CLINICAL REVIEW

Application Type	NDA
Submission Number	22-450
Submission Code	N000
Letter Date	May 13, 2009, June 23, 2009, June 26, 2009
Stamp Date	May 15, 2009, June 23, 2009, June 26, 2009
PDUFA Goal Date	November 13, 2009
Reviewer Name	Christina Fang, M.D., M.P.H.
Review Completion Date	October 17, 2009
Established Name	Acetaminophen IV injection
(Proposed) Trade Name	(b) (4)
Therapeutic Class	Analgesic and antipyretic
Applicant	Cadence Pharmaceuticals, Inc.
Priority Designation	3P
Formulation	IV solution containing acetaminophen (10 mg/mL)
Dosing Regimen	1 g every 6 hours or 650 mg every 4 hours in adults 7.5-15 mg/kg by age and body weight in pediatric
Indication	Acute pain and fever
Intended Population	Hospitalized patients

TABLE OF CONTENTS

1. RECOMMENDATIONS/RISK BENEFIT ANALYSIS

1.1 Recommendation on Regulatory Action

IV acetaminophen injection is recommended for a regulatory action of approval based on clinical findings, pending adequate response from the Applicant to address all the non clinical deficiencies.

The recommendation for approval is based on an acceptable benefit/risk ratio according to my review of clinical efficacy data and Dr. Spaulding's review of clinical safety data submitted in NDA 22-450.

The antipyretic efficacy of IV acetaminophen injection for treating fever is supported by positive findings from the fever study (b) (4)

The analgesic efficacy of IV acetaminophen injection for treating mild to moderate pain is supported by positive findings from the study of post operative pain associated with laparoscopic surgery (b) (4)

The use of IV acetaminophen at recommended dosage is considered reasonably safe based on the lack of new safety signals or unexpected events in clinical trial database, the known safety profile of the acetaminophen moiety, and the anticipated short-term use of the IV formulation and close safety monitoring in a hospital setting.

(b) (4)

1.2 Risk Benefit Analysis

The benefits of treating fever with IV acetaminophen have been shown in terms of clinically meaningful treatment differences from placebo in the degree of temperature reduction and the percentage of patients with temperature reduction to a lower degree.

(b) (4)

(b) (4)

(b) (4) Although IV acetaminophen alone is not expected of capable of treating post-operative pain that is severe in nature, it is considered therapeutically beneficial in use as a supplement to opioid treatment in patients who might not be able to use larger doses of opioid analgesics.

In evaluation of safety data collected from hospitalized patients, acetaminophen-induced toxicities might overlap with clinical abnormalities associated with surgical complications, concurrent illness, and concomitant medication, making it a challenge to assess the causal relationship between the study drug and adverse events.

(b) (4)

Safety data were pooled from five pediatric clinical studies in 355 subjects (47 neonates, 64 infants, 171 children, and 73 adolescents), including 305 treated with the IV acetaminophen under NDA review and 50 (43 neonates and 7 infants) treated with Perfalgan® in the population PK study by Palmer et. al. The longest exposure was about five days in 61 pediatric patients (1 neonate, 5 infants, 26 children, and 33 adolescents) and more than six days in four pediatric patients (refer to Listing 16.2.1.15 of the study report) in Study CPI-APA-352, which was the only pediatric study with more than two days of exposure. Neonates appeared to be the subpopulation with the least exposure to the proposed formulation of IV acetaminophen (exposure in four neonates with the longest exposure of about 5 days in one of the four neonates). Based on pooled safety data from the five studies there were no reports of deaths and 30 (8.5%) reports of serious AEs, which were not considered as caused by acetaminophen treatment according to Dr. Spaulding's safety review. AE-related dropouts occurred in five cases (1.4%), all due to elevation of liver function parameters that might be related to multiple contributing factors. The most common AEs reported in ≥ 5% pediatric subjects exposed to IV acetaminophen were nausea, vomiting, constipation, pruritus, agitation and atelectasis. There were no new safety signals or unexpected adverse events identified in the pediatric studies.

The most important safety concern with the use of IV acetaminophen is the potential risks for hepatic toxicities associated with much higher peak exposures (72 to 88% higher Cmax after a single 1 g dose, 53% higher Cmax after q6 hour repeated dosing and 97% higher Cmax after q4 hour repeated dosing of 1 g IV acetaminophen)

compared to that of oral formulation, in the subpopulation of hospitalized patients with increased risks to drug-induced liver toxicities due to volume depletion, concurrent illness, multiple treatments, and hepatic and/or renal impairments. (b) (4)

In pediatric clinical studies of IV acetaminophen (none had a placebo control) the overall incidence of hepatic AEs was 3.9% (14 reported in 355 pediatric patients). There were four cases (1.1%) of serious hepatic AEs and five dropout cases (1.4%) due to hepatic AEs. Hepatic abnormalities in all nine cases involved liver enzyme elevations and normal total bilirubin, and were judged to be possibly related to acetaminophen treatment. No cases in the pediatric database were identified based on the criteria of Hy's Law based on Dr. Spaulding's safety review.

