

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
022450Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: September 13, 2010

To: Bob Rappaport MD, Director
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Through: Melina Griffis RPh, Team Leader
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(DMEPA)

From: Richard Abate, RPh, MS, Safety Evaluator
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Subject: Label and Labeling Review

Drug Name(s): Ofirmev (Acetaminophen) Injection 1000 mg/100 mL

Application
Type/Number: NDA 022450

Applicant: Cadence Pharmaceuticals

OSE RCM #: 2010-1118

1 INTRODUCTION

This review provides comments from the Division of Medication Error Prevention and Analysis regarding potential medication error issues identified with the proposed container label, carton and insert labeling for Ofirmev (Acetaminophen) Injection, NDA 022450 submitted by Cadence on May 4, 2010 and May 19, 2010. DMEPA previously provided comments regarding the proposed labels and labeling in OSE reviews # 2009-1010 and 2009-2204. The labels and labeling included in the resubmission and the amendment include revisions based on DMEPA's prior recommendations.

2 MATERIAL REVIEWED

Using Failure Mode and Effects Analysis,¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the revised product labels and labeling submitted May 19, 2010 to identify vulnerabilities that may lead to medication errors. See Appendices for samples of the draft container label and carton labeling.

3 CONCLUSIONS AND RECOMMENDATIONS

Our Label and Labeling Risk Assessment indicates the Applicant revised the proposed container label and carton labeling to include our prior comments and require no additional revisions. The insert labeling includes revisions to Full Prescribing Information Dosage and Administration, Section 2, as recommended by DMEPA in OSE review # 2009-1010. However, the presentation of information within this section introduces vulnerability to confusion that could lead to medication errors. The risks we have identified can be addressed and mitigated prior to drug approval. We provide recommendations below.

3.1 COMMENTS TO THE DIVISION

Insert Labeling –Section 2.4 Instructions for Intravenous Administration

The Applicant uses the phrase (b) (4) to describe an example of a separate empty, sterile container. This statement provides an opportunity for misinterpretation by practitioners as the word (b) (4) could imply that Ofirmev may be further diluted prior to administration. However, Ofirmev does not require further dilution.

DMEPA recommends the use of the phrase “plastic intravenous container” as an alternative (b) (4)

We would be willing to meet with the Division for further discussion, if needed. Please copy the DMEPA on any communication to Cadence with regard to this review. If you have further questions or need clarifications, please contact Abolade Adeolu, project manager, at 301-796-4264.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

REFERENCES

OSE Review # 2009-1010, Acetaminophen Injection Label and Labeling Review, October 6, 2009, Abate, R.

OSE Review # 2009-2204, Ofirmev Label and Labeling Review, December 17, 2009, Abate, R.

APPENDICES

(b) (4)



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22450	ORIG-1	CADENCE PHARMACEUTICA LS INC	Ofirmev (acetaminophen for injection)

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/s/

RICHARD A ABATE
09/13/2010

MELINA N GRIFFIS
09/13/2010

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09/15/2010

EXECUTIVE SUMMARY

Extensive published data, which include prospective and retrospective epidemiologic data, and case series, have not shown an increase in major malformations compared to the background rate in the general population. The prospective cohort study from the Danish National Birth Cohort, which includes data from 88,142 women who were exposed to acetaminophen during pregnancy (includes 26,424 first trimester exposures) provides the most comprehensive and robust data, and forms the basis of the sponsor's proposed labeling language. Although the sample size is large, the study does not rule out the possibility for undetected associations between drug exposure and increased risk for specific malformations. Data regarding the presence or absence of increased risk for specific malformations are inconsistent and, therefore, are not of sufficient quality to include in labeling.

Data regarding acetaminophen exposure during pregnancy and childhood wheeze and asthma risk are concerning; however, they are also inconsistent. Asthma is a complex disease with a multifactorial etiology that is still not completely understood. Limitations in study design, confounding factors, and inconsistencies in outcomes prevent drawing conclusions about causality. Childhood wheeze and asthma often resolve on their own, so more long term data are needed to truly define the risk.

Further studies are needed to investigate this potential safety signal, but because acetaminophen is so broadly used in the pregnant population and acetaminophen products involve many different sponsors, this issue goes beyond the scope of this application. MHT will collaborate with the Office of Surveillance's Division of Epidemiology and OND divisions that oversee acetaminophen containing products to evaluate how to best collect this data.

The Maternal Health Team also reviewed available data on prenatal acetaminophen exposure and acetaminophen use during lactation. There are insufficient data regarding prenatal acetaminophen exposure and adverse pregnancy outcomes. Lactation studies show that a small amount of acetaminophen is secreted in breast milk; the resulting calculated infant daily dose is much less than the therapeutic infant dose.

The sponsor proposed pregnancy category (b) (4) for intravenous acetaminophen based on human data that do not show an increased in risk for major malformations following prenatal exposure to oral acetaminophen. However, the human data evaluating a potential association between prenatal acetaminophen exposure and the occurrence of persistent wheezing and asthma in children are not negative, and therefore, do not support a pregnancy category (b) (4) especially in the presence of animal developmental toxicity data on oral acetaminophen that suggest potential risk of adverse developmental and reproductive outcomes. The sponsor has not conducted reproductive and developmental studies with intravenous acetaminophen. In addition, FDA toxicologists reviewed published preclinical data and determined that the intravenous formulation of acetaminophen contains a higher concentration of 4-aminophenol, a known toxic metabolite of acetaminophen, than oral formulations. This metabolite has been associated with malformations and resorptions in animals. Due to a lack of reproductive toxicology studies with intravenous acetaminophen in this application, and the inability to characterize the toxicity

associated with 4-aminophenol, the Division's toxicologists recommended that Ofirmev be labeled with a pregnancy category C. The MHT concurs with this recommendation.

INTRODUCTION

On May 13, 2009, Cadence Pharmaceuticals Inc. submitted a new drug application to the Division of Anesthesia Analgesia and Rheumatology Products (DAARP) for Ofirmev, an intravenous formulation of acetaminophen. This is a 505 b2 application, and therefore, the sponsor is relying on previously published/and or Agency reviewed clinical data. The proposed indication is for treatment of acute pain and fever. On October 8, 2009, the Division requested that the Maternal Health Team review the literature on the use of acetaminophen during pregnancy and assign a pregnancy category. The original application did not provide adequate human and/or animal data sources and analysis to support the sponsor-proposed pregnancy category (b)(4) designation or to adequately inform the Pregnancy and Nursing Mothers sections of labeling, therefore MHT recommended that DAARP request this information from the sponsor. This review addresses the sponsor's December 10, 2009 submission, which responds to the Agency's request for data to support the Pregnancy and Nursing Mothers sections of labeling. Please see Dr. Carlic Huynh and Dr. Dan Mellon's pharmacology/toxicology review for a discussion of the published data on reproductive and developmental toxicity submitted in support of this application.

BACKGROUND

Acetaminophen was approved by FDA in 1951, prior to the 1979 regulations that established pregnancy categories, and there are no approved acetaminophen containing products labeled with a pregnancy category based on acetaminophen content and any acetaminophen-associated risk. Acetaminophen is found in more than one hundred prescription and nonprescription products and is the analgesic and antipyretic used most commonly by pregnant women.^{1,2} Nonsteroidal anti-inflammatory drugs are used less often during pregnancy based on their association with an increased risk for fetal complications due to premature closure of the ductus arteriosus when used at or after 30 weeks gestation.

Acetaminophen plays an important role to treat fever during pregnancy, both for symptomatic treatment and to prevent adverse pregnancy outcomes. First trimester fever has been associated with an increased risk for neural tube defects³, and fever during pregnancy can result in maternal dehydration and fetal tachycardia. Although it is difficult to distinguish between the adverse effect associated with the underlying cause of fever versus the fever itself, maternal fever during labor is a risk factor for adverse neonatal and developmental outcomes, including neonatal

¹ Werler MM, Mitchell AA, Hernandez-Diaz S, Honein MA. Use of over-the-counter medications during pregnancy. *Am J Obstet Gynecol* 2005;193(pt 1):771-7.

² Headley J, Northstone K, Simmons H, Golding J; ALSPAC Study Team. Medication use during pregnancy: data from the Avon Longitudinal Study of Parents and Children. *Eur J Clin Pharmacol* 2004;60:355-61.

³ Neural Tube Defects. ACOG Technical Bulletin Number 44, July 2003.

seizures, encephalopathy, cerebral palsy, and neonatal death^{4,5,6}. The Centers for Disease Control and the American College of Obstetricians and Gynecologists websites recommend that pregnant women with influenza use acetaminophen (Tylenol®) to treat fever.

Intravenous acetaminophen has been marketed internationally since 2001 by Bristol Myers-Squibb, and it is currently available in approximately 80 countries. Cadence Pharmaceuticals acquired marketing rights for the United States and Canada in 2006.

SPONSOR'S PROPOSED PREGNANCY LABELING

The sponsor proposes the following language for the Pregnancy subsection of Ofirmev labeling:

(b) (4)



Reviewer comments

⁴ Impey L, Greenwood C, Black R, et al. The relationship between intrapartum maternal fever and neonatal acidosis as risk factors for neonatal encephalopathy. *AJOG* 2008;198(1):49.

⁵ Impey L, Greenwood C, et al. Fever in labour and neonatal encephalopathy: a prospective cohort study. *Br J Ob Gyn* 2001;108(6):594-597.

⁶ Jordan DN, Jordaan JL, Association of maternal fever during labor with neonatal and infant morbidity and mortality. *Obstetrics and Gynecology* 2001;98(6):1152-1153.

According to the FDA Toxicologists' review of published reproductive toxicology data, there are insufficient data to characterize the risk associated with the 4-aminophenol metabolite, which is present at higher concentrations in the intravenous formulation and associated with teratogenic effects and resorptions in animals. This is consistent with the regulatory definition of pregnancy category C.

REVIEW OF SPONSOR'S SUBMISSION AND PUBLISHED DATA

Studies that show no increase in malformations

1- Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. Am J Obstet Gynecol 2008; 198:178.e1-178.e

A prospective cohort study of acetaminophen exposure in pregnant women was conducted using the Danish National Birth Cohort (DNBC), a population-based study that enrolled 101,041 pregnant women from 1996 to 2003. Acetaminophen exposure information was obtained through patient questionnaires and interviews, and pregnancy outcomes were obtained from national hospitalization and birth registers. Data for the DNBC are collected at the first prenatal visit (which usually occurs in the first trimester in Denmark) by a self-administered questionnaire, and at four follow-up telephone interviews during the pregnancy. Pregnant women are asked about the use of any kind of analgesic and to identify the drugs from a list of 44 specific products including acetaminophen alone or in combination, including both over-the-counter and prescribed drugs. Participants are also asked about use of other drugs not included in the list, and specifically about drugs used for muscle or joint diseases, fever, and inflammation or infections. For each drug reported, the woman is asked to specify gestational weeks of use.

For this study, duration of exposure was defined as total number of weeks exposed within each trimester. Pregnancy outcomes of women from the DNBC database, who had live born singletons and who provided information on acetaminophen use in the first trimester, were analyzed. Stillbirths, abortions (spontaneous and induced), ectopic pregnancies, hydatiform mole, twins, and triplets were excluded. Children were monitored until they were diagnosed with a congenital abnormality diagnosis in the National Hospital Registry, left the country, or died, or until Jan. 12, 2006 (end of the study follow-up), whichever came first.

Analysis of outcomes from live born singleton children born to 88,142 women who used acetaminophen during pregnancy (included 26,424 first trimester exposures) did not show an increased prevalence of congenital abnormalities (hazard ratio= 1.01, 0.93-1.08) compared with nonexposed children (n = 61,718). The rate of malformations (4.3%) was similar to the general

population rate. Researchers controlled for the following potential confounders in their analysis: indication for use (including fever), advanced maternal age, diabetes, epilepsy, and obesity. Limitations of the study include lack of dose information, and lack of information on abortions and stillbirths.

Reviewer comments

1. *This is the largest study published to date regarding congenital malformations following prenatal acetaminophen exposure and provides the basis for the sponsor's proposed pregnancy category ^(b)₍₄₎ and pregnancy labeling.*
2. *The prospective design, the large number of patients, and confirmation of outcomes by medical records are all strengths of the study.*
3. *Although this study excluded abortions and stillbirths, these outcomes are analyzed in another study, which is discussed later in this review.*

2- Feldkamp M, Meyer R, Krikov S, et al. Acetaminophen Use and Risk of Birth Defects. *Obstetrics and Gynecology* 2010; 115 (1):109-115.

