&C Red #33 and FD&C Blue (b) (4) black raspberry flavor.

Hydrocodone bitartrate USP used in the test formulation was manufactured by (b) (4) (b) (4)

The proposed combination drug product is manufactured and supplied by Mikart, Inc. 2090 Marietta Blvd, Atlanta, GA 30318. This facility's EES status is acceptable. The drug product release specifications include appearance, pH, specific gravity, identification, and assays for preservatives, impurity, residual solvents and microbial limits.

Stability data conducted in 16 oz and 4 oz HDPE bottles support a 24 month expiry.

The one outstanding product quality issue identified during review of the last submission, that the product release specification lacks a test and acceptance criterion for Burkholderia cepacia, has been addressed. Specifically, the product's release and stability specifications have each been updated to include testing for Burkholderia cepacia with the acceptance criterion for this test being "absent"(refer to microbiology reviewer John Metcalfe's review).

4. Nonclinical Pharmacology/Toxicology

No new non-clinical pharmacology/toxicology studies were required or performed for this application.

5. Clinical Pharmacology/Biopharmaceutics

The Applicant submitted 5 clinical pharmacology studies to support the BE of guaifenesin to the listed reference product (Table 1). The bioequivalence of hydrocodone was already demonstrated (the 90% CI for the ratio of the geometric means of the test/reference products for the AUC and C_{max} were within 80 – 125%) in study S11-0028, a single-dose, randomized, three-treatment crossover study under fasting condition in 42 male and female healthy volunteers aged 18 to 64 years. In that study, the geometric mean ratio (test/listed) of AUC 0–t, AUC $_{0-\infty}$, and C_{max} were 0.990 (90% CI = 0.947, 1.035), 0.996 (90% CI = 0.951, 1.043), and 0.871 (90% CI= 0.825, 0.920), respectively.

This review will focus on study 1147601, the pivotal clinical pharmacology study which demonstrated BE between the test and reference guaifenesin components.

Table 1. List of Applicant's submitted BE studies

Study #	Study Design*	# of subjects	Reference listed drug
11267601	3-way XO	17	Children's Mucinex® Chest Congestion Guaifenesin Syrup manufactured by (b) (4)
11267602	2-way XO	30	Guaifenesin Syrup manufactured by (b) (4)
11267603	2-way XO	29	Children's Mucinex® Chest Congestion
11267604	2-way XO	36	Children's Mucinex® Chest Congestion
11467601*	2-way XO	36	Refenesen™ Mucus Relief Expectorant

*Study 11467601 was the pivotal BE study for guaifenesin
Source: Clinical pharmacology review by Dr. Yunzhao Ren

Bioequivalence for guaifenesin
Study 1147601:
Design
Study 11467601 was the pivotal study conducted by Mikart, Inc. to address guaifenesin BE deficiency from the prior submission. It was an open-label, randomized, single-center, single-dose, two-treatment, two-period, two-sequence, crossover study under fasted conditions comparing equal doses of guaifenesin (400 mg/10 mL) from the test product and the listed product. A total of 36 healthy adults enrolled and completed the 2-period study. A total of 18 PK samples per subject per period were collected within 5-hour post-dose. There was a 24 hour washout between treatments. Subjects received the following 2 treatments:

Test product (A): Hydrocodone bitartrate, Guaifenesin, and Pseudoephedrine HCl oral solution 2.5 mg/200 mg/30 mg per 5 mL (supplied by (b) (4))

Listed product (B): Refenesen™ Mucus Relief Expectorant (guaifenesin), 200 mg/5 mL distributed by Reese Pharmaceutical

Reference ID: 3754888

Results

The results showed that Applicant's test guaifenesin product was BE to the listed product. The geometric mean ratio (test/listed) of AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were 0.969 (90% CI = 0.920, 1.020), 0.967 (90% CI = 0.919, 1.019), and 0.925 (90% CI= 0.850, 1.007), respectively (Table 2).

