CLINICAL REVIEW

Application Type	Supplemental New Drug Application (sNDA)
Application Number(s)	022202 S-013
Priority or Standard	Standard
Submit Date(s)	November 9, 2018
Received Date(s)	November 9, 2018
PDUFA Goal Date	September 9, 2019
Division/Office	Division of Anesthesia, Analgesia, and Addiction Products (DAAAP)/OND
Reviewer Name(s)	Lisa Wiltrout
Review Completion Date	August 2, 2019
Established/Proper Name	Diclofenac potassium soft gel capsules (DPSGC)
(Proposed) Trade Name	Zipsor®
Applicant	Assertio Therapeutics, Inc
Dosage Form(s)	25 mg capsule
Applicant Proposed Dosing Regimen(s)	One capsule every 6 hours as needed for pain
Applicant Proposed Indication(s)/Population(s)	Relief of mild to moderate acute pain in adults and pediatric patients 12 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Relief of mild to moderate acute pain in adult and pediatric patients 12 years of age and older

Throughout this review, the Applicant's drug product may be called Zipsor®, diclofenac potassium soft gel capsules, DPSGC, or the moiety, diclofenac potassium.

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
alk phos	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
$AUC_{0\text{-last}}$	area under the plasma concentration-time curve from time 0 to the time of last measurable concentration
$AUC_{0\text{-inf}}$	area under the plasma concentration-time curve from time 0 to infinity
AUC_{τ}	area under the plasma concentration-time curve from time 0 to the end of the dosing period
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CL/F	Total body clearance
C_{max}	maximum measured plasma clearance
CMC	chemistry, manufacturing, and controls
C_{min}	minimum measured plasma clearance
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CYP2C9	cytochrome P450 C29
DAAAP	Division of Anesthesia, Analgesia, and Addiction Products
DB	double-blind
DMC	data monitoring committee
DPMH	Division of Pediatrics and Maternal Health
DPSGC	diclofenac potassium soft gel capsules
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	electrocardiogram

eCTD	electronic common technical document
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IV	intravenous
JIA	juvenile idiopathic arthritis
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
NSAID	non-steroidal anti-inflammatory drug
OCS	Office of Computational Science
OL	open-label
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PLLR	Pregnancy and Lactation Labeling Rule
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PT	pharmacology/toxicology
PSUR	Periodic Safety Update report
R	randomized
REMS	risk evaluation and mitigation strategy

SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
t_{max}	time to reach maximum plasma concentration
$t_{½}$	apparent terminal half-life calculated from the terminal phase
ULN	upper limit of normal
V_z/F	apparent volume of distribution during the terminal phase
WBC	white blood cell
WR	Written Request
WRO	written response only

1. Executive Summary

1.1. Product Introduction

NDA 022202 Supplement 013 is a pediatric efficacy supplement for Zipsor® (DPSGC). The Applicant, Assertio Therapeutics, Inc, submits this efficacy supplement to support the addition of pediatric patients 12 years to 17 years of age to the indication, to support the inclusion of pediatric pharmacokinetic (PK), efficacy, and safety data in the prescribing information, and in fulfillment of post-marketing requirement 1053-1. Zipsor® (NDA 022202) was originally approved on June 16, 2009 for the indication of relief of mild to moderate acute pain in adults. The approved dosing regimen in adults is Zipsor® 25 mg by mouth every 6 hours as needed for pain. The proposed dosing regimen in pediatric patients 12 years to 17 years of age is the same as the approved regimen in adults. Zipsor® is a non-steroidal anti-inflammatory drug product. The active pharmaceutical ingredient (API) in Zipsor® is diclofenac potassium. The product is packaged in a proprietary potassium salt-based soft gelatin capsule dosage form designed to improve release and absorption of the API and reduce time to onset of pain relief[1].

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support expanding the indication for DPSGC to include relief of mild to moderate acute pain in pediatric patients 12 years to 17 years of age. The Applicant submitted data from Study XP21L-402, an open-label (OL), pharmacokinetic (PK) and safety study of DPSGC 25 mg administered every 6 hours as needed for up to 4 days in pediatric patients 12 years to 17 years of age with mild to moderate acute pain. The study demonstrated comparable diclofenac PK parameters after oral administration of DPSGC between the pediatric population 12 years to 17 years of age and the adult population. In general, for NSAIDs, the Agency has determined that analgesic efficacy in the adult population may be extrapolated to the pediatric population down to the age of two years because the underlying pathology for pain and exposure response to NSAIDs are similar in both populations. Therefore, the PK data from Study XP21L-402 support extrapolating analgesic efficacy from adults to the pediatric population 12 years to 17 years of age for the proposed indication.

The Applicant submitted this supplemental application (S-013) to fulfill one of three Pediatric Research Equity Act (PREA) postmarketing requirements (PMRs). PMR 1053-1 is a required pediatric study under PREA of the PK and safety of Zipsor® in pediatric patients ages 12 years to 17 years with mild to moderate pain. The PK and safety data included in this submission

[1] While this is the Applicant's rationale for the product formulation, the Agency has not made a finding that the features of this product provide an advantage over other formulations on time to onset of pain relief.

adequately address the PMR for Zipsor in the pediatric population 12 years to 17 years of age. I conclude that the information submitted in this supplement fulfills PMR 1053-1.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Zipsor® is indicated for the treatment of mild to moderate acute pain in adults. The Applicant proposes including pediatric patients 12 years to 17 years of age to the indication. I recommend approval of this pediatric efficacy supplement if the Applicant and the Division reach an agreement on labeling.

Pain is the most common reason people seek medical care. Pain has been misunderstood and undertreated in children and remains an unmet medical condition in this population. There are fewer FDA-approved pharmacologic treatment options for pain management in children than in adults. Acetaminophen and non-steroidal anti-inflammatory drugs are the primary treatment options for mild to moderate acute pain in children. There is currently no FDA-approved prescription naproxen, ketorolac, or diclofenac for the acute pain indication in the pediatric population.

The Agency has determined that findings of efficacy in the adult population may be extrapolated to the pediatric population down to the age of two years for the NSAID class because the underlying pathology for pain and exposure response to NSAIDs are similar in both populations. The Applicant submitted pediatric pharmacokinetic data from an open-label, uncontrolled study in adolescents 12 years to 17 years of age. These data demonstrate that the pharmacokinetic profile of Zipsor® in adolescents is comparable to the adult population. Therefore, analgesic efficacy with Zipsor® in the pediatric population 12 years to 17 years of age can be extrapolated from adult data.

After review of both the submitted safety data and the postmarket safety data, there are no new safety signals with use of Zipsor® in adolescents. Common adverse events from the multiple-dose, uncontrolled studies include nausea, headache, constipation, and abdominal pain. The FDA Adverse Event Reporting System can adequately monitor for any long-term adverse events that may occur with off-label use of Zipsor® in the pediatric population. There is no need for risk mitigation beyond the information provided in the prescribing information. Approval of Zipsor® in the pediatric population 12 years to 17 years of age will provide an additional pharmacologic treatment option for the treatment of mild to moderate acute pain.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Acute pain is defined as mild, moderate, or severe pain of sudden onset that is usually the result of a disease, injury, or inflammation and lasts less than three to six months in duration. • Pain is the most common reason people seek medical care. • Untreated pain has a significant impact on quality of life with physical, social, and economic ramifications. • Pain has been misunderstood, misdiagnosed, and mistreated in children. • It is now understood that pain in pediatric patients must be managed to minimize the development of hyperalgesia, to decrease morbidity and mortality, and to prevent long-term negative consequences.	Pain is the most common reason people seek medical care. Untreated pain has a significant impact on quality of life with physical, social, and economic ramifications. Pain has been misunderstood and undertreated in children and remains an unmet medical condition in this population.
Current Treatment Options	• A multimodal approach to pain management, using a combination of non-pharmacologic and pharmacologic strategies, is most appropriate for both adults and children. •Non-pharmacologic approaches to pain management include rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, hypnosis, and relaxation techniques. •Pharmacologic approaches to pain management are escalated as pain intensity increases. •Mild to moderate pain is primarily managed with non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs. • Alternative treatment options for mild to moderate pain include topical anesthetics, antidepressants, and anticonvulsants. • Moderate to severe pain is managed with lower potency opioid analgesics alone or in combination with non-opioid analgesics. • Moderate to severe pain that is not responsive to lower potency opioid	Many FDA-approved pharmacologic treatment options exist for pain management in adults; however, the selection of FDA-approved pharmacologic treatment options for pain management in the pediatric population is more limited. Given the limited availability of FDA-approved drugs to treat pain in children, many drug products are used off-label for pain management in the pediatric population. Acetaminophen and non-steroidal anti-inflammatory drugs are the primary treatment options for mild to moderate acute pain in children. There is currently no FDA-approved prescription naproxen, ketorolac, or diclofenac for the acute pain indication in the pediatric

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	analgesics is managed with higher potency opioid analgesics. • Given the limited availability of FDA-approved drugs to treat pain in children, many drug products are used off-label for pain management in the pediatric population. • Some analgesics with FDA approval for use in the pediatric population include APAP (oral and intravenous), ibuprofen (oral and intravenous), aspirin, naproxen, Flector® topical system, codeine/APAP, hydrocodone/APAP, fentanyl (intravenous and transdermal), buprenorphine (intravenous), and OxyContin (intravenous).	population.
Benefit	• Analgesic efficacy with use of Zipsor® in the adult population may be extrapolated to the pediatric population 12 years to 17 years of age because the underlying pathology for pain and exposure response to NSAIDs are similar in both populations and the pharmacokinetic profile of Zipsor® in the pediatric population is comparable to the adult population.	The available data demonstrated substantial evidence of efficacy for the intended population.
Risk and Risk Management	• The safety database for Zipsor® in the adolescent population included 125 pediatric subjects from two Phase 4 open-label, uncontrolled, multiple-dose studies and one Phase 3 randomized, active-controlled, single-dose study. • The safety database was augmented with a small amount of safety data from the published literature on 60 subjects exposed to either a single-dose of Zipsor® twice per day for 3 to 14 days. • The most common adverse events with Zipsor® from the multiple-dose, uncontrolled studies were nausea (14.3%), headache (10.2%), constipation (8.2%), and abdominal pain (4.1%). • Review of the safety data yielded no new safety signals with use of Zipsor®	There are no significant safety concerns with use of Zipsor® in the pediatric population 12 to 17 years of age. There is no need for risk mitigation beyond the information provided in the prescribing information. The FDA Adverse Event Reporting System can adequately monitor for any long-term adverse events that may occur with off-label use of Zipsor®. Based on a complete review of the available data in this pediatric efficacy supplement, I recommend an Approval action.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in adolescents. • Review of the postmarket safety data did not raise any new safety concerns regarding use of Zipsor® in adults and adolescents. • Monitoring in the postmarket setting for long-term adverse events in the pediatric population is warranted as Zipsor® may be used off-label for chronic pain. • The FDA Adverse Event Reporting System can adequately monitor for any long-term adverse events that may occur with off-label use of Zipsor®. • Zipsor® has a safety profile in the pediatric population 12 years to 17 years of age that is similar to the adult population.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application

X	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 6.2 and Section 6.3
		□	Observer reported outcome (ObsRO)	
		□	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant seeks to update the Zipsor® prescribing information with PK, efficacy, and safety data from studies conducted in the pediatric population 12 years to 17 years of age. The Applicant is proposing to revise the Zipsor® indication from "relief of mild to moderate acute pain" in adults to "relief of mild to moderate acute pain in adults and pediatric patients 12 years of age and older."