This population-based, case-control study from the National Birth Defects Prevention Study (NBDPS) investigates whether exposure during the first trimester of pregnancy to single ingredient acetaminophen increases the risk of major malformations. The NBDPS evaluates major birth defects ascertained from 10 centers in the United States designed to investigate genetic and environmental causes of birth defects. The case group includes live births, stillbirths, and pregnancy terminations with selected major birth defects identified through population-based birth-defect registries. The study included women who delivered between January 1, 1997, and December 31, 2004, and participated in the telephone interview. Type and timing of acetaminophen use designated based on maternal report. The information requested from each participant with regard to acetaminophen use included product name, start and stop date, duration of use, and frequency of use. Women reporting first-trimester acetaminophen use of a combination product were excluded, resulting in a total of 11,610 children in the case group and 4,500 children in the control group for analysis.

The results show that acetaminophen use in the first trimester does not appear to increase the risk of major birth defects. Among women reporting a first-trimester infection and fever, use of acetaminophen was associated with a statistically significantly decreased odds ratio (OR) for anencephaly or craniorachischisis (adjusted OR 0.35, 95% confidence interval [CI] 0.08–0.80), encephalocele (adjusted OR 0.17, 95% CI 0.03–0.87), anotia or microtia (adjusted OR 0.25, 95% CI 0.07–0.86), cleft lip with or without cleft palate (adjusted OR 0.44, 95% CI 0.26–0.75), and gastroschisis (adjusted OR 0.41, 95% CI 0.18–0.94).

The analysis controlled for underlying maternal illness. Limitations of the study include lack of dose information, possible misclassification of exposure due to maternal self-reporting, and recall bias.

Reviewer comment

The protective effect of acetaminophen in terms of first trimester exposure and decrease in certain birth defects needs to be corroborated by other investigators.

3- Other studies

Cleves, M.A.; Savell Jr., V.H.; Raj, S.; Zhao, W.; Correa, A.; Werler, M.M.; Hobbs, C.A. and the National Birth Defects Prevention Study. Maternal use of acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), and muscular ventricular septal defects. Birth Defects Research (Part A) 70:107-113, 2004.

Using data from the Centers for Disease Control National Birth Defects Prevention Study, the authors did a case-control study to analyze possible associations between muscular ventricular septal defects (mVSDs) and maternal use of acetaminophen or nonsteroidal anti-inflammatory drugs during all stages of pregnancy. Liveborn infants with mVSDs from October 1, 1997 through December 31, 1998 were included in the study. Controls were randomly selected from infants born during the same time period. Mothers completed an extensive interview covering preconceptual, periconceptual, and pregnancy exposures to medication. Women were specifically asked about use of acetaminophen, NSAIDs, and other medications. Information on timing of exposure, frequency and duration of use were obtained. Mothers of 168 cases and 692 controls were included in the analysis.

Acetaminophen use during the first trimester of pregnancy was reported by 62% of case mothers and 57% of control mothers. Reported use of acetaminophen increased to 77% of case mothers and 72% of control mothers for any time during pregnancy. The analysis controlled for indication and maternal fever and did not identify any significant associations between the occurrence of ventricular septal defects and maternal use of acetaminophen or NSAIDs.

Limitations include lack of dose information, and possible misclassification of exposures due to reliance on maternal recall.

Jick H, Holmes LB, Hunter JR, Madsen S, Stergachis A. First-trimester drug use and congenital disorders. JAMA 1981;246(4):343-346.

The authors examined the prevalence of major congenital disorders among the infants of women who used a wide variety of drugs during the first trimester of pregnancy in a prepaid health plan in which automated recording of prescriptions filled and disorders diagnosed at birth was available. Data from Group Health Cooperative of Puget Sound insurance records involved 6,837 live births between July 1, 1977 through December 31, 1979.

There were 493 women with prescriptions for acetaminophen, of whom three (0.6%) had infants with a congenital disorder. The authors concluded that no strong associations between acetaminophen and congenital disorders were found. This study is limited by the lack of data on non-prescription medication use.

Aselton P, Jick H, Hilunsky A, Hunter JR, Stergachis A; First-trimester drug use and congenital disorders. *Obstet Gynecol* 65:451-5, 1985.

This study uses the same database as the previous study by Jick et al to determine the prevalence of major congenital disorders for the period of January 1, 1980 through June 30, 1982. The study included 6509 mothers, 350 of whom filled prescriptions for acetaminophen, and 347 of whom filled prescriptions for acetaminophen with codeine during the first trimester.

In the women who had first trimester exposure to acetaminophen, with and without codeine, no significant increase in malformations was identified. There were 2 infants (0.6%) with congenital disorders born to mothers who used acetaminophen alone, and 3 (0.9%) with congenital disorders born to mothers who used acetaminophen and codeine. This study, like the previous one, is limited by the lack of data on non-prescription medication use.

Heinonen OP et al: *Birth Defects and Drugs In Pregnancy*, Littleton, Publishing Sciences Group, 1977, pp 286-95.

The authors conducted a nested case-control study using data from the National Collaborative Perinatal Project, which monitored 58,282 mother-child pairs during which medication exposures were recorded at the initial prenatal visit and ascertained prospectively. Possible associations between medication exposures and congenital malformations were identified by comparing the malformation incidence for individual agents with the overall incidence in the sample.

Among the 58,282 mother-child pairs, 781 mother-child pairs had acetaminophen exposure any time during pregnancy and of these, 226 mother-child pairs had acetaminophen exposure during the first four months of pregnancy. There were seventeen malformed children (cases) exposed to acetaminophen prenatally, 14 of whom were exposed during the first trimester. Malformed cases were no more likely to have prenatal acetaminophen exposure than nonmalformed controls.

Zierler S, Rothman KJ: *Congenital heart disease in relation to maternal use of Bendectin and other drugs in early pregnancy. N Engl J Med* 313:347-52, 1985.

The authors performed a case-control study of congenital heart disease in Massachusetts and exposure to a variety of medications during pregnancy. There were 298 cases identified from the New England Regional Infant Cardiac Registry and from death certificates, and 738 control infants were randomly selected from birth certificates. Mothers responded to a 14-15 minute telephone questionnaire on medication use during pregnancy, and interviews were conducted about 13 months after delivery. Investigators reviewed medical records for exposure information in 77% of cases and 76% of controls.

This study found no association between congenital heart disease and maternal acetaminophen use during pregnancy. Prevalence odds ratios for acetaminophen were 0.93 (90% confidence interval 0.69–1.2) and 1.4 (90% confidence interval 0.58–3.4) for questionnaire and obstetric

record-derived exposures, respectively, consistent with a lack of effect of acetaminophen exposure on cardiovascular malformations. Exposure to other medication, indication, and maternal age were controlled for.

Nelson MM, Forfar JO. Association between drugs administered during pregnancy and congenital abnormalities of the fetus. Br Med J 1971;1:523-7.

The authors conducted a case-control study in the United Kingdom to compare medication histories of 458 mothers of infants with congenital malformations (175 with major and 283 with minor malformations) with 911 mothers of infants without congenital malformations. All mothers were interviewed regarding drug use during pregnancy before discharge from the maternity unit; this was corroborated by at least one other source: the physician, the pharmacy records, or the hospital records. Only exposures that were corroborated by this “double check” system were included in the study.

There was no association between acetaminophen exposure during pregnancy and congenital malformations. Limitations include the small number of acetaminophen exposures (19/458 cases vs. 27/911 controls).

McElhatton PR, Sullivan FM, Volans GN. Paracetamol overdose in pregnancy. Analysis of the outcomes of 300 cases referred to the teratology information service. Reprod Toxicol 1997; 11:85-94.

Using cases referred to the Teratology Information Service (TIS) in collaboration with the London National Poisons Information Services, McElhatton and colleagues conducted a prospective study to investigate the outcome of pregnancy in 300 women who had self administered an acetaminophen overdose between 1984 and 1992. This study was an expanded follow-up of a previous review of 115 cases⁷. Acetaminophen overdose was the most common reason for referral to the TIS. Overdose was defined as any consumption of a drug not for therapeutic purposes because in the authors’ experience patients usually underreport the dose they took. At the time of referral to the TIS, a questionnaire was completed with available information regarding the overdose and was subsequently sent to the referring center/physician for additional missing information. Outcomes were determined through physician confirmation within two weeks of the referral to TIS and within two months after the expected time of delivery to determine the pregnancy outcome. Data on 300 outcomes are reported in this study.

There were 90 cases that involved exposure to acetaminophen in addition to other drugs. Of these, 65 involved acetaminophen combination products. Overdoses occurred in all trimesters: 118 (39%) in the first trimester, 103 (34%) in the second trimester, and 79 (26%) in the third trimester. The results included 219 normal live-born infants (including two sets of twins), 11 live-born infants with malformations, 16 spontaneous abortions, two late fetal deaths,

⁷ McElhatton PR, Sullivan FM, Volans GN, Fitzpatrick R. Paracetamol poisoning in pregnancy: an analysis of the outcomes of cases referred to the Teratology Information Service of the National Poisons Information Service. Hum Exp Toxicol 1990; 9:147-153.

and 54 elective abortions. None of the malformations was associated with first trimester acetaminophen exposure. All of the spontaneous abortions and one fetal death occurred subsequent to a first trimester overdose. The other fetal death occurred after a second trimester overdose. Ten (63%) of the spontaneous abortions occurred within three weeks of the overdose.

Among the live-born infants, there were no reported clinical signs of renal or hepatotoxicity up to six weeks of age. Post-mortem examinations in three aborted fetuses did not show signs of renal or hepatic damage. One hundred and sixty (53%) mothers received some form of treatment. Thirty-three mothers were treated with acetylcysteine, 16 with methionine, and the remaining had treatments that included ipecac, charcoal, and gastric lavage. Based upon the results, the authors concluded that there is no overall increase in malformations, fetal loss or toxicity following acetaminophen overdose.

Reviewer comment:

The sponsor's submission includes data from other studies which this reviewer has not discussed in this review due to small sample size or limitations in study design. The prospective cohort study from the Danish National Birth Cohort provides the most comprehensive and robust data, and forms the basis of the sponsor's proposed labeling language. Although the data are reassuring, it is possible that rare malformations may have been missed. It may be useful to include other epidemiologic data to labeling to support the findings from this study.

Studies that show an increase in overall malformations

Thulstrup AM et al. Fetal growth and adverse birth outcomes in women receiving prescriptions for acetaminophen during pregnancy. Am J Perinatology 1999; 16(7); 321-26.

A two fold increase in the prevalence of congenital abnormalities was observed in a case-control study using data from the Danish North Jutland Pharmaco-Epidemiological Prescription Database. The study was restricted to multiparous women exposed up to 30 days before conception and/or during pregnancy. Out of 55 women exposed during the first trimester, there were six newborns with malformations. There was one ventricular septal defect, two congenital dislocations of the hip of which one did not require treatment, one stenosis of the tear canal, one unspecified hernia and one megalocornea.

Reviewer comments

There is no pattern of malformations, which makes one suspect that these are random findings. The small number of patients in this study makes it impossible to draw any conclusions regarding these findings, and it is not clear whether outcomes from women living in this limited geographical location can be generalized to other populations. In addition, the study did not control for maternal conditions that led to acetaminophen use, such as sustained fever, which can also increase the risk for congenital malformations.

Studies that show an increase in specific malformations

Abnormalities of the ear, face, and neck

Rebordosa C, Kogevinas M, Horváth-Puhó E, et al. Acetaminophen use during pregnancy: effects on risk for congenital abnormalities. Am J Obstet Gynecol 2008; 198:178.e1-178.e

Data from the Danish National Birth Cohort (study design discussed previously on p. 5 of this review) showed an increased prevalence for “medial cysts, fistula, and sinus” (congenital abnormalities of the ear, face, and neck) among children born to women exposed to acetaminophen during pregnancy with an adjusted hazard ratio of 2.15 (1.17-3.95). The authors expressed caution in interpreting this finding, which they state may have been due to the multiple comparison nature of the study.

Reviewer comments

The authors do not draw any conclusions from the study findings. These malformations have never been previously reported with acetaminophen exposure.

Gastroschisis

A case-control surveillance program from the Slone Epidemiology Unit (Boston University School of Public Health), which focused on first trimester drug acetaminophen use and gastroschisis (n=76), reported a "nonsignificant elevation" of relative risk (RR = 1.7; 95% CI (1.0-2.9)) for pregnancies including acetaminophen use⁸. A subsequent study⁹ by the same investigators identified 206 infants with gastroschisis and found a small but statistically significant increase in risk associated with acetaminophen exposure (odds ratio=1.5, 95% confidence interval 1.1-2.2).

Torfs et al were unable to demonstrate a significant association between maternal acetaminophen use in the first trimester and increased risk for gastroschisis in another case-control study that included 110 infants with gastroschisis¹⁰.

Reviewer comments

While case-control studies are useful for confirming findings in other epidemiology studies and for generating hypotheses about potential outcome associations, these conflicting data need to be corroborated with data from other study approaches. At this time, the data are conflicting and do not allow us to draw any conclusions regarding an association between acetaminophen exposure in utero and gastroschisis.

⁸ Werler MM, Mitchell AA, Shapiro S: First trimester maternal medication use in relation to gastroschisis. *Teratology* 45:361-7, 1992.