Table 2. Study 11467601: Comparison of PK of guaifenesin between the test product (A) and the listed product (B)

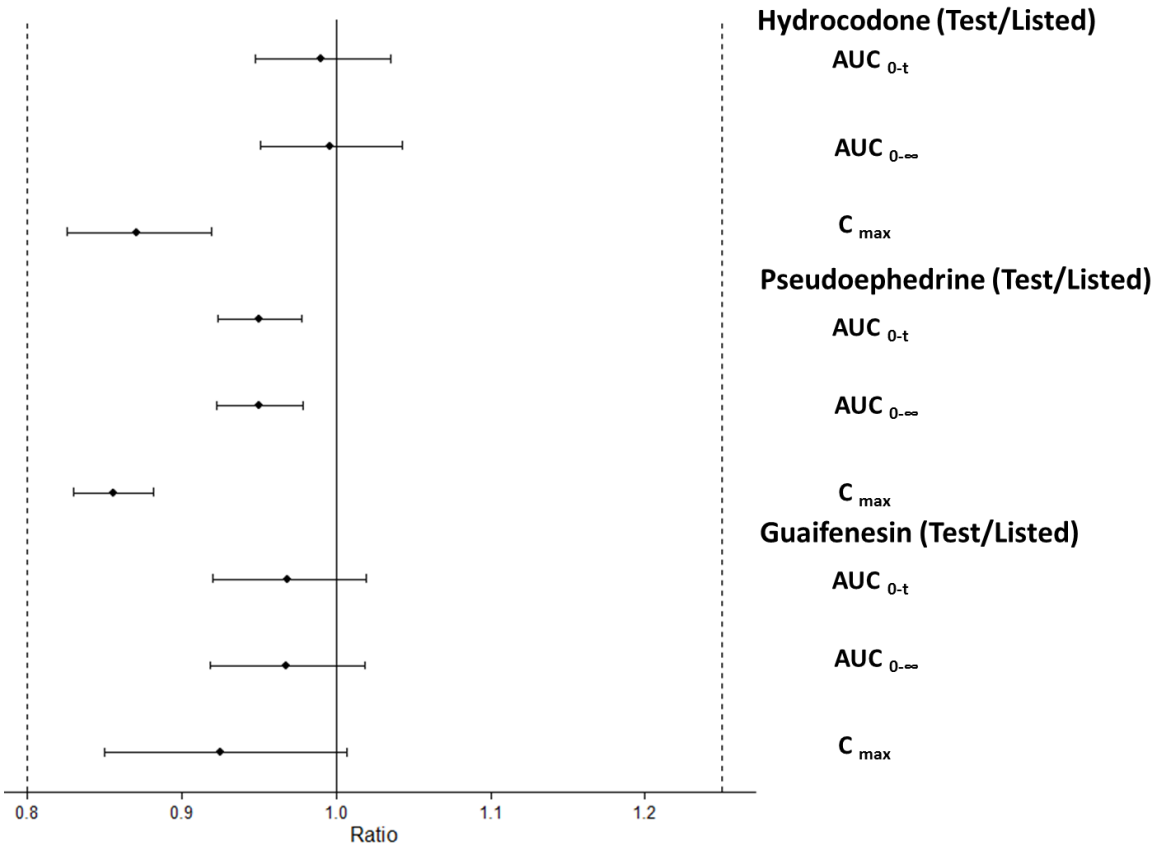
Parameter	Test product (A)*	Listed Product (B)*	Ratio (A/B)	90% Lower Limit of Ratio	90% Upper Limit of Ratio
AUC_{0-t} (ng·h/mL)	2519	2601	0.9687	0.9203	1.0197
AUC_{0-inf} (ng·h/mL)	2603	2690	0.9674	0.9188	1.0186
C_{max} (ng/mL)	2015	2178	0.9253	0.8500	1.0072
T_{max} (hour)	0.42 (0.17 – 1.5)	0.42 (0.25 – 0.83)	-	-	-

* Least-squares geometric means for areas and peak concentrations. Tmax reported as median (range).
Means were adjusted by treatment, sequence and period in a general linear model.
Source: adapted from CSR report-body-11467601, page 7, Table 2.1

A summary of the PK data demonstrating BE between both the hydrocodone (from previous submission) and guaifenesin test products and their respective reference products can be found in Figure 1.