Unintentional overdose from co-administration of IV acetaminophen and combination products containing acetaminophen is another major safety concern. Because acetaminophen alone is not capable of treating surgical pain that is severe in nature (pain associated with major surgical procedures), there is a strong need for opioid analgesics, which have been commonly prescribed as opioid/acetaminophen combination agents. (b) (4)

In general, the use of IV acetaminophen in a hospital setting is considered reasonably safe as supported by the safety findings from clinical studies with the consideration of known safety profile of acetaminophen established from extensive clinical studies and the OTC marketing experience in the U.S. for many years. The duration of use is anticipated to be limited to two to three days when IV access is still available. Close monitoring of the amount of IV infusion and safety monitoring of adverse events and laboratory abnormalities with the use of IV acetaminophen are expected to be available around the clock in a hospital setting. Warnings in the product labeling about the use of IV acetaminophen in patients at high risks for liver toxicities and about the concomitant administration of other acetaminophen containing drug products should help to reduce the risks.

The benefit/risk ratio is considered acceptable in my opinion.

1.3 Recommendations for Postmarketing Risk Management Activities

(b) (4)

1.4 Recommendation for other Postmarketing Study Commitments

(b) (4)

2. INTRODUCTION AND REGULATORY BACKGROUND

2.1 Product Information

IV acetaminophen injection (IV APAP) is an IV formulation containing 1000 mg acetaminophen in 100 mL solution (10 mg/mL) for the management of acute pain and fever.

The established name of the product is acetaminophen IV injection and the proposed trade names Acetavance™ and (b) (4) were not considered acceptable by DMEPA. The review of the newly submitted trade names is still pending. The active ingredient of the product, acetaminophen is the acetate amide of p-aminophenol. The proposed dosage for acetaminophen IV injection is 1000 mg q6 hour or 650 mg q4 hours up to a maximum daily dose of 4000 mg in *adults and adolescents weighing ≥ 50 kg*; 15 mg/kg q6 hours or 12.5 mg/kg q4 hours up to a maximum daily dose of 75 mg/kg in *adults and adolescents weighing <50 kg as well as in children age ≥2 to 12 years old*; 12.5 mg/kg q6 hours or 10 mg/kg q4 hours up to a maximum daily dose of 60 mg/kg in *infants age 1 to <2 years old*; 10 mg/kg or 12.5 mg/kg q6 hours up to a maximum daily dose of 50 mg/kg in *infants age 29 days to <1 year old*; 7.5 mg/kg q8 or q6 hours up to a maximum daily dose of 30 mg/kg in *full term neonates age up to 28 days old*; 7.5 mg/kg q8 hours up to a maximum daily dose of 22.5 mg/kg in *premature neonates with postmenstrual age 32 to 36 weeks,* as summarized in the table below.

Table 2.1-1 Dosage by Age Group

Age group	Dosage	Maximum single dose	Minimum dosing interval	Maximum daily dose (in 24 hours)
Adults and adolescents, weighing ≥ 50 kg	1000 mg q6h or 650 mg q4h	1000 mg	4 hours	4000 mg
Adults and adolescents, weighing <50 kg	15 mg/kg q6h or 12.5 mg/kg q4h	15 mg/kg	4 hours	75 mg/kg
Children: ≥2-12 years old	15 mg/kg q6h or 12.5 mg/kg q4h	15 mg/kg	4 hours	75 mg/kg
Infants: 1-<2 years old	12.5 mg/kg q6h or 10 mg/kg q4h	12.5 mg/kg	4 hours	60 mg/kg
Infants: 29 days to <1 year old	10 mg/kg or 12.5 mg/kg q6h	12.5 mg/kg	6 hours	50 mg/kg
Full term neonates: up to 28 days old	7.5 mg/kg q8h or 7.5 mg/kg q6h	7.5 mg/kg	6 hours	30 mg/kg
Premature neonates: postmenstrual 32-36 weeks	7.5 mg/kg q8h	7.5 mg/kg	8 hours	22.5 mg/kg

2.2 Currently Available Treatment(s) for Proposed Indication(s)

Non parenteral formulations of acetaminophen and a number of drugs of the NSAID class are currently available for treating fever and mild to moderate pain. IV formulation of ketorolac and ibuprofen are available for treating mild to moderate pain and IV ibuprofen is available for treating fever in the U.S.