⁹ Werler MM, Sheehan JE, Mitchell AA: Maternal medication use and risks of gastroschisis and small intestinal atresia. *Am J Epidemiol* 155(1):26-31, 2002.

¹⁰ Torfs CP, Katz EA, Bateson TF, Lam PK, Curry CJR: Maternal medications and environmental exposures as risk factors for gastroschisis. *Teratology* 54:84-92, 1996.

Studies on risk of wheezing and asthma in children who were exposed to acetaminophen in utero

Shaheen SO et al. Paracetamol use in pregnancy and wheezing in early childhood. *Thorax* 2002; 57: 958-63.

This prospective cohort study used the population based UK Avon Longitudinal Study of Parents and Children (ALSPAC) data from 9,400 children to evaluate a possible association between prenatal exposure and wheezing in children at 30-42 months of age. The ALSPAC is a prospective study of 14,541 pregnancies that resulted in 14,062 live births, of which 13,988 survived to one year. Women were enrolled as early in pregnancy as possible based on estimated date of delivery between 1 April 1991 and 31 December 1992. On the basis of actual deliveries during this time period, approximately 85-90% of eligible pregnant women enrolled in the study. The study collected information through multiple plain language questionnaires completed by the pregnant woman during pregnancy and by care givers for the child starting at six months of age and yearly thereafter.

Through questionnaires, women were asked twice during pregnancy (at 18–20 weeks and 32 weeks) about their usage of paracetamol and aspirin. Frequency of exposure was classified as every day, most days, sometimes, or not at all. Only 0.2% of mothers reported daily use of paracetamol at 18-20 weeks, so the authors combined this category with use on “most days” for data analysis in this study. Six months after birth, mothers were asked whether the infant had been given paracetamol during the first six months of life with the following response choices: never, one episode only, or two or more episodes. In addition, at six months after birth and at yearly intervals thereafter, mothers were asked about wheezing and eczema symptoms in their child.

The authors included many potential confounding factors in the regression models used during data analysis. These potential confounders are shown in Table 1. The study controlled for maternal history of asthma, smoking and infection during pregnancy. While the primary exposure of interest was paracetamol use during pregnancy and infancy, the authors also evaluated aspirin use during pregnancy to examine whether any associations with prenatal paracetamol were specific of common to analgesics more generally given their shared indications for use.

The authors showed that frequent paracetamol use (use every day or most days) in late pregnancy (20–32 weeks), but not in early pregnancy (<18–20 weeks), was associated with an increased risk of wheezing in offspring at 30–42 months of age [adjusted odds ratio (OR) compared with no use 2.10 (95% CI 1.30 to 3.41); p=0.003], particularly if wheezing started before 6 months of age [OR 2.34 (95% CI 1.24 to 4.40);p=0.008].

Study limitations include lack of information on dose, use of combination products and other medications. Postnatal infection, exposure to other medications, and exposure to acetaminophen after 6 months of age were also not accounted for. The study was also limited by the small number of patients who used paracetamol frequently (1 % of the study population).

Reviewer comments

- 1. The classification used to define frequency of exposure defined as “sometimes” is not very precise, as a patient may interpret this as three times a week or once every few months.*
- 2. In order to explain the study findings the authors propose a theory that is based on the decline in fetal lung glutathione transferase (GST) activity after 15 weeks gestation. GST conjugates the toxic metabolite of paracetamol, N- acetyl-p-benzoquinoneimine (NAPQI),*

with glutathione into a non-toxic metabolite. Glutathione is an antioxidant that is found in respiratory tract lining fluid¹¹. A decline in GST activity may result in an accumulation of this toxic metabolite and a decline in glutathione, which in turn may cause oxidative stress and damage to fetal airway epithelium and increase vulnerability of the airways to more damage after birth, leading to postnatal asthma.

Shaheen SO, Newson RB, Henderson AJ, Headley JE, Stratton FD, Jones RW et al. Prenatal paracetamol exposure and risk of asthma and elevated immunoglobulin E in childhood. Clin Exp Allergy 2005; 35:18-25.

Re-evaluation of the above cohort at 69 to 81 months of age was done by a questionnaire at 81 months of age that asked whether the child had wheezing or was diagnosed with asthma in the past 12 months.

The results showed an association between asthma and in-utero acetaminophen exposure in 1,062 children reportedly diagnosed with asthma, who were born to mothers who used acetaminophen during the second half of pregnancy. For mothers who took acetaminophen “sometimes” between 20 and 32 weeks of pregnancy, there was an association with asthma (OR 1.22, 95% confidence interval 1.06-1.41, $p=0.0037$). However, for mothers who took acetaminophen “most days or daily” during this period, there was no statistically significant association between asthma and maternal acetaminophen use, even though the odds ratio was higher (odds ratio=1.62, 95% confidence interval 0.86-3.04, $P=0.0037$). The authors explain the discrepancy in these results as being due to the very small number of children in the “most days or daily” exposure group ($n=66$). Limitations of the study include those previously discussed (listed above).

Reviewer comments

- 1. The risk of asthma at age 6-7 associated with occasional paracetamol use in late pregnancy was small. The risk of asthma at age 6-7 associated with frequent use was not statistically significant.*
- 2. Due to limitations that include the inaccurate assessment of exposure frequency and dosing, and the small number of patients in the frequent use group, it is difficult to draw conclusions from this study.*

Rebordosa C, Kogevinas M, Sørensen HT, Olsen J. Prenatal exposure to paracetamol and risk of wheezing and asthma in children: a birth cohort study. Int J Epidemiol 2008; 37(3):583-90.

Using Danish National Birth Cohort data of 66,445 18-month old children and 12,733 seven year old children of women who participated in an interview regarding exposure to acetaminophen during pregnancy, the authors examined the association between prenatal paracetamol exposure and wheezing and asthma in children at ages 18 months and 7 years. Women were interviewed twice during pregnancy, and post-natally when the child was six months old and eighteen months

¹¹ Eneli I et al. Acetaminophen and the risk of asthma. Chest 2005;127;604-612.

old. Pregnant women were asked about the use of any kind of analgesic and to identify the drugs from a list of 44 specific products including paracetamol. The same procedure was followed for drugs used to treat joint and muscle diseases, inflammations, infections, fever, allergy, asthma and several other diseases. The women were also asked to indicate the specific gestational weeks of use, on a week-by-week basis. Duration of exposure was defined as total number of weeks exposed within each trimester. Information about paracetamol use by the child was obtained at the 6 and 18-months-old interviews. When the children were 18-months-old, their mothers were asked if the child had ever had wheezing and if a physician had ever diagnosed them with asthma or bronchitis. At the 7-year interview, the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire was used to get information about their child's asthma symptoms, physician-diagnosed asthma, wheezing episodes and wheezing in the past 12 months. Using Danish residents' unique civil registration numbers to link to the Danish National Hospital Registry all children's hospitalizations due to asthma and bronchitis were identified.

The authors found a small but statistically significant increased risk of physician-diagnosed asthma or bronchitis among children at 18 months [relative risk (RR) = 1.17, 1.13-1.23], hospitalizations due to asthma up to 18 months (hazard ratio = 1.24, 1.11-1.38) and physician-diagnosed asthma at 7 years (RR = 1.15, 1.02-1.29). Multiple analyses were done to evaluate risk for various respiratory outcomes based on trimester of exposure, and "any exposure" to acetaminophen. Exposure during all trimesters was associated with wheeze, but the highest risk was observed for acetaminophen use during the first trimester of pregnancy and persistent wheezing (wheezing at both 18 months and 7 years) (RR = 1.45, 1.13-1.85).

The authors controlled for the following potential confounders in their analyses: asthma in the mother, indication for use, and postnatal paracetamol exposure up to 18 months. Limitations of the study include: lack of dose information, the limited data on post-natal infections, and information about concomitant use of other medications. There are also no data on use of paracetamol in children after 18 months of age.

Reviewer comments

- 1. This is the only study that has medical record data to confirm hospitalizations due to asthma in the child.*
- 2. Although data were obtained regarding number of weeks of exposure during pregnancy, the authors do not present the results. It would have been helpful to have relative risk ratios based on total exposure.*
- 3. The results from this study regarding trimester of exposure and risk of wheeze differed from the other studies (greater risk following first trimester exposure). These authors propose a different theory to explain their study findings. They hypothesize that the increased risk of asthma following first trimester exposure may be due to the inability of the fetus to metabolize paracetamol, as glucuronidation (one of the ways paracetamol is metabolized) doesn't develop in the fetus until the second trimester.*

4. *The authors concluded that further investigation is needed, especially regarding the potential duration of an effect and the importance of combined prenatal and postnatal exposures.*

Persky V, Piorkowski J, Hernandez E, Chavez N, Wagner- Cassanova C, Vergara C, Pelzel D, Enriquez R, Gutierrez S, Busso A. Prenatal exposure to acetaminophen and respiratory symptoms in the first year of life. *Ann Allergy Asthma Immunol* 2008; 101(3):271-8.

The authors recruited a total of 345 women during the first trimester of pregnancy and followed up with their children through the first year of life. Only pregnant women at risk of having children with asthma (defined as the unborn child having a first-degree relative with asthma or allergies) were enrolled in the study. Use of acetaminophen in pregnancy was determined by questionnaire in the first trimester, at four to five months of gestation, at seven to eight months of gestation, and at the first post-partum visit. Information on dose or frequency of use was not collected. Respiratory outcomes were determined by questionnaire when the child was 4-6 weeks old, 6 months old, 12 months old, or when the child was 6 and 9 months old. The mother was asked if the child had any episodes of wheezing, coughing, Emergency Room visits for respiratory symptoms, and whether a doctor had told them that their child has asthma.

After controlling for potential confounders, the authors showed that the use of acetaminophen in middle to late (but not early) pregnancy was significantly related to wheezing in the child (odds ratio, 1.8; 95% confidence interval, 1.1-3.0) and to wheezing that disturbed sleep (odds ratio, 2.1; 95% confidence interval, 1.1-3.8) in the child during the first year of life.

Infection during pregnancy, a family history of a first degree relative with asthma, smoking during pregnancy, post-natal exposure to acetaminophen in the first year of life, and Mexican ethnicity were controlled for. Limitations include the lack of information on dose or frequency of use, and the lack of data on childhood medication exposure and infection.

Reviewer comments

1. *Although the authors controlled for first degree relative with asthma, this is still a high risk population due to the urban setting and low socio-economic status.*
2. *The authors propose the same causal hypothesis as Shaheen, that is, that acetaminophen exposure in the second and third trimesters of pregnancy results in depletion of glutathione, which results in oxidative stress and damage to lung tissue, and subsequent respiratory symptoms in the child. The authors conclude that additional confirmation of the study findings are needed.*
3. *This reviewer noted that 65% of study participants were of Mexican background and only 4.8% were college graduates. It is not clear whether findings in this study are generalizable to other demographics.*

Perzanowski et al. Prenatal acetaminophen exposure and risk of wheeze at age 5 years in an urban, low-income cohort. Thorax Oct 22, 2009 e-pub

An ongoing, population-based cohort study of Dominican and African-American children in New York prospectively assessed the use of acetaminophen during pregnancy and current wheeze at five years of age in 301 children. Genotyping was conducted for GST (Glutathione S transferase) polymorphisms as the authors hypothesized that these genetic alterations, which are common in the study population, could increase the risk of asthma following in-utero exposure to acetaminophen. GST is the enzyme that conjugates the toxic metabolite of acetaminophen. The authors discuss that GST polymorphism has been associated with altered susceptibility to asthma and allergic responses with exposure to various pollutants.

Use of acetaminophen, ibuprofen and aspirin during pregnancy was determined by maternal questionnaire during the third trimester of pregnancy. The number of days of use in each trimester was recorded. Questionnaires about the child's health status were administered at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, and 60 months. A child was considered to have wheezed in years 1, 2 and 3 if at least one episode of wheeze was reported. At age five, current wheeze was defined as wheeze in the prior 12 months.

The authors found an association between prenatal acetaminophen exposure in the second trimester (adjusted RR 1.54; 95% CI 1.06-2.25;P=0.02) or third trimester (RR 1.55;95% CI 1.03-2.34;P=0.04) with wheeze at age five years. The risk increased with increasing number of days of prenatal exposure. An association was found between wheezing and the presence of a GSTP1 functional polymorphism, suggesting a mechanism involving the glutathione pathway.

The authors controlled for the following factors in their analyses: maternal asthma, exposure to smoking during pregnancy, psycho-social stressors, race/ethnicity, and post-natal acetaminophen, ibuprofen, and aspirin use up to age three. Study limitations included the lack of information on dose, indication, infection during pregnancy, and child infection. The authors state that another limitation is the small sample size and possibility of a false positive result due to multiple comparisons.

Reviewer comment

Similar to the previous study, this study population is a high risk population for development of childhood asthma due to the urban setting and low socio-economic status.