Acute pain is defined as mild, moderate, or severe pain of sudden onset that is usually the result of a disease, injury, or inflammation. Pain is considered acute when it lasts for less than three to six months in duration. An individual in acute pain may experience sharp, throbbing, burning, or stabbing sensations or may experience weakness, numbness, and tingling. Acute pain gradually resolves with healing of the underlying cause. Examples of acute pain include muscular or ligamentous sprains and strains, burns, bone fractures, abscesses, and the post-surgical experience. Untreated acute pain is problematic as it can lead to anxiety, depression, delayed healing, and longer hospitalization (McGrath, 2003 and Stephens, 2003). Untreated or inappropriately managed acute pain can also alter neural pathways making future pain worse and leading to the development of chronic pain (McGrath, 2003 and Stephens, 2003)

In the National Health Interview Survey (NHIS) from 2012, it was estimated that approximately 126 million Americans reported some pain in the preceding three months and nearly 40 million adults experienced severe levels of pain (Nahin, 2015 and NHIS, 2012). Pain is the most common reason people seek medical care (Fishman, 2007). Pain impairs sleep, impairs activities of daily living, and lowers work productivity. Untreated pain has a significant impact on quality of life with physical, psychological, social, and economic ramifications (King, 2013). Total U.S. healthcare costs for pain ranged from $560 to $635 billion in 2010 dollars (Gaskin, 2012).

Pain has been misunderstood, underdiagnosed, and undertreated in children. Barriers to treatment in children have included misperceptions that children do not experience pain and do not remember painful experiences, lack of adequate pain assessment, children's limited ability or inability to communicate pain, and fear of adverse effects from analgesic medications (American Academy of Pediatrics, 2001, Fein, 2012 and Kahsay, 2017). It is now understood that pediatric patients of all ages, from neonate to adolescent, experience pain. It is also understood that pain in pediatric patients must be managed to minimize the development of hyperalgesia, to decrease morbidity and mortality, and to prevent long-term negative consequences (McGrath, 2003 and King, 2013).

2.2. Analysis of Current Treatment Options

Pain has sensory, emotional, cognitive, and behavioral components; therefore, a multimodal approach to pain management, using a combination of non-pharmacologic and pharmacologic strategies, is most appropriate for both adults and children. Rest, ice, compression, and elevation (RICE), physical therapy, acupuncture, massage, biofeedback, hypnosis, and relaxation techniques are examples of non-pharmacologic approaches. Pharmacologic options are escalated as pain intensity increases. Mild to moderate pain is managed primarily with non-opioid analgesics, such as acetaminophen (APAP) and nonsteroidal anti-inflammatory drugs (NSAIDs). Alternative treatment options for mild to moderate pain include topical anesthetics, antidepressants, and anticonvulsants. Moderate to severe pain is managed with lower potency opioid analgesics alone or in combination with non-opioid analgesics. If pain is poorly controlled with lower potency opioid analgesics, then higher potency opioid analgesics are used. Regional anesthesia may also be used to manage moderate to severe pain (Kahsay, 2017, Lee, 2014, Verghese, 2010 and WHO Guidelines, 2012).

In general, there are more drug products available to treat pain in adults than in children. And there are more FDA-approved drug products for pain management in adults than in children. Given the limited availability of FDA-approved drugs to treat pain in children, many drug products are used off-label for pain management in the pediatric population.

APAP is FDA-approved for management of pain in adults and children 2 years and older. APAP is available in suppository, suspension, tablet, and solution dosage forms for rectal, oral, and intravenous (IV) administration. It may be purchased over-the-counter (OTC) or prescribed by a healthcare provider when used in combination with opioids or administered by the IV route. Hepatotoxicity in the setting of overdose is the main safety concern with APAP.

Ibuprofen, naproxen, diclofenac, ketorolac, and aspirin are examples of NSAIDs used to treat pain. NSAIDs are available in suspension, tablet, solution, and patch dosage forms for oral, IV, and topical administration. NSAIDs may be purchased OTC or prescribed by a healthcare provider. Caldolor® (IV ibuprofen) is FDA-approved for pain management in adults and children 6 months and older. OTC ibuprofen and aspirin are FDA-approved for pain management in adults and children 2 years and older. Flector® (diclofenac epolamine topical system) is FDA-approved for treatment of acute pain in adults and children 6 years and older. Aleve® (an OTC oral naproxen) is FDA-approved for pain management in adults and children 12 years and older. Prescription naproxen is FDA-approved for relief of signs and symptoms of polyarticular juvenile idiopathic arthritis (JIA) in children 2 years and older. However, there is currently no FDA-approved prescription naproxen (and no FDA-approved prescription diclofenac or ketorolac) for pain management in children. The associated risks with use of NSAIDs include cardiovascular, gastrointestinal, and renal toxicity. There is also an increased risk of bleeding. Aspirin use should be avoided in pediatric patients with viral infections because of the increased risk of Reye's syndrome in this setting.

Some examples of opioid analgesics with pediatric labeling for the acute pain indication include the following:

- Codeine/acetaminophen (APAP) - approved for children 12 years and older;
- Hydrocodone/APAP - approved for children 2 years and older;
- Fentanyl IV or transdermal and buprenorphine IV - approved for children 2 years and older;
- OxyContin IV – approved for children 11 years and older.

One crucial safety concern with use of any opioid analgesic is the risk of misuse, abuse, and addiction. Specific to the combination codeine/APAP and hydrocodone/APAP products is the risk of life-threatening respiratory depression and death in those who are ultra-rapid metabolizers. Common adverse events associated with opioids include nausea, vomiting, constipation, respiratory depression, drowsiness, dizziness, and physical dependence.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Zipsor® was approved in June 2009 for use in adults with the indication for the relief of mild to moderate acute pain. At the time of approval, pediatric studies were waived in the pediatric population ages birth to 1 year because there was evidence to suggest that the product would be ineffective or unsafe in that pediatric age range. Studies in the pediatric population ages 1 to 17 years were deferred. The NDA holder committed to the following three PMRs to fulfill PREA requirements at the time of Zipsor® approval:

- Deferred pediatric pharmacokinetic (PK), safety, and efficacy study in pediatric patients ages 12 years to 17 years with mild to moderate acute pain.
- Deferred pediatric PK, safety, and efficacy study in pediatric patients ages 2 years to (b) (4) (b) (4) 12 years with mild to moderate acute pain.
- Deferred pediatric study in pediatric patients ages 1 year to (b) (4) 2 years with mild to moderate acute pain.

In December 2009, the Division of Anesthesia, Analgesia, and Addiction Products (DAAAP) sponsored a workshop that gathered academic and clinical experts from the pediatric pain community. The workshop participants determined that the underlying pathology for pain is the same in adults and children over the age of two years. The workshop participants also concluded that findings of efficacy in the adult population and older children may be extrapolated to the pediatric population down to the age of two years for analgesics where the mechanisms of action are understood. Examples of analgesics in this category include opioids, NSAIDs, APAP, and local anesthetics. There was concurrence that the PK and safety of analgesics must still be evaluated using clinical studies in the pediatric population ages two years and older.

Given the workshop consensus that extrapolation of efficacy from adults to pediatric patients for certain analgesic products is acceptable, DAAAP released the Zipsor® NDA holder from the original PMRs in July 2010 and reissued them as follows:

- PMR 1053-1: PK and safety study of Zipsor® in pediatric patients ages 12 years to 17 years with mild to moderate pain.
- PMR 1053-2: PK and safety study of Zipsor® in pediatric patients ages 2 years to (b) (4) (b) (4) 12 years with mild to moderate pain.
- PMR 1053-3: Efficacy, safety, and PK study of Zipsor® in pediatric patients ages 1 year to (b) (4) 2 years with mild to moderate pain.

A Written Request (WR) was issued by the Agency on February 22, 2011 and the holder of NDA 022202 declined the WR. The WR included the following study requirements:

(b) (4)

Since the reissuance of the PMRs in July 2010, several deferral extensions have been granted and noncompliance letters have been issued to different holders of NDA 022202.

3.2. Summary of Presubmission/Submission Regulatory Activity

NDA 022202 has changed ownership three times since the initial approval of Zipsor® in 2009. Xanodyne Pharmaceuticals, Inc. was the original NDA holder. In June 2012, the NDA changed ownership from Xanodyne Pharmaceuticals, Inc. to Depomed, Inc. In August 2018, Depomed, Inc. reincorporated and changed its name to Assertio Therapeutics, Inc. Xanodyne conducted Study CL-000424, the safety and efficacy study in pediatric subjects ages 8-16, to determine the efficacy, safety, and tolerability of a single-dose of Zipsor® in the pediatric population and included the clinical study report (CSR) for Study CL-000424 with the original NDA submission. After Zipsor®'s approval, Xanodyne conducted Study XP21L-402, the PK and safety study in pediatric subjects 12 years to 17 years of age, to fulfill PREA PMR 1053-1. Depomed, Inc. conducted Study 81-0072, the safety and efficacy study in pediatric subjects 12 years to 17 years of age, and Study 81-0074, the PK and safety study in pediatric subjects ages 2 years to 12 years of age, to fulfill PREA PMRs 1053-1 and 1053-2. Assertio Therapeutics, Inc. did not conduct any pediatric studies with Zipsor®; however, Assertio Therapeutics, Inc. is the current NDA holder who submitted efficacy supplement S-013 in November 2018.