Reference ID: 3754888

Figure 1. Forest-plot display of guaifenesin BE results of study 11467601 from the current submission and hydrocodone and pseudoephedrine BE results of study S11-0028 from the prior submission. (Source: Table 2 and CSR study-report-s11-0028-ich-sections-1-15.pdf, page 53, Table 11.4.7.1)



Food effect
Study S11-0029 (previously reviewed):
Design
This was a single-dose food effect cross-over study to assess the impact of food on the bioavailability of Mikart's hydrocodone, pseudoephedrine, and guaifenesin oral solution that was submitted and reviewed at the time of the first submission by Dr. Arun Agrawal (review dated January 28, 2011). Eighteen healthy male and female subjects 18 to 64 years of age were randomized to receive a single open-label of dose of the proposed hydrocodone and guaifenesin oral solution under fed and fasting conditions with 15 subjects completing the study. At least a 7-day washout period was observed between the doses.

The systemic exposure of hydrocodone and pseudoephedrine were comparable between fed condition and fasted condition for both products. The T_{max} of hydrocodone and pseudoephedrine were delayed approximately 40 minutes and 25 minutes, respectively, under the fed condition compared to fasted condition, which is consistent with the observations from other cough and cold hydrocodone-containing immediate release preparations.

For guaifenesin, the AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} was 26%, 19%, and 54% lower under fed condition compared to fasted condition. The same trend has been observed with other

Reference ID: 3754888

approved prescription guaifenesin-containing cough and cold oral solutions. The AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of guaifenesin was 48%, 47%, and 69% lower under fed condition compared to fasted condition in NDA 205474. Food did not affect T_{max} of guaifenesin.

6. Clinical Microbiology

The ONDQA microbiology reviewer had previously identified a CMC deficiency in that the drug product release specification lacks a test and acceptance criterion for Burkholderia cepacia, an organism considered objectionable in non-sterile aqueous drug products. This issue has been adequately addressed (see Section 3).

7. Clinical/Statistical- Efficacy

The application relies on a comparison of the bioavailability of the proposed drug product to that of approved reference products hydrocodone, pseudoephedrine, and guaifenesin. No clinical efficacy studies were conducted to support this application.

8. Safety

The safety of the product is based on establishing bioequivalence of the proposed combination product compared to the approved reference product, Hycodan Syrup and Tablets, (NDA 5-213) and the OTC monograph for pseudoephedrine and guaifenesin. Since the guaifenesin component of the proposed drug product failed to meet the bioequivalency criteria, the safety of the proposed drug product could not be supported by the Agency's previous findings for single ingredient or combination products containing guaifenesin. However, in this most recent submission, the Applicant provided data to demonstrate the bioequivalence for the guaifenesin component of the proposed drug product to a guaifenesin reference drug. Since the Applicant had previously demonstrated bioequivalence for the hydrocodone and pseudoephedrine components, the safety of this combination product is now supported by the Agency's previous determination of safety and efficacy for all 3 components.

In the previously submitted clinical pharmacology studies (including adverse event reports from studies #S09-0009 and #S09-0010 which were previously reviewed under this NDA) in which a total of 120 healthy adult subjects received a single dose of 10 mL of an immediate release oral solution containing 5 mg hydrocodone bitartrate, 60 mg pseudoephedrine hydrochloride, and 400 mg guaifenesin there were a total of 34 adverse events (13 headache, 8 dizziness, 4 lightheaded, 3 hot flush, 3 hyperhidrosis, 2 pallor, and 1 drowsiness). These events were mild and resolved without intervention. For the 36 subjects in study 11467601 contained in this submission, there were a total of 16 adverse events, all designated as mild that included nausea (3), dizziness, headache, hyperhidrosis (2 each).