Kang EM, Lundsbert LS, Illuzzi JL, Bracken MB. Prenatal exposure to acetaminophen and asthma in children. Obstet Gynecol 2009; 114(6):1295-1306.

The authors prospectively followed 1,505 pregnant women and their children until 6 years of age to evaluate whether prenatal exposure to acetaminophen is associated with asthma in children. Between April 1997 and June 2000 pregnant women with physician diagnosed asthma and a random sample of pregnant women without asthma were enrolled from 56 private obstetric practices and 15 clinics at 6 hospitals in southern New England. Exposure information was obtained by questionnaire before 24 weeks gestation and within one month of delivery. In the

postpartum questionnaire, the mother answered questions regarding acetaminophen exposure during the last 3 months (information on second trimester exposure was not obtained). Information was obtained on dose, frequency, and indication of all medications used. Outcomes were determined by questionnaire at 6 years of age. The primary outcome was a history of physician diagnosed asthma, and wheezing in the last 12 months. The authors controlled for the following factors in their analyses: asthma in the mother, exposure to smoking during pregnancy and post-natally, child's use of antibiotics and child's infections and allergies.

This study showed that the use of acetaminophen did not increase the risk of asthma (aOR 0.76, 95% confidence interval [CI] 0.53–1.10). Study limitations included the lack of information on second trimester and post-natal acetaminophen exposure.

Reviewer comments

Unlike the previous studies, this study did not find an association between prenatal exposure to acetaminophen and asthma in children. This is the only study that has data on dose and the children's infections. The authors refute the previously proposed mechanistic hypotheses on the basis that the data on reduced pulmonary glutathione levels came from in-vitro studies, and it is unclear whether this effect occurs in-vivo. The authors also argued that the period of glutathione resynthesis in the lungs is very short, making it unlikely that oxidative stress would cause significant damage.

Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V, Pastor-Vivero MD, Mondejar-Lopez P, Valverde-Molina J. Is the effect of prenatal paracetamol exposure on wheezing in preschool children modified by asthma in the mother? Int Arch Allergy Immunol 2009; 149:33-37.

The authors conducted a retrospective epidemiological survey in Murcia, Spain involving 1741 children aged 3-5 years to evaluate the relationship between in-utero acetaminophen exposure and asthma. Parents were asked to complete a questionnaire when their child was 3-4 years old regarding acetaminophen use during pregnancy (never, once, or once a month) and their child wheezing during the last 12 months. Asthma in the mother and exposure to smoking were controlled for.

The study found a significant association between non-asthmatic mothers exposed at least once per month to acetaminophen and child wheezing (adjusted odds ratio 1.74, 95% confidence interval 1.15-2.61) although no relationship was found in mothers reporting a history of asthma. A limitation of this study is that recall bias may have played a role in these findings.

Table 1 on the following pages summarizes the characteristics and outcomes of these studies that examined the relationship between prenatal acetaminophen exposure and the incidence of wheezing and/or asthma in children.

Table 1: Summary of Prospective Asthma/wheezing studies

Study	Number of subjects	Timing of exposure	Outcome	Confounding factors/Study Limitations
<p>Shaheen 2002</p> <p>Shaheen 2005 (United Kingdom)</p>	<p>9,400</p> <p>8, 511</p>	<p>Frequent use 20-32 weeks</p> <p>“Sometimes” use 20-32 weeks</p>	<p>Wheeze at 30-42 months OR 2.10(95% CI 1.30-3.41, p= 0.003)</p> <p>Asthma at 6-7 years OR 1.22 (95% CI 1.06-1.41)</p>	<p>All of these confounders are found in both studies (the second study follows the children until age 6-7). No data on dose, or other medications used in pregnancy. No data on childhood medication exposure (other than acetaminophen and antibiotics) after 6 months of age. No data on acetaminophen use after 6 months of age. No data on childhood infection. Small number of patients in the frequent use group.</p>
<p>Rebordosa 2008 Denmark</p>	<p>66, 445 (includes number of 18 month old children)</p> <p>12,733(includes number of 7 year old children)</p>	<p>First trimester highest risk for persistent wheeze (wheeze at 18 months and 7 years)</p>	<p>Wheeze at 18 months and 7 years RR 1.45 (95% CI 1.13-1.85)</p> <p>Asthma or bronchitis at 18 months RR 1.17(95% CI 1.13-1.23)</p> <p>Asthma at 7 years RR 1.15 (95% CI 1.02-1.29)</p> <p>(data not reported in terms of frequency or total amount of use)</p>	<p>No data on dose. No data on use of acetaminophen in children after 18 months. No data on childhood medication exposure (other than acetaminophen). No data on childhood infection.</p>

Table 1: Summary of Prospective Asthma/wheezing studies

Study	Number of subjects	Timing of exposure	Outcome	Confounding factors/Study Limitations
Persky 2008 Chicago	345	Second and third trimester	Wheeze at 1 year OR 1.8 (95% CI 1.1-3.0)	No data on dose or frequency of use. No data on childhood medication exposure (other than acetaminophen). No data on childhood infection.
Perzanowski 2009 Inner city NYC Dominican Republic and African American	301	Second and third trimester	Wheeze at 5 years •following 2 nd trimester exposure RR 1.54 (95% CI 1.06-2.25) •following 3 rd trimester exposure RR 1.55 (95% CI 1.03-2.34) Risk increased with increasing number of days of exposure	No data on dose. No data on indication during pregnancy. No data on infection during pregnancy. No data on childhood infection.
Kang 2009 New England	1,055	First and third trimester (data on second trimester exposure not obtained)	No association with asthma at age 6	<i>This is the only study with dose information and information on childhood infection</i> No data on second trimester exposure or childhood acetaminophen exposure

Reviewer comments on asthma/wheezing studies

- 1. Four prospective studies (Shaheen 2002, Rebordosa, Persky, and Perzanowski) and one retrospective study (Garcia-Marcos) found an association between maternal acetaminophen use and early childhood wheeze (before six years of age), whereas one study (Kang) did not find an association between prenatal acetaminophen exposure and asthma. Two studies (Shaheen 2005 and Rebordosa) found an association between maternal acetaminophen use and asthma at age 7; however, one study (Kang) showed no association between acetaminophen exposure and asthma at age 6. There are conflicting findings in terms of risk association and trimester of exposure. Shaheen, Persky, and Perzanowski found an association between acetaminophen exposure during the second and third trimester and wheeze, whereas Rebordosa found the greatest risk associated with first trimester exposure.*
- 2. All these studies are limited by the fact that both acetaminophen exposure, and respiratory outcomes are self-reported and not confirmed by medical records.*
- 3. All the studies with positive findings of an association between prenatal acetaminophen use and asthma/wheeze in children do not have dose information. Therefore, the accuracy of the exposure data is an important limitation. Although the mothers' reporting on asthma may be accurate, wheezing may be misclassified, as parents may misinterpret noisy breathing, especially in the presence of a respiratory infection, as wheezing. Therefore for outcomes reported, accuracy is a concern, and misclassification bias is a possibility. Most of the studies that show an association with childhood wheeze/asthma did not control for childhood respiratory infections, and some did not control for childhood acetaminophen exposure, both of which have been suggested to be a risk factor for childhood asthma.*
- 4. Biologic plausibility theories have been proposed by some, and refuted by others. Findings consistent with the glutathione depletion theory have only been seen in-vitro, not in-vivo.*
- 5. While these study findings raise concerns regarding a possible association between prenatal acetaminophen exposure and childhood asthma, it is not possible to make definitive conclusions at the present time due to conflicting results, various confounders, and the complex pathophysiology of asthma.*

Adverse pregnancy outcomes

Rebordosa C et al. Use of acetaminophen during pregnancy and risk of adverse pregnancy outcomes. *Int J Epidemiology* 2009;38:706-714.

Data from the Danish National Birth Cohort of 98,140 women with singleton pregnancies who provided information on acetaminophen use during pregnancy were used to evaluate adverse

pregnancy outcomes. The cohort was linked to the Danish National Hospital Registry and the Medical Birth Registry, which covers all Danish hospitals, miscarriages and births in Denmark.

This study showed that mothers with pre-eclampsia had an increased risk of preterm birth (HR=1.55, 95% CI 1.03-1.26). No association was seen between acetaminophen use and miscarriage, stillbirth, or low birth weight. The authors concluded that the results do not provide strong support for a change in clinical practice, but that the findings should be further investigated.

Reviewer comment

It is not possible to determine whether acetaminophen played a causal role, or whether more women with pre-eclampsia took acetaminophen because they were being treated or self-treated for a headache, which is a symptom of pre-eclampsia. Women with pre-eclampsia are often delivered early for therapeutic reasons.

Li D-K, Liu L, Odouli R. Exposure to non-steroidal and anti-inflammatory drugs during pregnancy and risk of miscarriage: population based cohort study. Br Med J 2003; 327:368-372.

Kaiser Permanente conducted a population based cohort study to determine whether there is an association between NSAID use and increased risk of miscarriage. The study used a dataset that evaluated prenatal exposure to magnetic fields from 1996 through 1998. Researchers recruited and interviewed 1055 pregnant women in the San Francisco area after pregnancy was confirmed by a positive pregnancy test. Median gestational age at entry to the study was 40 days. At the interview, women were asked about medication use since their last menstrual period and the indication for usage. The study collected information on pregnancy outcomes up to 20 weeks gestation.

After adjusting for maternal age, smoking, education, race, gravity, history of previous miscarriage, use of a hot tub, and multivitamin use, acetaminophen was not associated with increased risk of miscarriage, whereas NSAID use was associated with an increased risk.

Post-marketing Safety Data

The sponsor reviewed Bristol Myers-Squibb's Periodic Safety Update Reports (PSURs) submitted to EU Member States, which include systematic analyses of safety data from the original European launch in 2001 through May 7, 2009. A total of twelve pregnancy-related serious adverse event reports were analyzed and showed the following:

- 1 fetus with multiple anomalies (VACTERL association) exposed to acetaminophen at 6 weeks gestation-not drug related

- 4 cases of maternal anaphylactic shock : 2 probably acetaminophen related; 2 probably not acetaminophen related
- 1 case of maternal rash-probably not acetaminophen related
- 1 case of maternal generalized pruritus-possibly acetaminophen related
- 1 case of maternal death-probably not acetaminophen related
- 1 case of neonatal death-probably not acetaminophen related
- 3 cases of pregnancy exposure with no outcome data

Reviewer comments

VACTERL (vertebral anomalies, anal atresia, cardiovascular anomalies, tracheo-esophageal fistula, esophageal atresia, renal or radial anomalies, and limb abnormalities) association is a non-random association of birth defects that has been associated with trisomy 18 and diabetes. There has been no previously reported association with in utero acetaminophen exposure.

The post-marketing safety data do not show pregnancy complications due to intravenous acetaminophen exposure.

Presence of Acetaminophen in Human Breast milk

1. Berlin CM Jr, Yaffe SJ, Ragni M. Disposition of acetaminophen in milk, saliva and plasma of lactating women. *Pediatr Pharmacol.* 1980; 1:135-41.

A single oral dose of 650 mg of acetaminophen was given to 12 nursing mothers who were 2 to 22 months post-partum. Milk levels were obtained at 3, 6, and 9 hours after maternal ingestion. The maximum milk level was 0.010 mg/ml. The authors calculated that an infant who ingested 3 ounces (90 ml) of breast milk every 3 hours would receive an average of 0.88 mg of acetaminophen or 0.14 % of the mother's absolute dosage. Using data from this study, an infant would receive a maximum of about 2% of the maternal weight-adjusted dose per day, and 3% of the maximum infant (from 29 days to 1 year of age) daily dose of 50 mg/kg/day¹².

2. Bitzen P-O, Gustafsson B, Jostell KG et al. Excretion of paracetamol in human breast milk. *Eur J Clin Pharmacol.* 1981;20:123-5.

Three lactating women who had decided to stop breastfeeding were given a single dose of 500 mg of acetaminophen. Breast milk levels were obtained at 2, 4, 6, 8, 10, and 12 hours after

¹² Based on a daily average intake of 150 ml/kg/day, the estimated maximum daily infant dose= 0.010 mg/ml X 150 ml/kg/day=1.5mg/kg/day. This is 2% of the maximum adult daily dose of 75mg/kg/day. .

maternal ingestion. The maximum observed concentration of acetaminophen in milk was 29.1 $\mu\text{mol/L}$ or 4.4 mg/L, based on acetaminophen's molecular weight of 151. This is equal to 0.1% of the single maternal dose. Using data from this study, an infant would receive a maximum of less than 1 % of the maternal weight-adjusted dose per day, and 1.3% of the maximum infant (from 29 days to 1 year of age) daily dose of 50 mg/kg/day¹³.

3. Notarianni LJ, Oldham HG, Bennett PN. Passage of paracetamol into breast milk and its subsequent metabolism by the neonate. Br J Clin Pharmacol. 1987;24:63-7.