The regulatory history for NDA 022202 in support of labeling changes for the pediatric population is summarized here and presented in Table 1 below.

(b) (4)

- In June 2013, Depomed, Inc. submitted a meeting package that included Protocol 81-0072, a proposed study to evaluate the efficacy and safety of Zipsor in 25 pediatric subjects 12 years to 17 years of age. Depomed, Inc. requested DAAAP's feedback on the proposed study as well as the adequacy of a proposed safety database consisting of (b) (4) pediatric subjects 12 years to 17 years of age.
- The Division responded in August 2013 with written response only (WRO) meeting minutes. The Division stated that the proposed study, including the sample size, proposed inclusion and exclusion criteria, study endpoints, and planned follow-up visit, appeared acceptable. The Division, in conjunction with the Division of Maternal and Pediatric Health (DPMH), concluded that a larger safety database of adolescent subjects treated for acute pain was needed to adequately characterize the safety profile of DPSGC. The Division recommended that the Applicant augment the safety database

with available safety information on diclofenac use in adolescents from published studies in the literature. The Division stated that clinical trial safety data from 50 adolescent subjects combined with safety data from the literature may be adequate to support labeling.

- In November 2013, Depomed, Inc. submitted a meeting package that included Protocol 81-0074, a proposed study to evaluate the PK and safety of diclofenac potassium oral solution in pediatric subjects 2 years to 12 years of age. Depomed, Inc. requested DAAAP's feedback on the proposed study as well as the adequacy of a proposed safety database consisting of (b) (4) pediatric subjects 2 years to 12 years of age.
- The Division responded in April 2014 with WRO meeting minutes. The Division stated that the proposed sample size of (b) (4) subjects was not adequate. The Division also stated that augmenting the safety database with safety data from the literature was unlikely to provide reliable safety information for this age group. Therefore, the Division emphasized the need for a clinical trial safety database of at least 50 subjects 2 to 12 years of age years who received at least one dose of study medication. The Division otherwise indicated that the proposed inclusion and exclusion criteria, study endpoints, and planned follow-up visit for Protocol 81-0074 appeared acceptable.

(b) (4)

- After the refuse to file letter, DepoMed, Inc. requested a pre-NDA WRO meeting with the Agency. Depomed, Inc. sought to reach agreement with the Division on their proposal to file two supplements, one for the pediatric population12 years to 17 years of age and another for the pediatric population 1 year to 12 years of age, that would (b) (4) fulfill PREA PMRs 1053-1, 1053-2, and 1053-3. The Agency granted the meeting and sent a WRO letter to the Applicant on August 22, 2017. In the WRO letter, the Agency agreed with the proposed approach of filing two supplements and agreed that the content of the two supplements appeared acceptable.
- In November 2018, Assertio Therapeutics, Inc. submitted a new efficacy supplement (S-013) with pediatric data from Studies XP21L-402, 81-0072, and CL-000424 in November 2018 to support Zipsor® labeling changes for the pediatric population 12 years to 17 years of age. S-013 is the subject of this review.

Table 1 Regulatory History for NDA 022202 in Support of Labeling Changes for the Pediatric Population

Regulatory Activity/ Date	Clinical Data	Requested Labeling Changes	Regulatory Deficiency(ies)	Agency Comments to Applicant
[redacted] (b) (4)				
Meeting Package Submission/ June 2013	Protocol 81-0072 and questions for the Division about Protocol 81-0072 and adequacy of the safety database for pediatric subjects ages 12 to 17 years	N/A	N/A	N/A
Type C WRO Meeting Minutes/ August 2013	Response to questions about Protocol 81-0072 and adequacy of the safety database for ages 12 to 17 years	N/A	N/A	The proposed sample size, endpoints, inclusion and exclusion criteria, and timing of F/U for Protocol 81-0072 appear acceptable. Augment the clinical trial safety database with available safety information from published studies in the literature.
Meeting Package Submission/ November 2013	Protocol 81-0074 and questions for the Division about Protocol 81-0074 and adequacy of the proposed safety database	N/A	N/A	N/A

Regulatory Activity/ Date	Clinical Data	Requested Labeling Changes	Regulatory Deficiency(ies)	Agency Comments to Applicant
Type C WRO Meeting Minutes/ April 2014	Response to questions about Protocol 81-0074 and adequacy of the proposed safety database	N/A	N/A	The proposed endpoints, inclusion and exclusion criteria, and timing for F/U for Protocol 81-0074 appear acceptable. The sample size of (b) (4) subjects is not adequate. Need clinical trial safety database of at least 50 subjects ages 2 – 12 years who received at least one dose of study medication.
[redacted]				(b) (4)
Efficacy Supplement (S-013) Submission/ November 2018	Safety and efficacy data in 25 pediatric subjects ages 12-17 (CSR for Study 81-0072) PK and safety data in 24 pediatric subjects ages 12-17 (CSR for Study XP21L-402) Safety and efficacy data in 97 pediatric subjects ages 8-16 (CSR for Study CL-000424)	Add safety, efficacy, and PK data in adolescents to the label	Subject of this review	N/A

As mentioned above, Depomed, Inc. submitted (b) (4) with pediatric data from Studies XP21L-402, 81-0072, and 81-0074 in December 2016. Upon review of the supplement for filing, the Division determined that the supplement was not sufficiently complete to permit a substantive review; therefore, a refuse to file letter was issued to the Applicant. The clinical deficiencies along with the information needed to resolve these deficiencies are listed in Table 2. The clinical deficiencies have been adequately addressed by the Applicant in the current efficacy supplement, S-013.

Table 2 Summary of Clinical Deficiencies and Information Needed to Resolve the Deficiencies in Efficacy Supplement (b) (4)

Clinical Deficiency	Information Needed to Resolve the Deficiency
(b) (4)	

3.3. Foreign Regulatory Actions and Marketing History

Not applicable as Zipsor® is not marketed outside the U.S.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable as there were no OSI audits requested for this supplemental NDA submission.

4.2. Product Quality

The chemistry, manufacturing, and controls (CMC) review was conducted by Daneli Lopéz Pérez, PhD with concurrence from Zedong Dong, PhD, and Ramesh Raghavachari, PhD. The Applicant did not propose any CMC changes in the manufacture of the drug substance, drug product, or labeling and requested categorial exclusion for this supplement. The CMC review team recommends approval of this supplement. Please see the review of Daneli Lopéz Pérez, PhD, for additional information.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology (PT) review was conducted by Dan Mellon, PhD. The PT review is pending. Please see the review of Dan Mellon, PhD, for a more detailed discussion of the nonclinical data included with this submission.

4.5. Clinical Pharmacology

The clinical pharmacology review was conducted by Srikanth Nallani, PhD and Yun Xu, PhD. DepoMed, Inc. submitted a labeling supplement (b) (4) in October 2012 to support revisions of (b) (4) (b) (4) The clinical team, however, concluded that there was (b) (4) (b) (4) Therefore, the Division determined that no changes would be made to the Zipsor® label at that time.

PK Comparisons Between Pediatric Patients and Adults

(b) (4) the Agency requested that the Applicant provide a summary of PK findings comparing the systemic exposures with various doses of diclofenac in pediatric patients 12 years to 17 years of age to the systemic exposures with various doses of diclofenac in adults. The Agency also requested that the Applicant evaluate the effect of bodyweight on AUC and clearance of diclofenac in pediatric patients 12 years to 17 years of age compared to adults.

The Applicant provided a comparison of adult and pediatric PK findings in the "Summary of Biopharmaceutic Studies" section of this submission. The Applicant also performed statistical analyses comparing the PK profiles of adults and pediatric patients and the effect of bodyweight on diclofenac AUC and clearance in adults and pediatric patients. These analyses are described in detail in the Pharmacokinetic Analysis Report included in this submission.

The Applicant evaluated data from the 25-mg DPSGC dose groups in healthy adults (Studies AAI-UC-119, AAI-US-142, OA170, and OA171), adult patients (Study CL-002000), and pediatric patients (Study XP21L-402) when comparing the PK findings and bodyweight values in adults and pediatric patients 12 years to 17 years of age.

A summary of the bodyweight values for adults and pediatric patients 12 years to 17 years of age is presented in Table 3 below. The Applicant concluded that the bodyweight values for the pediatric population were marginally statistically lower than those for the adult population.

Table 3 Summary of Bodyweight Values for Adult and Pediatric Populations

Population	N	Mean (kg)	SD	SE	Minimum (kg)	Maximum (kg)
A	283	71.0795	11.3438	0.6743	44.5000	98.8831
K	47	67.1383	11.3972	1.6625	47.7000	88.4000
Diff (1 - 2)	--	3.9412	11.3513	1.7880	--	--

Note: Diff (1-2) = difference between the mean values of A and K groups
A = adult; K = pediatric; SD = standard deviation; SE = standard error

Source: Summary of Biopharmaceutical Studies/S-013, Table 2.7.1-9, p. 25.

A comparison of the PK parameters following oral administration of a 25-mg dose of DPSGC in adults and pediatric patients is presented in Table 4. Statistical comparisons of C_{max} and T_{max} were not performed due to differences in sampling times between the studies. Since a statistical comparison of clearance was performed, the Applicant deemed it unnecessary to perform a statistical comparison of $t_{1/2}$. The Applicant concluded that despite small differences in bodyweight, there were no significant differences in PK values between the adult and pediatric populations for AUC_{last}, AUC_{inf}, and CL.