2.3 Availability of Proposed Active Ingredient in the United States

There are many acetaminophen containing products currently available in the United States. The information on these products is summarized in the table below by the active ingredient, dosage form and route of administration, strength of formulation, and NDA number of the reference list product (RLD) of the formulation.

Table 2-1 Products Containing Acetaminophen Approved for the U.S. market

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
Rx			
Acetaminophen; aspirin; codeine phosphate	Capsule; oral	150mg;180mg;30mg	081096
Acetaminophen;	Capsule; oral	650mg;50mg	088831

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
butalbital	Tablet; oral	650mg;50mg 325mg;50mg	089988 087811
Acetaminophen; butalbital; caffeine	Capsule; oral	500mg;50mg;40mg 325mg;50mg;40mg	040085 089007
	Solution; oral	325mg/15ml;50mg/15ml;40mg/15ml	040387
	Tablet; oral	750mg;50mg;40mg 500mg;50mg;40mg 325mg;50mg;40mg	040496 089451 088616
Acetaminophen; butalbital; caffeine; codeine phosphate	Capsule; oral	325mg;50mg;40mg;30mg	020232
Acetaminophen; caffeine; dihydrocodeine bitartrate	Capsule; oral	356.4mg;30mg;16mg	040109
	Tablet; oral	712.8mg;60mg;32mg	040316
Acetaminophen; codeine phosphate	Solution; oral	120mg/5ml;12mg/5ml	085861
	Suspension; oral	120mg/5ml;12mg/5ml	086024
	Tablet; oral	650mg;60mg 650mg;30mg 300mg;60mg 300mg;30mg 300mg;15mg	089363 089231 088629 085055 040223
Acetaminophen; hydrocodone bitartrate	Capsule; oral	500mg;5mg	Not RLD
	Solution; oral	500mg/15ml;10mg/15ml 500mg/15ml;7.5mg/15ml 325mg/15ml;10mg/15ml 325mg/15ml;7.5mg/15ml	040508 081051 040834 040482
	Tablet; oral	750mg;10mg 750mg;7.5mg 660mg;10mg 650mg;10mg 650mg;7.5mg 500mg;10mg 500mg;7.5mg 500mg;5mg 500mg;2.5mg 400mg;10mg 400mg;7.5mg 400mg;5mg 325mg;10mg 325mg;7.5mg 325mg;5mg 300mg;10mg 300mg;7.5mg 300mg;5mg no	040094 089736 040084 081223 089689 040100 089699 088058 089698 040288 040288 040288 040148 040148 040099 040556 040556 Not RLD
Acetaminophen; oxycodone hydrochloride	Capsule; oral	500mg;5mg	088790
	Solution; oral	325mg/5ml;5mg/5ml	089351
	Tablet; oral	650mg;10mg 500mg;10mg 500mg;7.5mg 500mg;5mg 400mg;10mg 400mg;7.5mg 400mg;5mg 400mg;2.5mg 325mg;10mg 325mg;7.5mg 325mg;5mg 325mg;2.5mg	040341 Not RLD 040341 089775 040692 040698 040687 040679 040434 040434 040330 040330

Active ingredient	Dosage Form; Route	Strength	RLD, NDA#
		300mg;10mg 300mg;7.5mg 300mg;5mg 300mg;2.5mg	040608 040608 040608 040608
Acetaminophen; pentazocine hydrochloride	Tablet; oral	650MG;EQ 25MG BASE	018458
Acetaminophen; propoxyphene hydrochloride	Tablet; oral	650MG;100MG 500MG;100MG 325MG;100MG 325MG;50MG	017122 Not RLD Not RLD Not RLD
Acetaminophen; tramadol hydrochloride	Tablet; oral	325MG;37.5MG	021123
OTC			
Acetaminophen	Suppository; rectal	650mg 325mg, 120mg, 80mg	018337 Not RLDs
	Tablet (caplet), ER; oral	650mg	019872
	Tablet (geltab), ER; oral	650mg	019872
Acetaminophen; aspirin; caffeine	Tablet; oral	250mg;250mg;65mg	020802
Acetaminophen; clemastine fumarate; pseudoephedrine hydrochloride	Tablet; oral	500mg;eq 0.25mg base;30mg	021082
Acetaminophen; dexbrompheniramine maleate; pseudoephedrine sulfate	Tablet, ER; oral	500mg;3mg;60mg	019453

Source: Orange book, 2009 edition.