Four breastfeeding women who were two to eight months postpartum were given a single 1 g dose of acetaminophen. Milk samples were taken every half hour for up to 3.5 hours after maternal ingestion. The mean maximum concentration of acetaminophen in milk was 10.3 mg/L. Using data from this study, an infant would receive a maximum of 2 % of the weight-adjusted maternal dose per day¹⁴. This dose is about 3% of the maximum infant (from 29 days to 1 year of age) daily dose of 50 mg/kg/day

4. Matheson I, Lunde PK, Notarianni LJ. Infant rash caused by paracetamol in breast milk? Pediatrics 1985; 76(4):651-652.

A maculopapular rash developed on the upper trunk and face of a two month old breastfeeding infant whose mother had taken 1 g of acetaminophen per day for two days. The rash subsided when the acetaminophen was discontinued, and recurred two weeks later after another dose of 1 g was taken by the mother. A similar case¹⁵ of a maculopapular rash was reported in a one month old infant who was exposed to acetaminophen through breast milk.

Reviewer comments

All of these studies show that only a small amount of acetaminophen is secreted in human breast milk; amounts in milk are much less than doses usually given to infants. Given the positive dechallenge/rechallenge in the Matheson case report, maternal acetaminophen use and infant exposure to acetaminophen through human milk may have played causal role in the maculopapular rash in this particular infant.

DISCUSSION AND CONCLUSIONS

In response to the sponsor's analysis of the published data on exposure to acetaminophen during pregnancy and lactation, this review provides a comprehensive and critical evaluation of the

¹³ Based on a daily average intake of 150 ml/kg/day, the estimated maximum daily infant dose= $0.0044 \text{ mg/ml} \times 150 \text{ ml/kg/day} = 0.66 \text{ mg/kg/day}$. .

¹⁴ Based on a daily average intake of 150 ml/kg/day, the estimated maximum daily infant dose= $0.0103 \text{ mg/ml} \times 150 \text{ ml/kg/day} = 1.545 \text{ mg/kg/day}$

¹⁵ Garcia MB, Vicedo CM, Lozano MJ, Villén MN. Cutaneous hypersensitivity induced by acetaminophen in breast milk. Rev Esp Pediatr 1998; 54(6):534-536.

submitted data provided to support pregnancy labeling for Ofirmev (intravenous acetaminophen).

Major malformations

Extensive published data, including prospective and retrospective epidemiologic data and case series, have not shown an increase in major malformations compared to the background rate in the general population. The prospective cohort study from the Danish National Birth Cohort (DNBC) provides the most comprehensive and robust data, and forms the basis of the sponsor's proposed labeling language. Because acetaminophen is available without a prescription, one limitation of the epidemiologic studies is that ascertainment of use is based on patient questionnaires. This could result in recall bias and incorrect information about duration and extent of exposure, including a lack of dosing information. Although the data are reassuring, it is possible that rare malformations may have been missed. It may be useful to include other epidemiologic data in addition to the DNBC study to labeling to support the findings from this study.

Data regarding specific malformations are inconsistent, and therefore are not of sufficient quality to include in labeling.

Childhood wheezing/asthma

Data regarding acetaminophen exposure during pregnancy and childhood wheeze and asthma risk are concerning; however, they are also inconsistent and are limited by potential confounders and data limitations. In all of these studies, both acetaminophen exposure and respiratory outcomes are self-reported and not confirmed by medical records. These limitations in study design and confounding factors do not provide clear evidence of a causal association. Biologic plausibility theories have been proposed by some, and refuted by others. Asthma is a complex disease and its etiology is multifactorial and still not completely understood. Furthermore, childhood wheeze and asthma often resolve on their own, therefore more long term data with medical record confirmation of outcomes is needed to truly define the risk.

Further studies are needed to investigate this potential safety signal due to the widespread use of acetaminophen in the pregnant population and the American population as a whole. The four studies that demonstrate a statistically significant increased risk of persistent wheezing and/or asthma in children following prenatal exposure to acetaminophen suggest that the increased risk is a modest 20-30%. Other studies in adults and children suggest that acetaminophen exposure at other times during the life cycle could also be associated with an increased risk for asthma. However, given the widespread use of acetaminophen by the population in the United States and the active ingredient's almost ubiquitous presence in nonprescription cough and cold medicines, reducing nonessential prenatal exposure and exposure in general to acetaminophen could have a substantial public health impact.

The DAARP and MHT reviewers discussed the need for additional data to further evaluate the potential association between acetaminophen exposure and wheezing/asthma – prenatally and potentially in adults and children as well. A post-marketing requirement for a pregnancy exposure registry for intravenous acetaminophen alone would not be able to adequately address this unmet scientific need. A broader and more comprehensive evaluation of acetaminophen use

for all dosage forms and indications may be more appropriate. These data may be relevant to all acetaminophen containing products. Therefore, it is prudent to wait on placing information in product labeling about the potential association between prenatal acetaminophen exposure and increased risk of persistent wheezing and asthma in childhood until the Agency has a better understanding of the data. Once CDER staff complete a more critical and in-depth analysis of this body of data and its limitations, the issue about whether and how to communicate this information in labeling should be revisited.

Adverse pregnancy outcomes

There are insufficient data regarding prenatal acetaminophen exposure and adverse pregnancy outcomes.

Acetaminophen and lactation

Lactation studies show that a small amount of acetaminophen is secreted in breast milk; this amount is much less than the therapeutic infant dose.

Sponsor's proposed pregnancy labeling

The sponsor proposed pregnancy category (b) (4) for Ofirmev labeling, based on negative human data regarding malformations. Although human data regarding malformations are negative, the asthma data are not negative, and therefore do not support a pregnancy category (b) (4). In addition, the sponsor has not conducted reproductive and developmental studies of intravenous acetaminophen. Based on FDA toxicologists' review of published preclinical data, intravenous acetaminophen has a higher concentration of a toxic metabolite, 4-aminophenol, than oral acetaminophen. This metabolite has been associated with malformations and resorptions in animals. Due to a lack of reproductive toxicology studies with intravenous acetaminophen in this application, and the inability to characterize the toxicity associated with 4-aminophenol, MHT concurs with the Division's toxicologists' recommendation that Ofirmev be labeled pregnancy category C.

RECOMMENDATIONS

1. Do not accept sponsor's proposed pregnancy category (b) (4) assign a pregnancy category C based on inadequate reproductive toxicology data with Ofirmev.
2. Accept sponsor's revised Pregnancy and Nursing Mothers labeling, along with MHT's suggested changes.
3. Consult the Office of Surveillance and Epidemiology, Division of Epidemiology to provide (1) an in-depth epidemiological assessment of available study data and (2) suggestions about feasible approaches to further evaluate the potential association between acetaminophen use and the risk for wheezing and asthma, especially with regard to prenatal exposure to acetaminophen.
4. Involve the Office of Nonprescription Products, Division of Nonprescription Clinical Evaluation in discussions regarding potential approaches to obtaining data on the

potential association between acetaminophen use and the risk for wheezing and asthma. to establish the best method to collect data on childhood respiratory outcomes following acetaminophen exposure during pregnancy.

5. Public communications related to the Agency's action on this NDA should present nonclinical developmental toxicity study findings and available human data in a factual, plain language manner. Messaging should include the following: All medicines offer treatment benefits but they also have risks; like all medicines, pregnant women should use acetaminophen only when clearly needed; treatment of fever and pain during pregnancy is important for the health of the mother and her developing baby; if you are pregnant, speak to your doctor about the best way to treat your fever or pain.
6. The MHT suggests the following revisions to the sponsor's submitted Pregnancy and Nursing Mothers labeling subsections. (Appendix A includes the labeling with documented insertions and deletions)

Highlights

----- **USE IN SPECIFIC POPULATIONS**-----
Pregnancy: No animal or human data. Use only if clearly needed (8.1)
Nursing Mothers: Caution should be exercised when administered to a nursing woman (8.3)

8.1 Pregnancy

Pregnancy Category C.

There are no studies of intravenous acetaminophen in pregnant women; however, epidemiological data on oral acetaminophen use in pregnant women show no increased risk of major congenital malformations. Animal reproduction studies have not been conducted with intravenous acetaminophen, and it is not known whether Ofirmev can cause fetal harm when administered to a pregnant woman. Ofirmev should be given to a pregnant woman only if clearly needed.

The results from a large population-based prospective cohort, including data from 26, 424 women with live born singletons who were exposed to acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological studies showed similar results.

(b) (4)

8.2 Labor and Delivery

There are no adequate and well-controlled studies with TRADENAME during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

8.3 Nursing Mothers

While studies with TRADENAME have not been conducted, acetaminophen is secreted in human milk in small quantities after oral administration. Based on data from more than 15 nursing mothers, the calculated infant daily dose of acetaminophen is approximately 1 – 2% of the maternal dose. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use. Caution should be exercised when TRADENAME is administered to a nursing woman.

**APPENDIX A:
MHT recommended revisions to sponsor's labeling for Pregnancy and Nursing Mothers**

(Additions are underlined, and deletions are struck out.)

(b) (4)

While reproduction studies have not been conducted with intravenous acetaminophen, studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.85 times the human dose (based on body surface area) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2-times the maximum human daily dose (MHDD = 4 grams/day), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not occur in animals that received oral acetaminophen at doses 0.3-times the MHDD (based on body surface area).

In a continuous breeding study, pregnant mice received 0.25, 0.5 or 1.0% acetaminophen via the diet (357, 715 or 1430 mg/kg/day) . These doses are approximately 0.42, 0.85, and 1.7 times the MHDD respectively (based on body surface area). A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

8.2 Labor and Delivery

There are no adequate and well-controlled studies with TRADENAME during labor and delivery; therefore, it should be used in such settings only after a careful benefit-risk assessment.

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/s/

LEYLA SAHIN
02/10/2010

Karen B FEIBUS
02/10/2010

I agree with the content and recommendations contained in this review. In addition, I am signing on behalf of CDR Lisa Mathis, MD who also concurs.



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: December 17, 2009

To: Bob Rappaport, MD, Director
Division of Analgesia, Anesthesia, and Rheumatology Products

Through: Melina Griffis RPh, Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis (DMEPA)

From: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis (DMEPA)

Subject: Label and Labeling Review

Drug Name(s): Ofirmev (Acetaminophen) Injection 1000 mg/100 mL vials

Application Type/Number: NDA 22450

Applicant/sponsor: Cadence Pharmaceuticals

OSE RCM #: 2009-2204

1 INTRODUCTION

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for the labels and labeling for Acetaminophen Injection (NDA 22450) on October 6, 2009 in which we made recommendations to revise the container labels and carton labeling to minimize errors. The Applicant provided revised labels and labeling which also include the addition of the proposed proprietary name, Ofirmev, in response to these recommendations.

2 MATERIAL REVIEWED

DMEPA reviewed our recommendations regarding the Acetaminophen Injection labels and labeling contained in OSE review #2009-1010 dated October 6, 2009. In addition, we reviewed the Applicant's revised container labels and carton labeling dated October 30, 2009. (See Appendices)

3 CONCLUSIONS AND RECOMMENDATIONS

We note that DAARP inadvertently omitted sending one of our recommendations to the Applicant. This recommendation requested that a warning against dispensing the entire vial for Ofirmev doses less than 1000 mg be added to the container label and carton labeling. Thus, our recommendations also include revised language related to this recommendation in section 3.1 below.

We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Abolade Adeolu, project manager, at 301-796-4264.

3.1 COMMENTS TO THE APPLICANT

A. Container Label (1000 mg/100 mL vial)

1. As presented in the revised container labels, the graphic (b) (4) in the proposed proprietary name, Ofirmev, makes this final letter of the name appear to be part of the graphic rather than part of the name and thus effects the readability of the proprietary name. We recommend revising the graphic as to not interfere with the readability of the proprietary name.
2. The presentation of the proprietary name and the product strength (b) (4) reduces the prominence of the established name. Revise the presentation of the established name so that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21 CFR 201.10 (g)(2).

3. Include the following statement following the single use statement on the principle display panel, “Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing.” The storage directions may be relocated to the side panel if space affects the readability of these statements.

B. Carton Labeling (1 x 24 vials)

1. Include the following statement prior to the storage instructions, “Doses less than 1000 mg require aseptic transfer to a separate container prior to dispensing.”

REFERENCES

OSE review # 2009-1010. Label and Labeling Review for Acetaminophen Injection, Abate, R. October 6, 2009.

APPENDICES

Appendix A: Revised Container labels for Ofirmev 1000 mg/100 mL vial with the administration sling.