Table 4 PK Parameters After Oral Administration of DPSGC 25 mg in Adult and Pediatric Populations

	Adult[a]	Pediatric (12–17 years)[b]	
N	283[a]	47[b]	p-value
Dose (mg)	25	25	--
C_{max} (ng/mL)	929.033 ± 426.206	641.128 ± 442.030	Not assessed
T_{max} (hr)	0.618 ±0.408	1.025 ± 0.617	Not assessed
AUC_{last} (ng•hr/mL)	640.421 ±189.951	613.589 ±178.119	0.46
AUC_{inf} (ng•hr/mL)	661.694 ±193.905	673.674 ±199.193[c]	0.82
CL (ng/L)	41.17 ±12.40	43.46 ±12.61[c]	0.23
$t_{½}$ (hr)	1.291 ±0.916	1.714 ±0.760[c]	Not assessed

AUC = area under the concentration - time curve from time 0 to the last measurable concentration (AUC_{last}) or extrapolated to infinite time (AUC_{inf}); CL = apparent clearance; C_{max} = maximum observed concentration; $t_{½}$ = half-life; T_{max} = time of maximum observed concentration

[a]Combined (healthy + patient) data for 25-mg treatment from studies AAI-US-119; AAI-US-142, OA170, OA171, CL-002000

[b]Combined single-dose and multiple-dose data from Study XP21L-402

[c]n = 45

Source: Summary of Biopharmaceutic Studies/S-013, Table 2.7.1-10, p. 26.

The Applicant also performed statistical analyses to compare the effect of bodyweight on diclofenac AUC and CL in the adult and pediatric populations. The results of these analyses demonstrated that bodyweight had minimal impact on AUC_{last}, AUC_{inf}, and CL for both adult and pediatric patients.

The Applicant argues that the results of the above-mentioned statistical analyses comparing the

PK profiles, the bodyweight, and the impact of bodyweight on diclofenac AUC and CL in the adult and pediatric populations support PK-based extrapolation of efficacy data from adults to pediatric patients 12 years to 17 years of age.

The clinical pharmacology team reviewed the Applicant's summary of PK comparisons between adult and pediatric populations after oral administration of DPSGC 25 mg included in this submission. The clinical pharmacology team concluded that the submitted data is consistent with PK observations noted in the previous clinical pharmacology review dated April 11, 2013. The clinical pharmacology team also proposed some labeling changes to the Specific Populations portion of Section 12.3 Pharmacokinetics of the prescribing information. Please see the most recent clinical pharmacology review of Srikanth Nallani, PhD, with concurrence from Yun Xu, PhD, dated July 10, 2019.

Reviewer Comment: I agree with the Applicant's conclusion that the PK profiles of the adult population and pediatric population 12 years to 17 years of age after oral administration of DPSGC 25mg are similar; therefore, efficacy of DPSGC in pediatric patients 12 years to 17 years of age can be extrapolated from efficacy data in adults.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant's Zipsor® clinical development program for the pediatric population 12 years to 17 years of age focused on establishing the PK and safety characteristics of the drug product. The clinical development program consisted of one Phase 4 PK and safety clinical trial, Study XP21L-402, that was completed in March 2012, and one Phase 4 safety and efficacy clinical trial, Study 81-0072, that was completed in May 2014. The Applicant conducted Studies XP21L-402 and 81-0072 to evaluate the safety and PK and safety and efficacy, respectively, of Zipsor® in adolescents 12 years to 17 years of age. No adequate and well-controlled clinical trials demonstrating efficacy were required in this clinical development program because the Division concluded that the efficacy of DPSGC in the pediatric population 12 years to 17 years of age can be extrapolated from adults if the PK profiles are comparable and safety in the pediatric population 12 years to 17 years of age is adequately evaluated.

The Applicant also references an older pediatric clinical trial, Study CL-000424, that was conducted during the Zipsor® clinical development program for adults and completed in June 2002. Study CL-000424 was a Phase 3, active-controlled, parallel-group, single-dose clinical trial to evaluate the safety and tolerability of DPSGC in the pediatric population 8 years to 16 years of age. The Sponsor for Zipsor® at the time did not intend to promote use of the drug product in the pediatric population. However, the Sponsor recognized the potential for off-label use of Zipsor® in pediatric patients and wanted to characterize the safety profile of the product in patients 8 years to 16 years of age. A high-level review of Study CL-000424 was conducted when the original NDA was submitted in 2007.

More details on Study XP21L-402, Study 81-0072, and Study CL-000424 are provided Table 5.

Table 5 Listing of Clinical Trials Relevant to NDA 022202 Supplement 013

Trial Identity	NCT no.	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Study Duration/ Treatment Length/ Follow Up	No. of Patients Enrolled	Study Population	No. of Centers And Countries
Controlled Studies to Support Efficacy								
None								
Studies to Support Safety								
81-0072	01982539	Multicenter, OL, safety, tolerability, and efficacy study of Zipsor® in pediatric patients ages 12 – 17 years with mild to moderate acute pain	Zipsor® 25 mg by mouth every 6 hours as needed for pain	Safety Endpoints – Incidence of AEs Clinical laboratory test results Vital signs and PE findings Efficacy Endpoints – Percent change in NPRS score from baseline to hour 1 and 2 after first dose of Zipsor®	Max 4 weeks/ Up to 4 days/ Daily telephone F/U while on Zipsor®/Final visit 7-14 days after first dose of Zipsor®	25	Pediatric patients ages 12 – 17 years with mild to moderate acute pain	Two sites in the United States
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)								
XP21L-402	Not applicable	Multicenter, OL, PK and safety study of Zipsor® in pediatric patients ages 12 – 17 years with mild to moderate acute pain	Zipsor® 25 mg by mouth every 6 hours as needed for pain	PK Endpoints – PK profile after single and multiple doses of Zipsor® 25 mg Safety Endpoints – Incidence of AEs Clinical laboratory test results Vital signs and PE findings	Max 4 weeks/ Up to 4 days/ Final visit 48 hours after last dose of Zipsor® and telephone F/U 7 ± 2 days after final visit	24	Pediatric patients ages 12 – 17 years with mild to moderate acute pain	One site in the United States
AAI-00395/CL-000424	Not applicable	R, parallel-group, DB, safety and efficacy study of two strengths of Zipsor®	Zipsor® 25 mg by mouth (Group A) Zipsor® 50 mg by mouth (Group B)	Efficacy Endpoints – Individual and time-weighted Sum of all PSR scores Individual and time-weighted DPRR and DIS scores Time to rescue medication Overall Global Evaluation Safety Endpoints – AEs	2 days/ Single dose of Zipsor®/ Follow up Day 2	97 47 (Group A) 50 (Group B)	Pediatric patients ages 8 – 16 years undergoing insertion of either orthodontic separators or arch wires	Two sites in the United States

5.2. Review Strategy

The Applicant submitted PK data from Study XP21L-402 to support the efficacy of DPSGC in the pediatric population ages 12 - 17. As discussed in Section 4.5 of this review, the clinical pharmacology team previously reviewed Study XP21L-402, deemed the study acceptable from the clinical pharmacology perspective, and concluded that the systemic exposure of diclofenac following oral administration of DPSGC 25 mg in pediatric patients ages 12 – 17 is comparable to the systemic exposure of diclofenac following oral administration of DPSGC 25 mg in adults under fed conditions. Therefore, the efficacy of DPSGC in the pediatric population ages 12 – 17 has been adequately evaluated by the clinical pharmacology team. I will summarize the design, conduct, and PK findings of Study XP21L-402 in Section 6.1 of this review.

The Applicant submitted efficacy data from Study 81-0072 and Study CL-000424 to additionally support the efficacy of DPSGC in pediatric patients 12 years to 17 years of age. The Applicant argued for the inclusion of efficacy results from both trials in the prescribing information. I reviewed the design and conduct of both studies and concluded that neither Study 81-0072 nor Study CL-000424 meets the evidentiary standards for an adequate and well-controlled study. Study 81-0072 was not blinded. Both studies had no placebo arm. And both studies were not powered for efficacy as the primary endpoint. Consequently, the efficacy data from both studies are not adequate to support the efficacy of DPSGC in pediatric patients 12 years to 17 years of age. Therefore, I will not evaluate the efficacy data from these studies, but instead will summarize the design, conduct, and efficacy findings of Study 81-0072 and Study CL-000424 in Sections 6.2 and 6.3, respectively, of this review.

The Applicant submitted safety data from Study XP21L-402, Study 81-0072, and Study CL-000424 to support the safety of DPSGC in the pediatric population 12 years to 17 years of age. The safety data from Studies XP21L-402 and 81-0072 was pooled given the similarities in study design, study population, and dosing regimen between these two studies. The safety data from Study CL-000424 was not pooled. I will evaluate both the pooled safety data from Studies XP21L-402 and 81-0072 presented in the integrated summary of safety (ISS) and the individual safety data from Study CL-000424 in Section 8 of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

For ease of reference, I have summarized all three studies submitted in this supplement in Section 6 of this review. Note that Study XP21L-402 is an OL, PK and safety study that provided no data in support of efficacy.

6.1. Study XP21L-402 A Phase 4, Open-Label Study of the Pharmacokinetics and Safety of Zipsor® (DPSGC) in Pediatric Subjects (Ages 12-17) with Mild to Moderate Acute Pain

Trial Design
Study XP21L-402 was a Phase 4, OL study designed to evaluate the PK and safety of a single dosage strength of DPSGC (25 mg) administered every 6 hours as needed for pain for up to 4 days in pediatric subjects 12 years to 17 years of age with mild to moderate acute pain. The study was conducted at one clinical site in the United States. Twenty-four (24) subjects were enrolled in the study and 23 subjects completed the study. The study consisted of a 2-week screening and washout period, a 4-day treatment period, a final study visit approximately 2 days after the last dose of study drug, and a follow-up telephone call approximately 1 week after the final study visit.

Eligibility
Subjects were eligible for the study if they were a male or female between 12 years to 17 years of age with mild to moderate acute pain (score of 1 - 2 on Pain Severity Rating scale) resulting from an acute painful condition, such as dysmenorrhea or muscle aches, or a painful surgical procedure, such as appendectomy, tonsillectomy, adenoidectomy, pyloric stenosis repair, umbilical hernia repair, rhinoplasty, septoplasty, strabismus repair, or laparoscopic splenectomy. Subjects reported pain using the Pain Severity Rating scale where 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. Subjects with severe pain (score = 3) were excluded from the study. Subjects who were receiving medications that may have caused a clinically significant condition when used concomitantly with diclofenac potassium or acetaminophen were excluded from the study. Subjects who were receiving medications that are known to strongly inhibit cytochrome p4502C9 were also excluded from the study.