A review of the literature (via a MEDLINE and EMBASE search), and a search of the AERS database for post-marketing safety information for the individual ingredients and any combination thereof were also conducted to support the safety of the proposed product. The post-marketing adverse events from the AERS database covered the period from January 1, 2003 through December 31, 2007 while the literature search covered the individual ingredient for the past 2 years and combination products for the past 10 years.

Reference ID: 3754888

Per federal regulation 21 CFR 314.50(d)(5)(vi)(b), a 120-day safety update including data from clinical studies, animal studies, and other sources is required. However, there are no additional animal or clinical safety studies the Applicant has conducted for the test drug and the test drug has not been manufactured and marketed. Thus, there was no new information to include in the safety update.

9. Advisory Committee Meeting

An advisory committee meeting is not necessary for this application. The active ingredients present in this product are well known as individual drug substances, and as previously discussed, based on the current monograph and the Agency's prior precedent, the combination of products of these classes are accepted for the proposed indications.

10. Pediatrics

(b) (4) the Applicant requested a waiver for children under 6 years of age. (b) (4) (b) (4)

This issue was discussed with the PeRC on April 29, 2012; the committee agreed that the PK and safety studies with the focus on the hydrocodone component were justified.products for the same age groups. The request for waiver for children under 6 years of age is based on the fact that the extended release hydrocodone cough and cold product, Tussionex, is contraindicated for use in children less than 6 years of age (because of the risk of fatal respiratory depression) as well as the risk of respiratory depression in young children caused by immediate release hydrocodone containing cough and cold products. It is then appropriate to waive studies for pediatric patients less than 6 years of age because of this safety concern. However, although hydrocodone is currently labeled for use in children down to 6 years of age, safety concerns regarding dose-related respiratory depression raise the issue of the need to be assured of the most appropriate dose for the pediatric population 6 years of age and older. In view of this dose-related safety concern, it is appropriate to require the Applicant to establish the appropriate dose of hydrocodone for the pediatric (less than 18 years) population. Hydrocodone was approved under Drug Efficacy Study Implementation (DESI) review and the basis for the dose selection for the pediatric population is unclear. The doses of pseudoephedrine and guaifenesin in the proposed combination product are the same as the doses in the Agency's approved OTC cough/cold monograph. Since the Agency is not aware of any new safety concerns with these ingredients at these doses and the current monograph is still in effect, the proposed doses for pseudoephedrine and guaifenesin in this combination solution should be acceptable; however pharmacokinetic (PK) data for adequate dose selection and additional safety data should be required for the hydrocodone component. This issue was discussed with the PeRC on April 29, 2012; the committee agreed that the PK and safety studies with the focus on the hydrocodone component were justified. The timelines agreed to with the company were consistent with those previously agreed to for other recently approved cough and cold products.

11. Other Relevant Regulatory Issues

Withdrawal and Abuse Potential

The Controlled Substances Staff (CSS) was consulted to give their opinion on the abuse potential for the Applicant's hydrocodone containing triple combination product during a previous review cycle. The CSS was concerned that the other ingredients could potentiate the abuse potential of hydrocodone and recommended that this potential be studied with animal and/or human studies (Memorandum, Consult on NDA 22-279, N000, Controlled Substance Staff, March 27, 2009). On June 12, 2009, a CDER regulatory briefing was held to discuss the need for abuse potential studies for these products. The consensus from the panel was that abuse potential assessment was not required for these combination products. These combinations are currently in Schedule III and have abuse potential class labeling and it is not clear that the information from abuse potential studies will impact scheduling. Further, these types of combinations have been on the market for years and there has been no safety concern raised regarding an increase in the abuse potential of these combinations. The panel recommended that a post-marketing signal could trigger the need for abuse potential studies for these products.