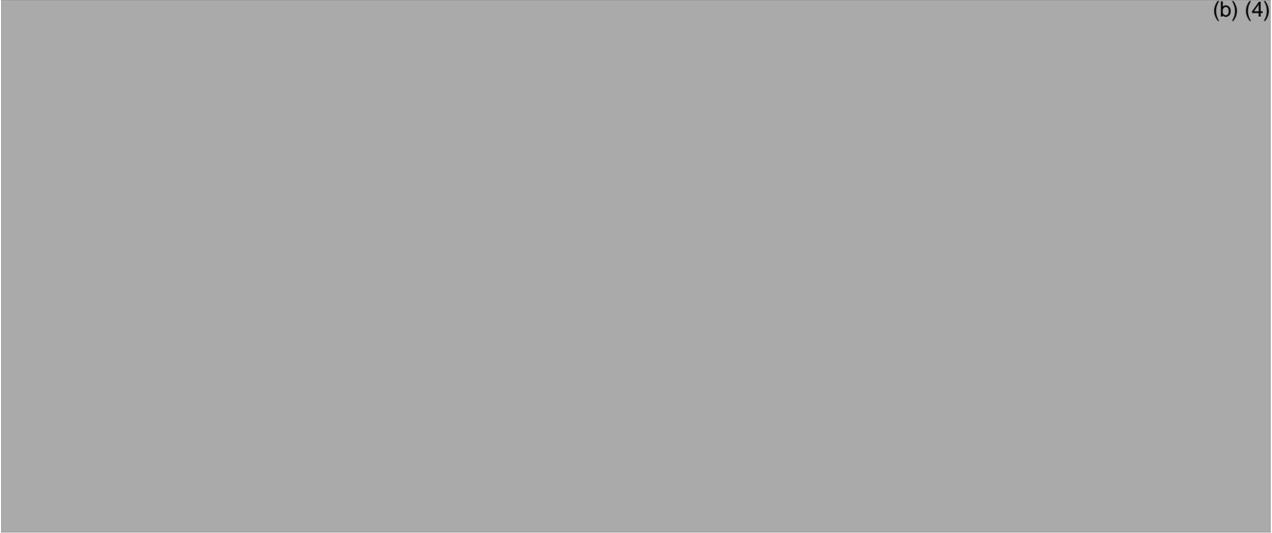


Appendix B: Revised Container labels for Ofirmev 1000 mg/100 mL vial without the administration sling.



Appendix C: Revised Carton labeling for Ofirmev 1000 mg/100 mL vial

(b) (4)



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

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/s/

RICHARD A ABATE
12/17/2009

MELINA N GRIFFIS
12/17/2009

CAROL A HOLQUIST
12/17/2009

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

****PRE-DECISIONAL AGENCY MEMO****

Date: October 27, 2009

To: Sharon Turner-Rinehardt – Regulatory Project Manager
Ramani Sista – Regulatory Project Manager
Division of Anesthesia, Analgesia, and Rheumatology Products (DAARP)

From: Mathilda Fienkeng – Regulatory Review Officer
Division of Drug Marketing, Advertising, and Communications (DDMAC)

**Subject: DDMAC draft labeling comments
NDA 22-450 TRADENAME (acetaminophen) injection for intravenous use**

DDMAC has reviewed the proposed product labeling (PI) for TRADENAME (acetaminophen) Injection for Intravenous use (IV Acetaminophen), submitted for consult on August 20, 2009.

The following comments are provided using the updated proposed PI sent via email on October 14, 2009 by Ramani Sista.

DDMAC notes that the May 15, 2009 version of the proposed PI submitted by the sponsor was replaced with the revised version of August 12, 2009, including the tradename. Please submit the revised proposed carton and containers from the sponsor for DDMAC comments. If you have any questions about DDMAC's comments, please do not hesitate to contact us

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as B4 (CCI/TS) Immediately Following this Page



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/s/

MATHILDA K FIENKENG
10/27/2009

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: October 5, 2009

TO: Ramani Sista, Regulatory Project Manager
Christina Chang, M.D., Medical Officer
Division of Anesthesia, Analgesia and Rheumatology Products

FROM: Susan Leibenhaut, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Jean M. Mulinde, M.D.
Acting Team Leader
Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #22-450

APPLICANT: Cadence Pharmaceuticals, Inc.

DRUG: Acetaminophen Injection for Intravenous (IV) Use

NME: No

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: For use in acute pain and fever in adult and pediatric patients

CONSULTATION REQUEST DATE: July 9, 2009

DIVISION ACTION GOAL DATE: November 11, 2009
PDUFA DATE: November 13, 2009

I. BACKGROUND:

Cadence Pharmaceuticals Inc. has submitted NDA 22-450 for Acetaminophen Injection for intravenous (IV) use. The sponsor proposes the indication for the treatment of acute pain and fever. This is a routine audit request to assess data integrity and human subject protection for clinical trials submitted in support of this application.

Clinical inspections were conducted in response to a routine audit request to assess data integrity and human subject protection for clinical trials conducted for approval. The efficacy results of three studies are important in making a regulatory decision with regard to drug approval. The sites were selected based on the higher proportions of patients enrolled (with more protocol deviations) than the other sites in three clinical studies.

The protocols inspected include:

- A. Protocol RC210 3 002, entitled “A Phase 3, Randomized, Double-blind, Placebo and Active Controlled Study to Assess the Analgesic Efficacy and Safety of Repeated Administration of Injectable Acetaminophen IG for the Treatment of Postoperative Pain Following Orthopedic Surgery”
- B. Protocol CPI-APA-304, entitled “A Phase III Randomized Double-Blind, Placebo-Controlled, Multi-Center, Parallel-Group, Repeated-Dose Study of the Analgesic Efficacy and Safety of Intravenous Acetaminophen Versus Placebo for the Treatment of Postoperative Pain after Abdominal Laparoscopic Surgery”
- C. Protocol CPI-APF-302, entitled “A Phase III, Randomized, Double-Blind, Placebo-Controlled, Single-Dose Study of the Efficacy and Safety of Intravenous Acetaminophen Versus Placebo for the Treatment of Endotoxin-Induced Fever in Healthy Adult Males.”

II. RESULTS (by Site):

Name of Clinical Investigator (CI) and Location	Protocol #/ # of Subjects	Inspection Date	Final Classification
CI #1 Dr. Jonathan Jahr, MD University of California Davis Medical Center 4150 V. Street, Suite 1200 PSSB Bldg., Sacramento CA 95817	RC210 3 002/ 65 subjects	August 31 to September 4, 2009	Pending (Preliminary classification VAI)
CI #2 Lowell Reynolds, MD Loma Linda University Center for Pain Management 11406 Loma Linda Drive Suite 523 Loma Linda, CA 92534	RC210 3 002/ 49 subjects	August 11 to 12, 2009	NAI
CI#3 Steven Wininger, MD Precision Trials, 3815 East Bell Road, Suite 4500 Phoenix, AZ 85032	CPI-APA-304/ 39 subjects	August 24 to 26, 2009	NAI
CI#4 Stephen Daniels, DO Premier Research Group 3200 Red River, Suite 300 Austin, TX 78705	CPI-APF-302/ 60 subjects	September 2 to 3, 2009	NAI
CI#5 Howard Miller, MD Research Concepts Ltd. 7800 Fannin St. Houston, TX 77054	CPI-APA-304/ 44 subjects	August 18 to 21, 2009	Pending (Preliminary classification NAI)

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations.

1. Dr. Jonathan Jahr, MD
University of California, Davis Medical Center
4150 V. Street, Suite 1200, PSSB Bldg.,
Sacramento, CA 95817

Note: Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol RC210 3 002 at this site, 70 subjects were screened, 65 subjects were enrolled, and 61 subjects completed the study. Audits of informed consent documents for all subjects and complete audits of 25 subjects' records were conducted. Specific items reviewed included authenticity of the records, protocol adherence, adverse events, verification of primary endpoint data, and test article accountability.
- b. **General observations/commentary:**
 - i. The primary endpoint data were verifiable.
 - ii. The occurrence of fever in subject 56 was not reported as an adverse event.
 - iii. All other adverse events were reported.
 - iv. There was a protocol violation. Subject 056 was administered Motrin for fever between protocol monitoring periods T0 to T6.
 - v. The following subjects were discontinued or withdrawn from the study:
 - a. Subject 52 was terminated because of the use of a morphine sulfate pump.
 - b. Subject 108 withdrew consent.
 - c. Subject 436 experienced deep venous thrombosis.
 - d. Subject 473 was terminated because of Vicodin use.
 - e. Subject 478 was taken off study after three dose of test article.
- c. **Assessment of data integrity:** Although a number of regulatory violations were noted, it is unlikely that they significantly affect overall data reliability from the site. The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

2. Lowell Reynolds, MD
Loma Linda University Center for Pain Management
11406 Loma Linda Drive, Ste 523
Loma Linda, CA 92534

- a. **What was inspected:** For Protocol RC210 3 002 at this site, 63 subjects were screened, 48 subjects were enrolled and 43 subjects completed the study. An audit of informed consent documents for all subjects and a complete audit of 25 subjects' records were

- conducted. Specific records reviewed included, but were not limited to, consent forms, adverse events, verification of primary endpoint data, and test article accountability.
- b. **General observations/commentary:** There was no under-reporting of adverse events. No regulatory violations were identified during the inspection, and a Form FDA 483 was not issued.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
3. Steven Winger, MD
Precision Trials
3815 East Bell Road, Suite 4500
Phoenix, AZ 85032
 - a. **What was inspected:** For Protocol CPI-APA-304 at this site, 59 subjects were screened, 39 subjects were randomized, enrolled and completed the study. An audit of 20 randomly selected subjects' records was conducted.
 - b. **General observations/commentary:** There was no evidence of under-reporting of adverse events. All data sets including efficacy endpoints were reviewed, and no deficiencies were noted.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.
 4. Stephen Daniels, DO
Premier Research Group
3200 Red River, Suite 300
Austin, TX 78705
 - a. **What was inspected:** This was the only clinical site for Protocol CPI-APF-302. There were a total of 99 subjects screened and 60 subjects were enrolled and randomized. All subject files were reviewed for protocol deviations, adverse events and appropriateness of informed consents. Thirty subject files and pertaining records were reviewed thoroughly.
 - b. **General observations/commentary:** Four subjects received rescue medication and were withdrawn from the study. One of these subjects also had an adverse event. There was no underreporting of adverse events. Primary efficacy endpoint data were verified in the 30 files that had complete review. There were no deficiencies noted and no 483 was issued.
 - c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

5. Howard Miller, MD
Research Concepts Ltd.
7800 Fannin St. Suite 205
Houston, TX 77054

Note: Observations noted for this site are based on communications with the FDA investigator and review of the FDA Form 483. An inspection summary addendum will be generated if conclusions change upon receipt and review of the Establishment Inspection Report (EIR).

- a. **What was inspected:** For Protocol CPI-APA-304 at this site, 62 subjects were screened, 44 subjects were enrolled, and 38 subjects completed the trial. An audit of 25 subjects' records was conducted.
- b. **General observations/commentary:** There was no under reporting of adverse events and the end point assessments for the 25 subjects were verified.
- c. **Assessment of data integrity:** The study appears to have been conducted adequately, and the data generated by this site may be used in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The inspections of Drs. Reynolds, Wininger, Daniels and Miller did not find regulatory violations. The inspection of Dr. Jahr found violations as noted above. The data from all sites appear acceptable in support of the proposed indication.

The final classifications for the inspections of Drs. Miller and Jahr are pending. An addendum to this clinical inspection summary will be forwarded to the review division if additional observations of clinical and regulatory significance are discovered after reviewing the EIRs for Drs. Miller and Jahr.

{See appended electronic signature page}

Susan Leibenhaut, M. D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Jean M. Mulinde, M.D.
Acting Team Leader
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

SUSAN LEIBENHAUT
10/07/2009

JEAN M MULINDE
10/07/2009



Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: October 6, 2009

To: Bob Rappaport, MD, Director
Division of Anesthesia, Analgesia and Rheumatology Products

Through: Melina Griffis, RPh, Acting Team Leader
Carol Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Richard Abate, RPh, MS, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name(s): Acetaminophen Injection 1000 mg/100 mL vial

Application Type/Number: NDA 22-450

Applicant/sponsor: Cadence Pharmaceuticals

OSE RCM #: 2009-1010

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis evaluated of the container labels, carton and insert labeling for Acetaminophen Injection (NDA 22-450) and identified vulnerabilities that could lead to medication errors. Specifically, we raise concern with the proposed packaging configuration of this product, the proposed Dosage and Administration section of the insert labeling, and the presentation of the name and strength on the Container labels and carton labeling. We also provide recommendations in Section 5 that aim at reducing the risk of medication errors with regards to the proposed package design, product label, and labeling.

1 BACKGROUND

1.1 INTRODUCTION

This review is in response to a May 26, 2009 request from the Division of Anesthesia, Analgesia and Rheumatology Products for an assessment of the labels and labeling for the proposed product, Acetaminophen Injection (NDA# 22-450) for evaluation to identify areas that could lead to medication errors. This NDA will be the first acetaminophen injection product approved for use in the United States.