Treatment
Subjects took at least one capsule of DPSGC 25 mg by mouth for pain. The first oral dose was administered at the study center on Day 1. Subjects remained at the study center until the last blood sample was collected 6 hours after the first dose of study drug. If treatment for pain was still needed, subjects were given a second oral dose of DPSGC. Subjects were then discharged from the study center with a supply of study drug and rescue medication. Subjects were instructed to continue taking one capsule of study drug orally every 6 hours for pain for up to 4 days until treatment for pain was no longer needed. Subjects were also asked to record AEs, study drug administration, concomitant medication use, and rescue medication use in a patient diary. Subjects who took the study drug for 24 hours were required to return to the study center for administration of the fifth dose of DPSGC and additional blood sampling on Day 2.

PK and Safety Variables
Blood samples were collected for single- and multiple-dose PK assessments before the first and

fifth doses of study drug and at specified time intervals after the first and fifth doses of study drug (10, 20, 30, 40, 60, and 80 minutes and 2, 3, 4, 5, and 6 hours). Plasma concentrations of diclofenac in blood samples were determined using a validated bioanalytical method. Safety assessments included vital signs monitoring (weight, height, temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) at specified timepoints, physical examinations (PEs) and clinical laboratory tests (hematology, serum chemistry, urinalysis, urine pregnancy, and serum pregnancy) at screening, before the first dose of study drug, and at the final study visit, and adverse event (AE) documentation throughout the study.

Study Endpoints

PK

Standard single and multiple dose PK parameters including C_{max}, C_{min}, t_{max}, elimination rate constant (λz), $t_{1/2}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-}\infty}$, AUC_{τ}, total body clearance (CL/F), and apparent volume of distribution during the terminal phase (Vz/F)) were estimated.

Drug Concentration Measurements

The concentration of diclofenac in plasma samples was determined using a validated bioanalytical method.

Safety

The incidence of treatment-emergent AEs (TEAEs), serious AEs (SAEs), withdrawals because of AEs, and deaths was documented. PE findings were documented. The observed values and changes in vital sign measurements and clinical laboratory results were also documented.

Statistical Analysis Plan

This was an open-label, PK and safety study. No efficacy endpoints were specified for this study; therefore, a detailed review of the SAP was not required.

Protocol Amendments

There were two protocol amendments for Study XP21L-402, dated April 18, 2011 and June 16, 2011. The protocol amendments resulted in administrative changes to the protocol but did not affect the conduct of the study.

Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with Good Clinical Practice (GCP) requirements and all applicable regulations, including the US Code of Federal Regulations regarding clinical studies, and all national and local laws and regulations. The study also complied with the ethical principles described in the Declaration of Helsinki.

Financial Disclosure

The Applicant submitted FDA form 3454 certifying that no financial interests or agreements exist for the one clinical investigator who participated in Study XP21L-402.

Patient Disposition

Of the 24 subjects enrolled, 23 subjects (95.8%) completed the study.

Protocol Deviations
There were no major protocol deviations. Two subjects met exclusion criterion #7 (receiving medication that may cause a clinically significant condition when used concomitantly with diclofenac potassium or acetaminophen or not undergone a washout period of at least 30 days); however, one of the these subjects was discontinued from the study because he was unable to provide a PK sample as scheduled on Day 2 and, subsequently, a fifth dose of study drug was not administered.

Demographics
The majority of the subjects were male (58.3%) and Caucasian (62.5%) with a mean age of 15.3 years, a mean weight of 67.3 kg, and a mean height of 169.5 cm.

Other Baseline Characteristics
Pain severity at baseline was mild in 41.7% of subjects and moderate in 58.3% of subjects.

Treatment Compliance, Rescue Medications, and Concomitant Medications
Study personnel administered the first dose of DPSGC to all subjects and the fifth dose of DPSGC to subjects who took study drug for 24 hours. For hospitalized subjects, all medication administration was documented in the medical record. For discharged subjects, study drug administration was documented in a diary. All but one subject received Doses #1 through #5 of study drug. The allowed rescue medication was acetaminophen 12.5 mg/kg every 4 hours as needed for pain (max single dose 650 mg and max daily dose 2000 mg in 24 hours). Seventy-five percent (75%) of subjects used rescue medication during the study. All subjects used at least one medication prior to receiving the study drug. The four most commonly used medications were propofol (100%), ondansetron hydrochloride (95.8%), fentanyl (83.3%), and lidocaine (83.3%) for surgical procedures.

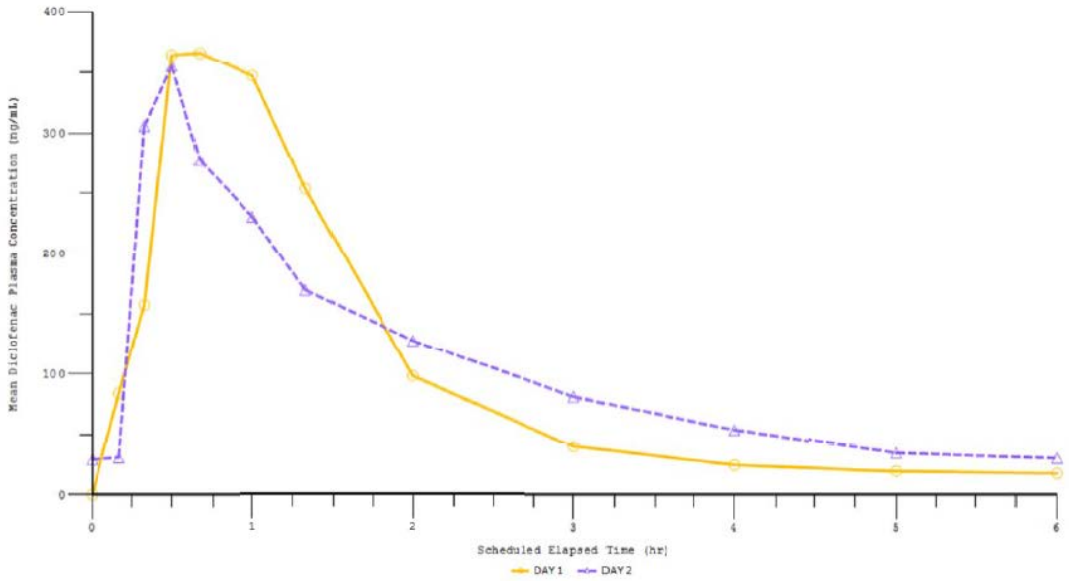
Reviewer Comment: The majority of subjects used rescue medication during the study suggesting that DPSGC alone was not adequate for pain management in this study population.

Prohibited Medications
Subjects were prohibited from taking medications that might cause a clinically significant condition when used concomitantly with diclofenac potassium or acetaminophen and medications known to strongly inhibit CYP2C9.

Efficacy Results
There were no efficacy results for this study.

PK Results
Mean diclofenac plasma concentration figures were created to support the PK results of the study. Figure 1 below displays both the mean profiled concentrations from the first dose on Day 1 (solid line) and the fifth dose of Day 2 (dashed line).

Figure 1 Mean Diclofenac Plasma Concentration Profile on Day 1 and Day 2 following DPSGC 25 mg Administration



Source: CSR Study XP21L-402, Figure 11-1, p.46.

PK parameters were estimated for diclofenac plasma concentrations that profiled Dose 1 (Day 1) and Dose 5 (Day 2). The results for both doses are summarized in Table 6 and Table 7.

Table 6 Summary of Diclofenac PK Estimates for Dose 1 (Day 1) Profile

Descriptive Statistic	C_{max} (ng/mL)	t_{max} (h)	$AUC_{0\text{-last}}$ (ng*h/mL)	$AUC_{0\text{-}\infty}$ (ng*h/mL)	λ_z (1/h)	$t_{1/2}$ (h)	CL/F (L/h)	Vz/F (L)
N	24	24	24	24	24	24	24	24
Arithmetic Mean	699	0.94	613	659	0.452	1.81	44.5	114.3
SD	464	0.42	185	208	0.172	0.92	13.9	60.3
%CV	66.4	44.9	30.3	31.5	38.0	51.0	31.3	52.8
Median	613	1.00	609	629	0.429	1.62	41.0	99.5
Minimum	219	0.33	329	374	0.134	0.82	24.1	50.7
Maximum	2210	2.00	1036	1103	0.847	5.19	76.0	258.9
Geometric Mean	581	NR	587	630	0.419	1.65	42.5	101.4

SD = standard deviation; %CV = coefficient of variation; N/A = not available; NR = not reported; CL/F = apparent total clearance; C_{max} = Maximum measured plasma concentration over the first pharmacokinetic dose profiled; t_{max} = time to maximum (peak) plasma concentration; $AUC_{0\text{-last}}$ = AUC from time of dose to last quantifiable sample collected before the second dose is given; $AUC_{0\text{-}\infty}$ = area under the plasma concentration versus time curve from Time 0 extrapolated to infinity; λ_z = elimination rate constant associated with the terminal (log linear) portion of the curve; $t_{1/2}$ = terminal half-life; CL/F = apparent renal clearance; V_z/F = volume of distribution

Source: CSR Study XP21L-402, Table 11-2, p. 49.

Table 7 Summary of Diclofenac PK Estimates for Dose 5 (Day 2) Profile

Descriptive Statistic	C_{max} (ng/mL)	t_{max} (h)	C_{min} (ng/mL)	$AUC_{0\text{-last}}$ (ng*h/mL)	AUC_{τ} (ng*h/mL)	λ_z (1/h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
n	23	23	23	23	21	21	21	21	21
Arithmetic Mean	581	1.12	18	614	632	0.480	1.60	42.3	98.2
SD	419	0.77	13	174	167	0.175	0.52	11.1	38.8
%CV	72.2	68.9	73.8	28.4	26.4	36.4	32.2	26.3	39.5
Median	483	1.00	10	600	602	0.453	1.53	41.5	102.5
Minimum	177	0.33	5	288	390	0.230	0.69	24.9	24.9
Maximum	1610	3.00	56	1002	1002	1.000	3.02	64.1	184.9
Geometric Mean	462	NR	14	590	611	0.455	1.52	40.9	89.9

%CV = coefficient of variation; N/A = not available; NR = not reported; SD = standard deviation; Vz/F = apparent volume of distribution; C_{max} = ; Maximum measured plasma concentration over the pharmacokinetic dose profiled; t_{max} time to maximum (peak) plasma concentration; AUC_{τ} = area under the plasma concentration versus time curve over the final dosing interval; $AUC_{0\text{-last}}$ = AUC from time of dose to last quantifiable sample collected before the second dose is given; $AUC_{0\text{-}\infty}$ = AUC from time of dose extrapolated to infinity; λ_z = elimination rate constant associated with the terminal (log linear) portion of the curve; $t_{1/2}$ = terminal half-life; CL/F = apparent renal clearance; V_z/F = volume of distribution

Note: τ = 6 hours

Note: Subject 01-02 did not receive a fifth dose; λ_z could not be estimated for Subjects 01-16 and 01-19.