2.4 Important Issues with Consideration to Related Drugs

The major safety concern with the use of acetaminophen is the drug induced hepatic injury with potentially serious outcomes, especially in high risk groups such as hepatic impairment or active hepatic disease, alcoholism, chronic malnutrition, severe hypovolemia, and severe renal impairment. Another important safety concern is unintentional overdose since acetaminophen is widely available in many different prescription and OTC combination and single-ingredient products.

2.5 Summary of Presubmission Regulatory Activity Related to this Submission

(b) (4)

(b) (4)

In terms of the pediatric study requirements the Division agreed with the Sponsor's proposal on cross-study comparison of relative bioavailability between pediatric and adult populations (letter dated January 29, 2007), the use of relative PK profiles to bridge adult efficacy to pediatric population in addition to pediatric safety data as basis of approval for pediatric indications, and treating data required for PWR and data required for pediatric approval separately (letter dated July 21, 2008).

2.6 Other Relevant Background Information

IV formulation of acetaminophen developed by Bristol-Myers Squibb (BMS) was first approved as Perfalgan® in France in 2001 and had been approved in approximately 80 countries to date.

Perfalgan® might have different quantitative composition, drug product specification, and impurity content (information not provided by the Applicant) from those of the IV acetaminophen formulation used in the current NDA. One population PK study of mostly neonates used Perfalgan®. Safety data from the study of Perfalgan® were pooled with the other pediatric studies in the Applicant's Integrated Safety Summary.

3. ETHICS AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Integrity

There were some minor inconsistencies between different parts of the submission. (b) (4)

Because the missing information was minor and not considered to change the study outcomes, additional analyses were not requested. The quality of the submission in terms of data organization, retrieval, and completeness was considered acceptable in general.

3.2 Compliance with Good Clinical Practices

The steps to ensure compliance with Good Clinical Practices (GCP) included approval of protocols and informed consent forms by the Institutional Review Boards (IRBs) before the initiation of the study, verification of the original copies of consent forms, checking consistency between CFR data and source documents, monitoring the receipt, storage, dispensing and return of clinical study drugs, etc. A quality assurance system was established in accordance with the current regulations and Good Clinical Practice to conduct study center audit by qualified personnel, to ensure independent and double data entry followed by manual edits and detailed computer-based checks, and to conduct systematic review of the entire database.

(b) (4)

(b) (4)

3.3 Financial Disclosures

The financial disclosure form signed by the Applicant certified that no financial arrangement with the listed clinical investigators (a complete list of all clinical investigators involved in clinical studies was attached to the form) had been made whereby study outcomes affected compensation as defined in 21 CFR 54.2(a); certified that each listed investigator was required to disclose to the Applicant whether the investigator had a proprietary interest in this product or a significant equity in the Applicant as defined in 21 CFR 54.2(b) did not disclose any such interests; and certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

4. SIGNIFICANT EFFICACY OR SAFETY FINDINGS RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry Manufacturing and Controls

(b) (4)

CMC portion of the application is considered adequate and acceptable to support a market approval of the product by the chemistry review team.

4.2 Clinical Microbiology (if applicable)

The manufacture and (b) (4) sterilization of acetaminophen injection is considered acceptable according to the Microbiology Reviewer Denise Miller (refer to the Microbiology Review for detail).

4.3 Preclinical Pharmacology/Toxicology

(b) (4)

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action for acetaminophen is not completely understood. Its analgesic activities appear to be due to elevation of the pain threshold. Its antipyretic activities may be related to its effects on the hypothalamic heat-regulating centers.

4.4.2 Pharmacodynamics

Acetaminophen has been shown to have analgesic and antipyretic activities in animal and human studies.

4.4.3 Pharmacokinetics

Pharmacokinetic (PK) data were obtained from (b) (4) two open label studies in pediatric populations. (b) (4)

(b) (4)

. The two pediatric PK studies were Study CPI-APA-102 (48-hour study) and Study EHRC #26095 (study of Perfalgan® conducted by Palmer et. al. in Australia) and served as database for population PK analyses.

(b) (4)

Key findings in pediatric studies and their comparison to adult PK profile

Using PK data obtained from Study CPI-APA-102 and the Palmer Study with normalization of dosing regimen by body weight, analyses by population PK model predicted consistency in AUC across age groups (infants, children, adolescents, and adults) after a single-dose exposure and at steady state. Only the neonate group had higher AUC than the other age groups in response to both single and repeated exposure. In comparison of urine metabolites between the age groups the percent of dose excreted in the urine as NAPQI appeared to be comparable among different pediatric age groups in Study CPI-APA-102 and comparable to that of adults. Age and body weight were identified as significant covariates for clearance (CL) and body weight alone as a significant covariate for central and peripheral volume of distribution (Vc and Vp) and for inter-compartmental clearance (Q).