The Division of Medication Error Prevention and Analysis (DMEPA) notified the Applicant that the Division of Drug Marketing, Advertising, and Communications found the proposed proprietary name, Acetavance, unacceptable for promotional reasons on June 25, 2009. In addition, following the submission of alternative proposed proprietary names on August 17, 2009, DMEPA notified the Applicant that the Division of Drug Marketing, Advertising, and Communications found the proposed proprietary name, (b) (4) unacceptable for promotional reasons on September 2, 2009.

1.2 PRODUCT INFORMATION

Acetaminophen Injection (NDA 22-450) is indicated for the treatment of acute pain and fever. Acetaminophen Injection is provided as a 10 mg/mL solution packaged in glass single-use vials containing 1000 mg/100 mL requiring no further dilution prior to administration. The dose for adult and adolescent patients weighing 50 kg or more is 650 to 1000 mg intravenously every four to six hours up to maximum of 4000 mg in 24 hours. The dose for children older than 2 years of age and adult or adolescent patients weighing less than 50 kg is 12.5 to 15 mg/kg intravenously every four to six hours up to a maximum of 75 mg/kg in 24 hours. (b) (4)

The dose of Acetaminophen Injection is administered as an infusion over 15 minutes. The vials of Acetaminophen Injection are stored at room temperature (20°C).

2 MATERIALS REVIEWED

2.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

Acetaminophen Injection is currently marketed internationally under the proprietary name Perfalgan in 80 countries worldwide. Therefore, DMEPA conducted a search of the Adverse Events Reporting System (AERS) on July 30, 2009 using the verbatim term “Perfalgan%” and the MedDRA reaction terms “Medication Errors” (HLGT), “Product Quality Issue” (PT) and “Product Label Issue” (HLT).

The reports were manually reviewed to determine if a medication error occurred. Duplicate reports were grouped together into cases. If an error occurred, the staff reviewed the cases to determine if the root cause could be associated with the labels, labeling, or packaging configuration of the product, and thus pertinent to this review. Those cases that did not describe a medication error were excluded from further analysis. The cases that did describe a medication error were categorized by type of error. We reviewed the cases within each category to identify factors that contributed to the medication errors.

2.2 LABELS AND LABELING

For this product the Applicant submitted labels and labeling as part of the May 15, 2009 original submission. (See Appendix A and B for images of proposed container label and carton labeling)

3 RESULTS

3.1 ADVERSE EVENTS REPORTING SYSTEM (AERS) DATABASE

Our search identified a total of four cases (n=4). Three of these cases were excluded because Perfalgan was a concurrent medication or no medication error was identified. The remaining case was a medication error involving an 83 year old female patient who received an overdose of Perfalgan (acetaminophen). Root causality for this error could not be determined based on the details provided in the case narrative.

3.2 LABELS AND LABELING

Using Failure Mode and Effects Analysis (FMEA),¹ the Division of Medication Error Prevention and Analysis (DMEPA) evaluated the packaging, container labels, carton labeling and insert labeling and identified the following vulnerabilities that could lead to medication errors:

3.2.1 *Product Design may contribute to Misdosing or Adverse Event.*

- A single, (b) (4) dosage form when there are multiple doses possible for this product. In addition, this product introduces a new route of administration available for acetaminophen.

¹ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

- The packaging configuration presents the risk of air embolism as stated in the Insert labeling.

3.2.2 *The DOSAGE and ADMINISTRATION Section of the Insert labeling does not effectively communicate (b) (4) adult dosing or a maximum acetaminophen dose.*

- The DOSAGE and ADMINISTRATION Section of the Insert labeling combines the (b) (4) dosing with the adults and adolescents which can be overlooked. The maximum doses listed in mg/kg for adults, adolescents and children lack a numeric maximum dose.
- The instructions for administering doses other than 1000 mg are prone to medication error. In addition, the directions for administration for “small volumes” are ambiguous.

3.2.3 *Presentation of Information on the Container and Carton.*

- The proposed proprietary name appears on the container label and carton labeling in two different colors of font.
- The presentation of the strength appears above the proprietary name on the container labels and carton labeling. In addition, the net quantity of the carton appears immediately following the established name on the carton labeling.

4 DISCUSSION

Acetaminophen Injection is marketed internationally under the proprietary name, Perfalgan. The proposed product will be the first Acetaminophen Injection product marketed in the United States. As such, we searched AERS to determine the medication error history of Acetaminophen Injection abroad. Our search found limited medication error cases. However, our Failure Mode and Effects Analysis of the proposed labels and labeling identified potential failure modes that represent sources for potential medication errors in the United States medication use system. (See Appendix C)

4.1 PROPOSED PACKAGING (100 mL VIAL)

4.1.1 (b) (4) 100 mL vial

The Applicant proposes to provide Acetaminophen Injection in a single strength (b) (4) glass vial containing 1000 mg/100 mL. (b) (4) implies the product does not require further dilution prior to administration and can be hung and directly administered without placing the medication in a different vehicle for administration. However, the Dosage and Administration Section of the labeling provides for doses of 650 mg and less depending on the patient’s age and weight resulting in a failure mode with the design of this product as excess drug must be removed from the container prior to administration. The failure to remove this excess drug or failure to remove an accurate amount of drug can result in error. Although this proposed packaging configuration provides convenient administration of adult and adolescent doses of 1000 mg, it may contribute to dosing errors in patients requiring a dose of less than 1000 mg.

4.1.2 Manipulation of Vial

The proposed Instructions for Use (Section 2.4) in the insert labeling instruct the practitioner to remove the unneeded amount of Acetaminophen Injection and infuse the remaining medication (the required dose) from the vial. Postmarketing surveillance demonstrates the need to remove drug from a (b) (4) vial to achieve the correct dose has contributed to wrong dose medication errors as healthcare providers mistakenly administered the entire contents of these vials rather than the intended dose which was less than the full volume of the container.² Medication errors could also occur when the acetaminophen vial reaches the patient care area after partial amounts have already been removed by the pharmacy. Practitioners may mistakenly believe the vial contains 1000 mg because the commercial label states 1000 mg despite the fact drug has already been removed by the pharmacy. Practitioners could recalculate the dose based on this label information which would result in an underdose of acetaminophen. Alternatively and more concerning is when the container of acetaminophen, following an adjustment made to the volume contained in the bottle, is mistakenly returned to stock and dispensed to another patient as a full 1000 mg vial which could lead to an underdose.

Requiring manipulation of any product prior to administration introduces opportunities for medication error. The proposed product requires manipulation for all doses below 1000 mg. Thus, the proposed single strength is neither ideal nor supported for the delivery of all doses required by the insert labeling.

4.1.3 Administration of Doses via a Syringe

The Instructions for Use section of the insert labeling states some smaller pediatric doses should be administered via a syringe using a syringe pump. Specifically, the proposed insert labeling instructs delivery of Acetaminophen Injection in a syringe and the use of syringe pump for “small volumes.” DMEPA acknowledges pediatric doses of intravenous medications are often administered in syringes using an infusion pump designed for syringes. However, the labeling does not define which volumes or mg doses are meant to be delivered in a syringe. This ambiguity in the labeling may lead to confusion and dosing errors. Thus, based on the lack of specific doses or volumes as part of the proposed Instructions for Use, DMEPA believes it is likely full vials of Acetaminophen Injection may be inappropriately dispensed for some pediatric doses. The proposed labeling should be revised to define what is considered a “small volume”.

4.2 NEW DOSAGE FORM AND CONCOMITANT ADMINISTRATION OF ACETAMINOPHEN

This proposed product provides for a new dosage form of Acetaminophen to be administered intravenously. Research in the hospital setting has shown prescribing the same or similar medications given concurrently by two routes of administration as a common source of medication error.³ In fact, the same study noted the oral and intravenous routes as the most common concurrent routes of administration when this error occurred. DMEPA believes the concurrent administration of acetaminophen containing products (e.g. opioid combination

² ISMP, *Fatal overdose uncovers need to rethink where pediatric IV medications are dispensed and administered*; ISMP Medication Safety Alert; Vol 13, Issue 2; January 31, 2008.

³ Lesar TS. Medication Prescribing Errors Involving Route of Administration. *Hosp Pharmacy*. 2006; 41(11): 1053-1066.

products) will likely occur in the inpatient setting. Therefore, the insert should include language that clearly states the maximum doses of acetaminophen are “**by any route**” to minimize the potential for acetaminophen overdose through concurrent use of acetaminophen containing products.

4.3 MAXIMUM DAILY DOSE OF ACETAMINOPHEN

The proposed insert labeling attempts to provide guidance to healthcare providers regarding the recommended maximum single and maximum total daily doses of acetaminophen. However, we note the maximum total daily doses in the Dosage and Administration Section do not include a statement that these maximum doses should be based on **all routes** of Acetaminophen administration (i.e. oral, rectal and intravenous). As noted in Section 4.2, concurrent administration of a medication by more than one route is an identified risk.

Additionally, the insert labeling lists the recommended doses and maximum total daily dose of Acetaminophen Injection (both single dose and daily dose of acetaminophen) in the same location for each patient age group. The maximum doses for adults and adolescents 50 kg and over are listed as a whole number (1000 mg and 4000 mg, respectively). However, the maximum doses for all other patient groups are expressed as weight-based or mg/kg instead of a whole number. Since dose calculations in older children weighing more than 66 kg could result in doses higher than 1000 mg, DMEPA recommends the inclusion of numeric maximum doses expressed as a whole number (e.g., up to 650 mg) for children ages 2 to 12 years to be consistent with the acetaminophen dosing for adults.

The Applicant provides additional strategies to reduce the risk of overdose of acetaminophen which were included in the submitted risk management plan. However, DMEPA believes providing more information in the insert labeling with regard to dose limits and potential for concurrent administration from multiple routes of administration also helps to minimize the risk of acetaminophen overdose when this proposed product enters the marketplace.

DMEPA also notes the pediatric doses for children ages 2 to 12 years is combined with the weight-based dosing for adults and adolescents weighing less than 50 kg. However, healthcare providers search pediatric references for pediatric medication dosing. This combined presentation in the proposed labeling places this needed information in an unexpected location making it more difficult to find the dose for this age group. Thus, we believe a separate presentation of the dosing requirements for children ages 2 to 12 years from adults and adolescents provides complete instructions for pediatric dosing and eases identification of this information in the labeling.

4.4 AGE AND WEIGHT OVERLAP

The Dosage and Administration section of the proposed insert labeling includes an overlap for dosing criteria in the weight of adult and adolescent patients (i.e., 50 kg) as well as the ages for pediatric patients (i.e. 1 year and 2 years of age). When a patient’s dosing criteria has an overlapping value and the Healthcare provider must choose between more than one dosing option, errors can occur. Therefore, the Dosage and Administration section of labeling should be revised so the doses for children (ages 2 to 12 years) appear separate from the Adults and adolescents and that there is no overlap in weight or age in the pediatric group or the adults and adolescent age group.

4.5 RISK OF AIR EMBOLISM

DMEPA notes the Applicant includes the following statement as part of Section 2.4 of the insert labeling: (b) (4)

Although not identified as a failure mode, this statement raises concern regarding the safe use of this product in clinical practice. Although labeling may be prudent in this case, DMEPA is concerned about this risk. An Information Request email was sent to the Sponsor regarding the inclusion of the statement on August 27, 2009. The Sponsor provided a response including post-marketing surveillance data on August 28, 2009. Thus, DMEPA defers to the clinical assessment as to whether this is an acceptable risk and if the label sufficiently addresses this risk.

5 CONCLUSION AND RECOMMENDATIONS

Our Label and Labeling Risk Assessment indicates that the proposed product design, container label, carton and insert labeling introduce vulnerability to confusion that could lead to medication errors. Some of the risks we have identified can be addressed and mitigated prior to drug approval, and thus we provide recommendations in the following sections that aim at reducing the risk of medication errors. Other recommendations should be considered prior to approval that may require the development of a new additional package size.

5.1 COMMENTS TO THE DIVISION

We would be willing to meet with the Division for further discussion, if needed. DMEPA intends to provide further comment at the forthcoming labeling meetings for NDA 22-450 to address our concerns with the use of the proposed product packaging configuration, specifically the Dosage and Administration Section of the insert labeling as described in Section 5.1.1 and 5.1.2.

Please forward the comments provided in Section 5.2 to the Applicant and copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review.

If you have further questions or need clarifications, please contact Chris Wheeler, project manager, at 301-796-0151.

5.1.1 General Comments

1. DMEPA believes the proposed single strength product configuration is error-prone as noted in Section 4.1. We recommend the Division consider whether the Applicant should develop an additional lower strength product similar to the Perfalgan 500 mg/50 mL vial which is specifically intended for lower doses.⁴
2. DMEPA recommends that a statement be included in the proposed labeling that emphasizes the maximum daily dose of Acetaminophen is based on **all routes** of administration (i.e., oral, rectal, and intravenous.) We recommend this statement

⁴ The United Kingdom's electronic Medicines Compendium (eMC) for Perfalgan 10mg/ml Solution for Infusion; http://emc.medicines.org.uk/medicine/14288/SPC/Perfalgan_10mg/ml_Solution_for_Infusion/ cited September 18, 2009.

to be included in at least Section 2.3 (General Dosing Information), Section 5 (Warnings and Precautions), and Section 10 (Overdose).