Inspections
The Division sent a request for inspection of the analytical and clinical sites to the Division of New Drug Bioequivalence Evaluation (DNDBE) and the Office of Study Integrity and Surveillance (OSIS) on January 29, 2015. DNDBE and OSIS responded on February 4, 2015, by recommending accepting the data without an on-site inspection because OSIS inspected the site listed below within the last four years. The inspectional outcomes from the inspections were classified as No Action Indicated.

Compliance with Good Clinical Practices
The clinical pharmacology study in this application was conducted in accordance with Good Clinical Practices, and in particular with the requirements of 21 CFR Part 314.50(3)(i). The Applicant certified that the clinical contractor conducted the study in compliance with Institutional Review Board regulations and with Informed Consent Regulations.

Financial Disclosures
The Applicant certified that there was no financial arrangement with the clinical investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). The Applicant stated that the clinical investigator of the clinical pharmacology studies in this application certified that he did not have a proprietary interest in the proposed product or a significant equity in the Applicant.

12. Labeling

Proprietary Name

The previously proposed trade name, Hycofenix, was reviewed and deemed to be acceptable by the Division of Medication Error Prevention and Analysis (DMEPA).

Physician Labeling

Appropriate labeling based on the labeling of recently approved similar hydrocodone-containing cough and cold products was submitted by the Applicant and has been reviewed by specific disciplines and consultants (OPDP, DMEPA, etc.). Minor edits in format, to remove

Reference ID: 3754888

promotional language, and bring the label up to date with current best labeling practices have been made. Final labeling has been agreed to.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action is approval. Mikart Inc. has submitted adequate data to support approval of hydrocodone, pseudoephedrine, and guaifenesin oral solution for use as an antitussive, decongestant, and expectorant in patients 18 years of age and older. The submitted bioavailability study demonstrated bioequivalence for the guaifenesin drug component and bioequivalence had already been established for the hydrocodone and pseudoephedrine components. As a result, the company is able to rely on the Agency's previous determinations of safety and efficacy for hydrocodone, pseudoephedrine, and guaifenesin.

- Risk Benefit Assessment

Based on the Agency's previous determination of safety and efficacy for hydrocodone, pseudoephedrine, and guaifenesin as antitussive, decongestant, and expectorant products, respectively, the overall risk and benefit assessment for the proposed cough and cold product is acceptable.

- Recommendation for Postmarketing Risk Management Activities

Hydrocodone is a Schedule II controlled substance known to have a certain level of abuse potential. Therefore, this combination product will be labeled as a Schedule II narcotic and will be available by prescription only. The abuse potential will be managed with appropriate labeling and routine pharmacovigilance.

- Recommendation for other Postmarketing Study Commitments

PREA PMR Studies

Although hydrocodone was approved under DESI and is currently labeled for use in children down to 6 years of age, safety concerns of dose-related respiratory depression over the last few years raise the issue of the need to be assured of the most appropriate dose for the pediatric population. In view of this concern, the Applicant will need to establish the dose and safety of hydrocodone for the pediatric (< 18 years of age) population by conducting PK and safety studies in children from 6 to less than 18 years of age. The following PREA-required studies and timelines have been agreed to with the Applicant:

1. A single-dose pharmacokinetic study whose primary objective is to identify the dose(s) of [redacted] (b) (4) for children (aged 6 to 11) and adolescents (aged 12 to 17 years). The population eligible for enrollment should be otherwise healthy children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment.

   Final Protocol Submission: 01/2016

Reference ID: 3754888

Trial Completion: 07/2017
Final Report Submission: 01/2018

2. An open-label multi-dose safety and tolerability study in children (aged 6 to 11) and adolescents (aged 12 to 17 years). The population eligible for the study would be children and adolescents with cough/cold symptoms for whom a combination product that includes an opioid antitussive would be an appropriate symptomatic treatment. The study will enroll a total of approximately 400 children aged 6 to 17 inclusive in two cohorts (6-11 years, 12 to 17 years).

   Final Protocol Submission: 07/2019
   Trial Completion: 01/2023
   Final Report Submission: 07/2023

Reference ID: 3754888

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

/s/

ANTHONY G DURMOWICZ
05/13/2015