Source: CSR Study XP21L-402, Table 11-3, p. 51.

Pre-dose diclofenac sample concentrations and paired 6-hour post-dosing diclofenac sample concentrations were tested using a paired t-test to evaluate for steady-state conditions. The results of the t-test evaluation did not identify a difference between pre-dose and 6-hour post-dose samples from the same subjects as presented in Table 8 below; therefore, the Sponsor concluded that steady-state conditions were achieved.

Table 8 Paired t-test Evaluation for Steady-State Conditions

Statistic	Overall (N = 24)
Predose	
n	23
Mean	28.85
6 hours	
n	21
Mean	27.03
Difference between predose and 6 hours	
n	21
Mean	1.32
Standard error	6.334
Lower limit, upper limit	-11.89, 14.54
P-value[a]	0.837

[a] P-value was based on a paired t-test.

Source: CSR Study XP21L-402, Table 11-1, p. 47.

The PK parameter $AUC_{0\text{-}\infty}$ (Dose 1, Day 1) was compared with AUC_{τ} (Dose 5, Day 2) using ln-transformed values for diclofenac to assess DPSGC performance after a single dose compared to multiple doses. There was little difference in the ratio of geometric least square means between the first and fifth doses as displayed in Table 9; therefore, the Sponsor concluded that diclofenac did not accumulate following multiple dose administration.

Table 9 Analysis of Variance Model on Diclofenac PK Parameters AUC_τ and $AUC_{0-\infty}$ Estimates

Statistic	Dose 5 AUC_τ (ng*h/mL)	Dose 1 $AUC_{0-\infty}$ (ng*h/mL)
Geometric least squares means	618.38	630.29
Difference of geometric least squares means	0.98	0.98
Standard error	0.061	0.059
Ratio of geometric least squares means	--	0.98
90% CI of ratio of geometric least squares means	--	(0.90,1.07)
P-value[a]	--	0.715

CI = confidence interval; AUC_τ = area under the plasma concentration versus time curve over the final dosing interval; $AUC_{0-\infty}$ = AUC from time of dose extrapolated to infinity.

Note: The analysis of variance model on AUC_τ and $AUC_{0-\infty}$ was performed on the natural log-transformed data, and least squares means were obtained by taking antilog of the difference between the least squares means of AUC_τ and $AUC_{0-\infty}$.

Source: CSR Study XP21L-402, Table 11-4, p. 52.

Safety Results

Discussed in detail in Section 8.2 of this review.

Conclusions

The following conclusions were made from Study XP21L-402:

1. Steady-state concentrations of diclofenac were observed with the fifth dose of DPSGC 25 mg on a 6-hour treatment regimen.
2. A 1-compartment PK profile was apparent at steady-state in this population.
3. Accumulation of diclofenac did not occur at steady-state in this population after administration of DPSGC 25 mg every 6 hours.
4. DPSGC was well-tolerated in the study.

Reviewer Comment: Study XP21L-402 was an adequately conducted PK and safety study demonstrating that DPSGC 25 mg dosed orally every 6 hours reached steady-state diclofenac concentrations with the fifth dose, had a 1-compartment PK profile at steady-state, did not result in diclofenac accumulation at steady-state, and was well-tolerated in the 12-year old to 17-year old pediatric population when used short-term for management of mild to moderate pain.

6.2. Study 81-0072 A Phase 4, Open-Label Study of the Safety and Efficacy of Zipsor® (DPSGC) in Pediatric Subjects (Ages 12-17) with Mild to Moderate Acute Pain

Trial Design

This was a Phase 4, OL study designed to evaluate the safety, tolerability, and efficacy of a single dosage strength of DPSGC (25 mg) administered every 6 hours as needed for pain for up to 4 days in pediatric subjects 12 years to 17 years of age with mild to moderate acute pain. The study was conducted at two clinical sites in the United States. Twenty-five (25) subjects were enrolled in the study and all 25 subjects completed the study. The study consisted of a 2-

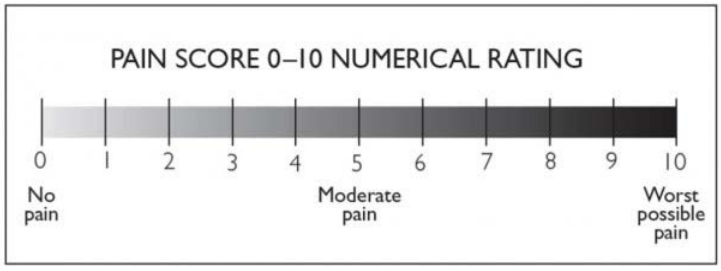
week screening and washout period, a 4-day treatment period, daily telephone follow-up during the treatment period for those who were not hospitalized, and a final study visit scheduled to coincide with the planned post-operative check (approximately 7-14 days after the first dose of study drug).

Eligibility

Male or female subjects between 12 years to 17 years of age with mild to moderate acute pain (score of 2-7 on the Numeric Pain Rating Scale (NPRS)) resulting from an acute painful condition or a surgical procedure, such as sinus endoscopy, ear surgery, tonsillectomy, adenoidectomy, rhinoplasty, or septoplasty were eligible for the study. Subjects reported pain using the NPRS where 0 = no pain, 5 = moderate pain, and 10 = worst pain possible. See an example of the NPRS in Figure 2 below. Subjects with severe pain (score ≥ 8) were excluded from the study. Subjects who met the following criteria were also excluded from the study:

- Subjects who received a long-acting nerve block for anesthesia.
- Subjects being treated for pre-existing hypertension were.
- Subjects who were receiving medications that may have caused a clinically significant condition when used concomitantly with diclofenac potassium or acetaminophen were excluded from the study.
- Subjects who were receiving medications that are known to strongly inhibit cytochrome p4502C9 were also excluded from the study.

Figure 2 Example of the Numerical Rating Pain Scale (Study 81-0072)



Source: www.physio-pedia.com/Numeric_Pain_Rating_Scale

Treatment

Subjects meeting study entry criteria were administered the first dose of study drug (DPSGC 25 mg) at the hospital 2 hours after discontinuation of IV analgesics or oral opioid treatment. Subjects were encouraged to refrain from using rescue medication for the first 2 hours after the first dose of DPSGC. Beyond the first 2-hour timeframe after the first dose of DPSGC, use of rescue medication was allowed in subjects who experienced an increase in pain. If treatment for pain was needed 6 hours after the first dose of DPSGC, then patients were administered a second dose of DPSGC. Subjects continued taking DPSGC as needed for pain every 6 hours for up to 4 days or until treatment for pain was no longer needed. Subjects who were discharged from the hospital before 4 days after starting the study drug were asked to record study drug administration, adverse events, concomitant medications, and rescue medications in a diary.

Efficacy and Safety Variables
Pain intensity was evaluated using the NPRS score before the first dose of DPSGC and at 1 hour and 2 hours after the first dose of DPSGC. Safety assessments included vital sign monitoring (weight, height, temperature, systolic and diastolic blood pressure, heart rate, and respiratory rate) at specific timepoints, physical examinations and clinical laboratory tests (hematology, serum chemistry, urinalysis, urine pregnancy, and serum pregnancy) at the screening/baseline visit and final visit, and AE monitoring throughout the study.

Study Endpoints
Efficacy
The percent change in NPRS pain score from baseline to the first and second hours after the first dose of DPSGC was documented.

Safety
The incidence of TEAEs, SAEs, withdrawals because of AEs, and deaths was documented. PE findings were documented. The observed values and changes in vital sign measurements and clinical laboratory results were also documented.

Statistical Analysis Plan
This was an OL, safety study with no placebo control arm. The study was not powered for efficacy as the primary endpoint. The study does not meet the evidentiary standards for an adequate and well-controlled trial to support the efficacy of DPSGC. Therefore, a detailed review of the SAP is not required.

A brief description of the SAP is provided here:
Two analysis populations were defined. The safety population was to include all subjects who received at least 1 one dose of study drug. The full analysis set (FAS) was to include all subjects who had available NPRS scores recorded on day 1 before first dose of DPSGC, received at least 1 dose of DPSGC, and completed at least 1 post-baseline NPRS score.
Safety data were analyzed as follows:

- Summaries of incidence rates (frequencies and percentages), severity, and relationship to study drug of individual AEs, SAEs, and TEAEs by system organ class (SOC) and preferred term (PT) were presented.
- Descriptive summaries of actual values and changes from baseline in clinical laboratory results and vital signs were presented.
- Abnormal changes in PE findings were summarized.

Efficacy data were analyzed as follows:

- The primary efficacy analysis (the percentage change in NPRS pain score) was descriptively summarized using mean, SD, minimum, maximum, and median. The 95% confidence interval of the mean for the primary efficacy analysis was also presented.
- Time to first use of rescue medication was analyzed using Kaplan-Meier survival curves.

Protocol Amendments
There was one protocol amendment for Study 81-0072 dated August 8, 2013. One exclusion criterion about hypertension was added and the wording of the phrase about pain ratings was changed to reflect average pain in the last 1 hour rather than average pain in the last 24 hours. No changes were made to any of the planned analyses.

Study Results
Compliance with Good Clinical Practices
The study was conducted in accordance with Good Clinical Practice (GCP) requirements and all applicable regulations, including the US Code of Federal Regulations regarding clinical studies, and all national and local laws and regulations. The study also complied with the ethical principles described in the Declaration of Helsinki.

Financial Disclosure
The Applicant submitted FDA form 3454 certifying that no financial interests or agreements exist for the two clinical investigators who participated in Study 81-0072.

Patient Disposition
Of the 25 subjects enrolled, all 25 subjects (100%) completed the study.