3. Revise the abbreviation ‘IV’ to read ‘Intravenous’ in the insert labeling. Although the abbreviation, ‘IV’ meaning intravenous, is generally understood by healthcare providers, DMEPA notes other abbreviations are often misinterpreted as ‘IV.’
4. DMEPA remains concerned about the risk of air embolism due to the packaging configuration of the product. However, the Applicant provided post-marketing safety data to the Agency in a Response Letter on August 28, 2009. DMEPA defers to the clinical assessment of the data provided by the Applicant.

5.1.2 Dosage and Administration Section

1. DMEPA recommends the age groupings be separated so that the doses for children (ages 2 to 12 years) appear separate from the Adults and adolescents and that there is no overlap in weight or age in the pediatric group. For example:
 - Adults and Adolescents (13 years and older) weighing \geq 50 kg.
 - Adults and Adolescents (13 years and older) weighing $<$ 50 kg
 - Children \geq 2 to 12 years of age



2. In addition to the paragraph for each age group, DMEPA recommends adding two tables that include the recommended dose in addition to the maximum single and daily doses for each age group.

For example:

Table 1. Dosing for Adults and Adolescents

Age group	Dose given every 4 hours	Dose given every 6 hours	Maximum Single dose	Maximum total daily dose of Acetaminophen (by any routes)
Adults and adolescents (13 years and older) weighing \geq 50 kg	650 mg	1000 mg	1000 mg	4000 mg in 24 hours
Adults and adolescents (13 years and older) weighing $<$ 50 kg	12.5 mg/kg	15 mg/kg	15 mg/kg (up to 750 mg)	75 mg /kg in 24 hours (up to 3750 mg)

Table 2. Dosing chart for Children (including neonates)

Age group	Dose	Frequency of use	Maximum Single dose*	Maximum total daily dose of Acetaminophen (by any route)#
Children \geq 2 to 12 years of age	12.5 mg/kg	every 4 hours	15 mg/kg	75 mg /kg in 24 hours

(b) (4)

* Up to 750 mg (or 1000 mg) maximum single dose

Up to 3750 mg (or 4000 mg) maximum total daily dose of acetaminophen

3. DMEPA recommends relocating Section 2.3 (General Dosing Information) to the beginning of the Dosage and Administration section as this information is relevant to all doses of this product. We also recommend a statement regarding concurrent use (i.e., TRADENAME should not be used concurrently with other medications containing acetaminophen.) be added to the General Dosing Information.
4. Revise section 2.4 as follows. The table containing drug compatibilities should remain as proposed.

The revised section should read as follows:

2.4 Instructions for Intravenous Administration

For adult and adolescent patients weighing \geq 50 kg requiring 1000 mg doses of TRADENAME, the dose is administered by inserting a vented intravenous set through the septum of the 100 mL vial. TRADENAME may be administered without further dilution. Examine the vial contents before dose preparation or administering. **DO NOT USE** if particulate matter or discoloration is observed. The contents of the vial should be administered intravenously over 15-minutes.

For doses less than 1000 mg, the appropriate dose must be withdrawn from the vial and placed into a separate container prior to administration. Using aseptic technique, withdraw the appropriate dose (650 mg or weight-based) from an intact sealed TRADENAME vial and place the measured dose in a separate container (evacuated sterile glass bottle or syringe) for intravenous infusion to avoid the inadvertent delivery and administration of the total volume of the commercially available container. The entire 100 mL vial of TRADENAME is not intended for use in patients weighing less than 50 kg. TRADENAME is a single-use vial, and the unused portion should be discarded.

As with all infusion solutions administered from glass vials, monitoring at the end of the infusion is advised in order to prevent the possibility of an air embolism, especially in cases where the TRADENAME infusion is being used as the primary infusion.

TRADENAME has been tested in commonly used intravenous infusion sets and syringes and has been shown to be stable for up to 6 hours. It is recommended that once the vacuum seal of the glass vial has been penetrated or transferred to another container, the dose of TRADENAME should be administered within 6 hours.

Table 3 lists commonly administered supportive care drugs and intravenous infusion solutions that are physically compatible for up to four hours at room temperature with TRADENAME and can therefore be administered in the same intravenous line. Do not add other medications to the TRADENAME vial or syringe.

Diazepam and chlorpromazine hydrochloride are physically incompatible with TRADENAME and should not be simultaneously administered.

5. Delete (b) (4) as this information is provided in the revised section 2.4 above.

5.2 COMMENTS TO THE APPLICANT

A General Comments

1. Delete the statement (b) (4) throughout the labels and labeling. The term (b) (4) may imply that the 1000 mg dose is a fixed dose for all patients. However, many patients will receive doses requiring less than 1000 mg of acetaminophen.
2. Present the proprietary name using only one color and one size font. The use of two colors as well as the bolding of only part of the name in the presentation of a proprietary name incorporates similar principles as Tall Man lettering by highlighting and providing prominence to only one portion of the name.

B. Carton Labeling (carton of 24 vials)

1. Revise the presentation of the established name so that the established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features per 21CFR 201.10(g)(2).
2. Revise the presentation of the strength to appear below the established name and above the route of administration. For example:

(b) (4)

(b) (4)

3. Relocate the quantity statement (24 vials) so that it appears in a location away from the product name and strength, preferably near the upper or lower edge of the label.
4. Revise the statement (b) (4) to read “Single Use Vial, discard unused portion.”
5. Include the following statement prior to the storage instructions, “Do not dispense this vial for doses less than 1000 mg.”

C. Container Labels (1000 mg/ 100 mL)

1. Revise the presentation of the established name as noted in Comment B1.
2. Revise the presentation of the strength to below the established name and above the route of administration. (See example in Comment B2 above.)
3. Revise the prominence of the strength presentation so that is it consistent with the proprietary name.
4. Revise the statement (b) (4) to read “Single Use Vial, discard unused portion.”
5. Include the following statement, “Do not dispense this vial for doses less than 1000 mg.”

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential post-marketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

APPENDICES

(b) (4)



Appendix C: Failure Mode and Effects analysis for Acetaminophen packaging and labeling.

Failure mode: All doses are provided by one dosage form	Causes	Effects	Managing the risk
<p>Not all doses of Acetaminophen Injection are 1000 mg</p>	<p>Proposed product is labeled as (b) (4)</p> <p>Proposed labeling provides for the dispensing of the product as designed and allowing healthcare providers who administer the product to adjust the volume of drug prior to giving dose.</p>	<p>Entire 1000 mg vial is infused resulting in overdose.</p>	<p>Provide product in strengths lower than 1000 mg for smaller doses.</p> <p>Propose labeling for all doses to be transferred to an appropriate container prior to administration.</p>
Failure Mode: Dose limits are based on Injection product alone.	Causes	Effects	Managing the risk
<p>Acetaminophen may be received from multiple sources.</p>	<p>Healthcare providers may order acetaminophen orally and intravenously concurrently.</p> <p>Oral combination opioid pain relievers are dosed using the opioid component of the product.</p> <p>Healthcare providers administering the oral product overlook the last administration of the injectable product.</p>	<p>Patient receives more than the maximum total daily dose of Acetaminophen.</p>	<p>Healthcare provider education regarding the use of multiple products containing Acetaminophen (included as part of the proposed risk management plan).</p> <p>Propose labeling which identifies maximum total daily dose of Acetaminophen includes all routes or sources.</p>

Failure Mode: No numeric dose limits for pediatric doses.	Causes	Effects	Managing the risk
<p>The proposed dosing for Acetaminophen Injection is weight-based (15 mg/kg single dose and 75 mg total daily dose) for Adults and Adolescents weighing less than 50 kg and children 2 to 12 years of age.</p>	<p>The dose for Adults and Adolescents is limited by the patient weight (up to 50 kg).</p> <p>Some older children can weigh more than 50 kg</p> <p>Healthcare providers are accustomed to seeing a numeric maximum dose limit for weight-based pediatric dosing. (e.g., up to 4000 mg maximum total daily dose)</p> <p>The children's dosing appears in two separate subsections of the proposed labeling.</p>	<p>Heavier children can received doses of acetaminophen in excess of 750 mg as a single dose or 3750 mg total daily of acetaminophen if weight is more than 50 kg. (Or receive more than 1000 mg as a single dose or 4000 mg total daily dose if weight is more than 66 kg).</p>	<p>Add a numeric maximum dose limit for the pediatric weight-based dosing in the labeling.</p>

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/s/

RICHARD A ABATE
10/06/2009

MELINA N GRIFFIS
10/06/2009

CAROL A HOLQUIST
10/06/2009

DSI CONSULT: Request for Clinical Inspections

Date: July 9, 2009

To: Constance Lewin, M.D., M.P.H, Branch Chief, GCP1
Tejashri Purohit-Sheth, M.D., Branch Chief (Acting), GCP2
Susan Leibenhaut, M.D.
Division of Scientific Investigations, HFD-45
Office of Compliance/CDER

Through: Christina Fang, MO
Division of Anesthesia, Analgesia, and Rheumatology Products,
HFD-170

From: Sharon Turner-Rinehardt, Regulatory Health Project Manager/ Division of
Anesthesia, Analgesia, and Rheumatology Products,
HFD-170

Subject: **Request for Clinical Site Inspections**

I. General Information

Application#: NDA 22-450

Applicant/ Applicant contact information (to include phone/email): Cadence Pharmaceuticals/ Tracy Ross-Teichert, tross@CadencePharm.com, Office: 858-436-1404

Drug Proprietary Name: ACETAVANCE (name was rejected so will change)/IV Acetaminophen for Injection

NME or Original BLA (Yes/No): No

Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): Yes

Is this for Pediatric Exclusivity (Yes/No): No

Proposed New Indication(s): Acute Pain and fever in adult and pediatrics

PDUFA: November 13, 2009

Action Goal Date: November 11, 2009

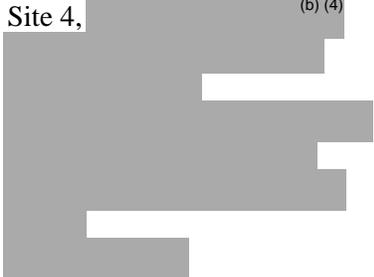
Inspection Summary Goal Date: October 6, 2009

DSI Consult

version: 5/08/2008

II. Protocol/Site Identification

Include the Protocol Title or Protocol Number for all protocols to be audited. Complete the following table.

Site # (Name,Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site 4, (b) (4)  Jonathan Jahr, MD, (310) 739-3952 (Note: Dr. Jahr is currently with UCLA Medical Center)	RC210 3002	65	Pain
Site 5, Lowell Reynolds, MD, Loma Linda University Center for Pain Management 11406 Loma Linda Drive, Suite 523, Loma Linda, CA 92534, (909) 558-6280	RC210 3002	49	Pain
Site 10, Howard Miller, MD, Research Concepts Ltd., 7800 Fannin, Houston, TX 77054 (713) 799-8900	CPI-APA-304	44	Pain
Site 15, Steven Winger, MD, Precision Trials, 3815 East Bell Road, Ste. 4500, Phoenix, AZ 85032 (602) 992-3162	CPI-APA-304	39	Pain
Stephen Daniels, DO Scirex Research Center 3200 Red River, Suite 300 Austin, TX 78705	CPI-APF-302	60	Fever

III. Site Selection/Rationale

Summarize the reason for requesting DSI consult and then complete the checklist that follows your rationale for site selection. Medical Officers may choose to consider the following in providing their summary for site selection.

Rationale for DSI Audits

The sites were selected based mainly on the higher proportions of patients enrolled (with more protocol deviations) than the other sites in the three pivotal studies. The efficacy results of the three studies are important in making a regulatory decision with regard to drug approval.

Domestic Inspections:

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

International Inspections:

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the DSI inspections to verify the quality of conduct of the study).

Five or More Inspection Sites (delete this if it does not apply):

We have requested these sites for inspection (international and/or domestic) because of the following reasons: The sites were selected based mainly on the higher proportions of patients enrolled (with more protocol deviations) than the other sites in the three pivotal studies. The efficacy results of the three studies are important in making a regulatory decision with regard to drug approval.

Note: International inspection requests or requests for five or more inspections require

sign-off by the OND Division Director and forwarding through the Director, DSI.

IV. Tables of Specific Data to be Verified (if applicable)

If you have specific data that needs to be verified, please provide a table for data verification, if applicable.

Should you require any additional information, please contact Sharon Turner-Rinehardt, RPM at 301-796-2254 or Christina Fang, MO at 301-796-1208.

Concurrence: (as needed)

_____ Medical Team Leader
_____ Medical Reviewer
_____ Division Director (for foreign inspection requests or requests for 5
or more sites only)

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this page is the manifestation of the electronic signature.**

/s/

Sharon Turner-Rinehardt
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