Relationship between acetaminophen metabolites and liver function markers

The levels of liver function markers (AST, ALT, and Bilirubin) were independent of the percent (amount) excreted as NAPQI production (acetaminophen mercapturate, 3'-[S-cysteinyl] acetaminophen, and 3'-S-methylacetaminophen) in (b) (4) pediatric populations based on the analyses of data obtained from (b) (4) CPI-APA-102.

5. SOURCES OF CLINICAL DATA AND REVIEW STRATEGY

5.1 Tables of Clinical Studies

Table 5.1-1 Overview of Pivotal Efficacy Studies

Study # Phase	Study Design	Sites	Treatments	N	Study Population Demographics	Use of Data	Review section
(b) (4)							

Table 5.1-2 Overview of Other Efficacy Studies

Study # Phase	Study Design	Sites	Treatments	N	Study Population	Note	Review section
(b) (4)							

Study # Phase	Study Design	Sites	Treatments	N	Study Population	Note	Review section
(b) (4)							
Pediatric studies							
RC210 3 006 Phase 3	Randomized double-blind (non-inferiority) active-controlled	18 France	APAP 1g IV PPA 2g IV Single dose	95 88 T 183	Pediatric inguinal herniorrhaphy	Active-controlled	5.3.4
CN145-001 Phase 3	Randomized, double-blind (non-inferiority) active-controlled	11 France	APAP 1g IV PPA 2g IV Single dose	35 32 T 67	Acute fever of infectious origin Inpatients	Active-controlled	5.3.4
CPI-APA-352 Phase 3	Open label	12 US	APAP; 40-75 mg/kg q4 or 6 h; 30-50 mg/kg q6 or 8 h, neonates IV	100	Pediatric Inpatients	Open label study	5.3.4

Source: Tabular listing of all clinical studies in section 5.2 of the NDA submission and individual study reports.

5.2 Review Strategy

(b) (4)

5.3 Discussion of Individual Studies

(b) (4)

FOLLOWING THIS PAGE, 36 PAGES WITHHELD IN FULL - B4

(b) (4)

5.3.4.3 Pediatric studies

There were three pediatric studies, Study RC210 3 006, CN145-001, and CPI-APA-352. None could be used to support efficacy for the reasons that Study RC210 3 006 and CN145-001 were active-controlled studies using unapproved drug (IV propacetamol) as a control and had a non inferiority design, and that Study CPI-APA-352 was an open-label study without controls. (Refer to Dr. Spaulding's review for safety assessment of pediatric studies.)

5.3.4.4 Conclusion

The results of these studies presented above could not be used to support efficacy for various reasons: (b) (4) ; open-label studies designed to evaluate safety as in Study (b) (4) CPI-APA-352; active-controlled studies with no demonstration of superiority on key efficacy parameters as in Study (b) (4) RC210 3 006, and CN145-001.

6. INTEGRATED REVIEW OF EFFICACY

Summary of Efficacy Results and Conclusions

(b) (4)

Acetaminophen IV treatments have been shown to be efficacious in treating fever and is considered beneficial in treating mild to moderate pain and in supplementing opioid analgesia in treating moderate to moderately severe post-surgical pain in a hospital setting (b) (4)

6.1 Proposed Indication

The proposed indication for acetaminophen IV injection is for the treatment of acute pain and fever.

6.2 Methods/Study Design

(b) (4)

FOLLOWING THIS PAGE, 4 PAGES WITHHELD IN FULL - B4

7. INTEGRATED REVIEW OF SAFETY

Refer to Dr. Spaulding's safety review for information in detail.

8. POSTMARKETING EXPERIENCE

Refer to Dr. Spaulding's safety review for information in detail.

9. APPENDICES

9.1 Literature Review and other Important Relevant Materials/References

Refer to Dr. Spaulding's safety review for information in detail.

9.2 Labeling Recommendations

Labeling will be reviewed separately.

9.3 Advisory Committee Meeting

There is no Advisory Committee Meeting planned for IV acetaminophen. Refer to Dr. Spaulding's safety review for summary information on previous Advisory Committee's recommendations with regard to safe use of acetaminophen containing products.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICALS INC	ACETAMINOPHEN FOR INJECTION FOR IV USE

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

/s/

CHRISTINA L FANG
10/23/2009

ELLEN W FIELDS
10/24/2009