Protocol Deviations
There were a significant number of protocol deviations in this study. One subject had a baseline NPRS of 0 and remained in the study when mild to moderate pain (NPRS 2-7) was required for study enrollment. Nine subjects received study drug less than 2 hours after discontinuation of IV analgesics. Four subjects took prohibited rescue medication. Two subjects took 6 capsules of study drug in the first 24 hours instead of 4 capsules of study drug in the first 24 hours. One of these subjects also took 5 instead of 4 capsules of study drug in the following 24 hours. Several assessments were also conducted outside of the scheduled window.

Reviewer Comment: These protocol deviations did not affect the primary objective of evaluating the safety and tolerability of DPSGC. Subjects taking DPSGC less than 2 hours after discontinuation of IV analgesics or oral opioid treatment provides additional information about the short-term safety of DPSGC in the setting of other analgesic medications. Subjects taking more DPSGC capsules than prescribed provides additional information about the short-term safety of DPSGC when it is misused. However, these protocol deviations likely affected the secondary objective of determining DPSGC efficacy at 1- and 2- hours after the first dose of DPSGC. Residual IV analgesics or oral opioids in the bloodstream may have falsely lowered NPRS scores collected 1 and 2 hours after the first dose of DPSGC. Additionally, use of prohibited rescue medications may have falsely lowered NPRS scores collected 1 and 2 hours after the first dose of DPSGC if the prohibited rescue medications were given before the pain scores were collected.

The need for rescue medication suggests that DPSGC alone was not sufficient for managing pain in this study population. Misuse of DPSGC also suggests that the dosing regimen of one 25-mg

DPSGC capsule every 6 hours may not have been adequate for pain management in this study. Nevertheless, these findings do not suggest that DPSGC would be ineffective for the approved indication of mild to moderate pain.

Demographics
The majority of subjects were male (64%) and Caucasian (92%) with a mean age of 14.9 years, a mean weight of 75.13 kg, and a mean height of 167.1 cm.

Other Baseline Characteristics
Baseline NPRS pain severity was 0 in 1 subject (4%), 2 in 8 subjects (32%), 3 in 6 subjects (24%), 6 in 4 subjects (16%), 5 in 2 subjects (8%), and 7 in 4 subjects (16%). The mean NPRS pain score at baseline was 3.8.

Reviewer Comment: The subject with no pain at baseline did not meet the inclusion criteria and should have been excluded from the study.

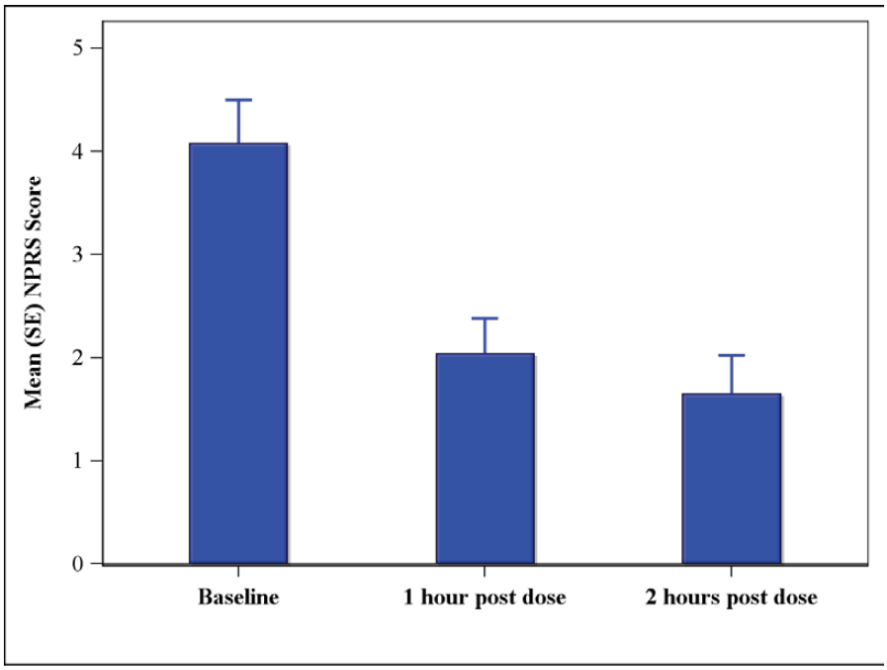
Treatment Compliance, Rescue Medications, and Concomitant Medications
Treatment compliance was measured by capsule count of any returned, unused study drug. All subjects were ≥ 80% compliant with the study drug. Subjects were encouraged to refrain from use of rescue medication within 2 hours post first dose of DPSGC. Allowed rescue medications were oxycodone 0.1-0.15 mg/kg or hydrocodone/acetaminophen 0.1-0.15 mg/kg as needed for an increase in pain after administration of DPSGC. Sixty-eight percent (68%) of subjects used rescue medication during the study. Almost half (48%) of the subjects had taken any prior medication with the largest number having taken ibuprofen (12%), followed by paracetamol (8%), and Anovlar, an oral contraceptive, (8%).

Prohibited Medications
Subjects were instructed to refrain from use of any other NSAIDs, opioid/NSAID combinations, or aspirin during the study.

Efficacy Results
Of the 25 subjects enrolled, 23 subjects (92%) met criteria for inclusion in the FAS. The FAS was the primary population for the primary efficacy analysis of percent change from baseline in NPRS scores.

Primary Efficacy Analysis
Pain intensity was assessed by recording subjects' NPRS scores at baseline, 1-hour after first dose of DPSGC, and 2-hours after first dose of DPSGC. The mean NPRS score at baseline was 4.1 (SD 2.0). The mean NPRS score at 1-hour post-dose was 2.0 (SD 1.61). The mean NPRS score at 2-hours post-dose was 1.7 (SD 1.77). These results are displayed in Figure 3.

Figure 3 Numerical Pain Rating Scale (NPRS) Scores by Time Point for FAS Population



Note: All 23 patients in the FAS had Baseline, 1-hour postdose, and 2-hour postdose NPRS measurements. Baseline was defined as the NPRS score taken just before first dose of the study drug.

Source: CSR Study 81-0072, Figure 11-1, p. 49.

Efficacy was assessed by calculating the percentage change observed in NPRS score from baseline to the first and second hours after the first dose of DPSGC. The mean percentage change from baseline values in NPRS scores to the first hour post-dose was -55.32 (SD 24.9; 95% CI -66.09, -44.55). The mean percentage change from baseline values in NPRS scores to the second hour post-dose was -60.25 (SD 41.55; 95% CI -78.22, -42.28). These results are summarized in Table 10.

Table 10 Efficacy Results for FAS Population (Study 81-0072)

Time Point Statistic	Total (N=25)
Baseline[a], N	23
Mean (SD)	4.1 (2.00)
Median	3.0
(Min, Max)	(2, 7)
1 hour postdose, N	23
Mean (SD)	2.0 (1.61)
Median	1.0
(Min, Max)	(0, 5)
Percentage change from baseline to 1 hour postdose, N	23
Mean (SD)	-55.32 (24.899)
95% CI for the Mean	(-66.09, -44.55)
Median	-57.14
(Min, Max)	(-100.0, 0.0)
2 hours postdose, N	23
Mean (SD)	1.7 (1.77)
Median	1.0
(Min, Max)	(0, 7)
Percentage change from baseline to 2 hours postdose, N	23
Mean (SD)	-60.25 (41.549)
95% CI for the Mean	(-78.22, -42.28)
Median	-66.67
(Min, Max)	(-100.0, 50.0)

CI = confidence interval; Max = maximum; Min = minimum; N = number of patients; SD = standard deviation
[a] Baseline NPRS scores were those obtained immediately before the first dose of study drug.

Source: CSR Study 81-0072, Table 11-1, p. 48.

Rescue Medication Analysis

The rescue medication analysis was performed on the safety population. Seventeen (17) of 25 subjects (68%) took rescue medication on a total of 25 occasions. There was more rescue medication use in the first two days of the study with a decline in use over the last two days of the study. Thirteen (13) out of 25 subjects (52%) used rescue medication on Days 1 and 2 while 5 out of 13 subjects (20%) used rescue medication on Day 3 and 4. The mean total dose of hydrocodone taken in combination with acetaminophen was 12.2 mg (SD 16.5 mg). The mean total dose of oxycodone taken was 1.4 mg (SD 1.4 mg). The median time to first use of rescue medication using Kaplan-Meier was 23.3 hours (95% CI 7.6, 83.3).

Reviewer Comment: More than half of subjects used rescue medication during the study suggesting that DPSGC alone was not adequate for pain management in this study population.

Safety Results

Discussed in detail in Section 8.2 of this review.

Conclusions

The following conclusions were made from Study 81-0072:

1. A single dose of DPSGC 25 mg decreased pain at 1 hour and 2 hours after the first dose of DPSGC in pediatric subjects 12 years to 17 years of age with mild to moderate pain.
2. DPSGC 25 mg was safe and well-tolerated in this study.

Reviewer Comment: *Study 81-0072 was an OL, safety study demonstrating that DPSGC 25 mg dosed orally every 6 hours as needed for pain was safe and well-tolerated in the pediatric population 12 years to 17 years of age when used short-term for management of mild to moderate pain. Efficacy conclusions cannot be drawn from the study because it had no placebo control and was not statistically powered for efficacy as a primary endpoint. As stated earlier, Study 81-0072 does not meet evidentiary standards for an adequate and well-controlled study to support the efficacy of DPSGC.*

6.3. Study CL-000424 A Phase 3, Randomized, Parallel-group, Double-masked, Single-dose Study of the Safety and Efficacy of DPSGC 25 mg and 50 mg in the Treatment of Orthodontic Discomfort in Pediatric Patients

Trial Design

This was a Phase 3, R, parallel-group, DB, single-dose study evaluating the safety and efficacy of two different dosage strengths of DPSGC (25 mg and 50 mg) in pediatric subjects 8 years to 16 years of age with orthodontic discomfort after undergoing insertion of either orthodontic separators or arch wires in either the maxilla, mandible, or both. The study was conducted at two sites. Ninety-seven (97) subjects were enrolled and all 97 subjects completed the study. The study consisted of a 30-day screening period, a single-dose treatment period, a follow-up period at the clinical site for 1 hour after the orthodontic procedure, and a follow-up period at home from the time of discharge from the clinical site until the morning of Day 2.

Eligibility

Healthy, male and female subjects 8 years to 16 years of age scheduled to undergo placement of either orthodontic separators or arch wires in either the mandible, maxilla, or both, were enrolled in the study. Subjects who used a prescription analgesic or an over-the-counter NSAID within 24 hours prior to the start of the orthodontic procedure were excluded from the study. Subjects exposed to aspirin or aspirin containing products within 5 days prior to the orthodontic procedure were excluded as well.

Treatment

Eligible subjects were randomized either Group A or Group B. Group A received one capsule of DPSGC 25 mg and one capsule of placebo 50 mg immediately after completion of the orthodontic procedure. Group B received one capsule of DPSGC 50 mg and one capsule of placebo 25 mg (Group B). Subjects were prohibited from using rescue medication for the first hour after dosing with DPSGC.

Rescue Medication

The allowed rescue medication was acetaminophen (dosing schedule and maximum dose not specified in the CSR).

Safety and Efficacy Variables

Safety assessments included a medical history and weight at screening, a urine pregnancy for girls of childbearing potential on Day 1 before the orthodontic procedure, and AE monitoring on Days 1 and 2. Vital signs and clinical laboratory tests were not collected. A surgery trauma rating was documented immediately after the orthodontic procedure. Pain intensity was assessed using the following pain scales:

Discomfort Index Scale (DIS)
Pain Severity Rating (PSR)
Dental Pain Relief Rating (DPRR) Scale
Overall Global Evaluation of pain

Description of pain scales:

Pain Severity Rating (PSR) Scale –

Subjects were asked to answer the statements, "My starting pain is:" at baseline and "My pain is:" after baseline, by selecting an adjective that best described their level of pain from a worksheet with a list of adjectives. The whole number value from 0 (None) to 3 (Severe) associated with the subjects' chosen adjective constituted their pain intensity.

Discomfort Index Scale (DIS) –

Subjects were asked to draw a line on a 0-100 mm visual analogue scale (VAS) that shows their level of pain at this time. The VAS included descriptive terminology (very comfortable, mild discomfort, and very uncomfortable) and small pictures ("happy" and "sad" faces) that shows their pain. The distance from the "happy" end of the VAS to the subject's drawn vertical line was the pain intensity score.

Dental Pain Relief Rating (DPRR) Scale –

Subjects were asked to answer the statement, "How much relief do you have from your starting pain?", by selecting an adjective that best described their level of pain relief from a worksheet with a 5-point pain relief rating scale. The whole number value from 0 (None) to 4 (Complete) associated with the subjects' chosen adjective constituted their pain intensity.

Overall Global Evaluation of pain –

Subjects were asked to answer the statement, "How would you rate this study medication as a pain reliever?", by selecting an adjective that best described their rating of the study medication as a pain reliever from a worksheet with a 5-point categorical scale. The whole number value associated with the subjects' chosen adjective constituted their rating.

The pain scales are presented in Figure 4.

Figure 4 Pain Scales used in Study CL-000424

Pain Severity Rating Scale (PSR)

☐ 0 None ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe

Dental Pain Relief Rating (DPRR)

☐ 0 None ☐ 1 A Little ☐ 2 Some ☐ 3 A Lot ☐ 4 Complete

Discomfort Index Scale (DIS): Record a distinct number between 0-100 mm. Do Not record a < or > sign before the number.

A. Chewing Grade _____ mm

B. Biting Grade _____ mm

C. Fitting your back teeth together Grade _____ mm

D. Fitting your front teeth together Grade _____ mm

Overall Global Evaluation

☐ 0 Poor ☐ 1 Fair ☐ 2 Good ☐ 3 Very Good ☐ 4 Excellent

Source: Annotated CRF, Study CL-000424, p.16.

Subjects completed the DIS, PSR, and DPRR at 0, 15, 30, 45, and 60 minutes after dosing with DPSGC. After discharge from the clinical site, subjects were instructed to complete the DIS, PSR, and DPRR every hour for up to 6 hours after dosing and within 1 minute of taking rescue medication, if applicable. If rescue medication was used, subjects were instructed to discontinue pain assessments and complete the Overall Global Evaluation of pain after receiving the first dose of rescue medication. If rescue medication was not used, subjects were instructed to complete the DIS, PSR, DPRR, and the Overall Global Evaluation of pain on the morning of Day 2. Completed pain scales were returned to the clinical site.

Study Endpoints

Safety

The incidence of TEAEs and SAEs was documented.

Efficacy

The individual pain intensity difference (PID) measurements at each timepoint were calculated [$PID_t=PSR_{baseline}-PSR_t$]. The time-weighted sum of PIDs (SPID) was calculated at each timepoint. The time-weighted sum of PIDs over the entire 6-hour evaluation period (SPID6) was calculated. The individual pain relief (PR) scores at each timepoint based on the DPRR were documented. The time-weighted DPRR over the 6-hour period (TOTPAR6) was calculated. The pain relief intensity difference (PRID) measurements at each timepoint were calculated [PID + PR at the corresponding timepoint]. The DIS scores at each timepoint were calculated. The Overall Global Evaluation of pain scores and the time to rescue medication use were documented as well.

Statistical Analysis Plan

This was a R, DB, active-controlled study with the primary intent of evaluating the safety and tolerability of a single-dose of DPSGC in pediatric subjects 8 years to 16 years of age. The study

had no placebo control arm and was not powered for efficacy as the primary endpoint. The study does not meet the evidentiary standards for an adequate and well-controlled trial to support the efficacy of DPSGC. Therefore, a detailed review of the SAP is not required.

A brief description of the SAP is provided below:
Two analysis populations were defined. The safety set was to include all subjects that received study drug. The FAS was to include all subjects who received study drug and had both a baseline and any post-dosing PSR scores.
Missing pain assessments were replaced using last observation carried forward (LOCF). For missing pain assessments after rescue medication, the pain assessment at the time of rescue medication was used.
Safety data were analyzed as follows:

- All AEs, TEAEs, and SAEs were summarized by treatment group and tabulated by SOC, by PT, and by severity.

Efficacy data were analyzed as follows:

- All efficacy parameters, except those measuring time-to an event, were analyzed using descriptive statistics.
- Time to use of rescue medication was analyzed using Kaplan-Meier survival curves.

Protocol Amendments
There was one protocol amendment for Study CL-000424 dated October 26, 2001. Some administrative changes were made, some clarifications of study procedures were made, an exclusion criterion for pregnant or nursing girls was added, and a statement about use of birth control in girls who are sexually active was added. No changes were made to the planned analyses.

Study Results
Compliance with Good Clinical Practices
The study was conducted in accordance with standards of Good Clinical Practice, as defined by the International Conference on Harmonization (ICH), the FDA, and all applicable federal and local regulations.

Financial Disclosure
In the original NDA submission, the Applicant submitted FDA form 3454 certifying that no financial interests or agreements exist for the two clinical investigators who participated in Study CL-000424.

Patient Disposition
Of the 97 subjects enrolled, 96 (99%) completed the study.

Protocol Deviations
There was one protocol deviation in this study. One subject (b) (6) in Group B (DPSGC 50 mg) took acetaminophen for a headache before the 6-hour pain assessment and did not record pain assessments at 6 hours post-DPSGC dosing and at Day 2.

Reviewer Comment: This protocol deviation did not affect the primary objective of evaluating the safety and tolerability of DPSGC.

Demographics
Most subjects were Caucasian, non-Hispanic (93.8%) with a mean age of 13.3 years, a mean weight of 52.4 kg, and a mean height of 160.5 cm. There were equal numbers of males and females (51.1% vs. 48.9%) in Group A (DPSGC 25 mg). There were more females than males (66% vs. 34%) in Group B (DPSGC 50 mg).

Other Baseline Characteristics
About half of subjects had a PSR rating of "none" at baseline (48.9% in Group A and 50% in Group B). About one-third of subjects had a PSR rating of "mild" at baseline (40.4% in Group A and 32% in Group B). Less than one-quarter of subjects had a PSR rating of "moderate" at baseline with more subjects in Group B than Group A (9 subjects [18%] vs. 5 subjects [10.6%]). No subjects had a PRS rating of "severe" at baseline. Mean orthodontic procedure duration was comparable between Group A and Group B (28.3 minutes and 26.6 minutes, respectively). More subjects in Group A than Group B (70.2% vs. 52%) had a mild trauma rating after the orthodontic procedure. More subjects in Group B than Group A (48% vs. 25.5%) had a moderate trauma rating after the orthodontic procedure. Two subjects in Group A and no subjects in Group B had a severe trauma rating after the orthodontic procedure. More than half of all subjects (61.9%) reported a medical condition with no significant differences in medical history between treatment groups.

Reviewer Comment: The low prevalence of pain in subjects at baseline raises the question as to whether an appropriate study population and/or study procedure was selected for the evaluation of DPSGC's efficacy. Analgesic efficacy cannot be determined in subjects with no documented pain at baseline. I would argue that DPSGC might have been no more effective than placebo if a placebo arm had been included in this study. This conclusion does not suggest that DPSGC would be ineffective for the approved indication of mild to moderate pain but rather that the design and conduct of Study CL-000424 failed to measure an improvement in pain.

Treatment Compliance, Concomitant Medications, Rescue Medications
Study medication was administered by study personnel. All subjects were 100% compliant with study medication. Less than one-quarter of subjects took concomitant non-analgesic medications, such as stimulant medication, allergy medication, birth control, and oral antibiotics, during the 2-day study period. Twenty-one subjects (27.8%), 8 subjects in Group A and 13 subjects in Group B, took concomitant analgesic medications (ibuprofen or acetaminophen) during the study. Concomitant analgesic medications were reportedly medications not intended as rescue medications. Eighteen subjects (18.6%) took rescue medication during the study.

Reviewer Comment: After review of the concomitant and rescue medication databases, I identified discrepancies in the number of subjects who took concomitant analgesic medications,

the number of subjects who took rescue medication, and the reason for use of concomitant analgesic medications.

Twenty-nine subjects (30%) rather than 21 subjects took concomitant analgesic medications during the study. Of these 29 subjects, 19 subjects (19.6%) took concomitant analgesic medications for the indications of increased oral pain, mouth pain, tooth pain, and dental pain. The pain indications listed above were most likely related to the dental procedure; therefore, concomitant analgesic medications were used as rescue medications in these subjects. The remaining 10 subjects (10.3%) took concomitant analgesic medications for pain indications likely unrelated to the dental procedure, such as headache, arm muscle pain, and leg injury.

I identified two subjects who were listed in the concomitant medication database as taking analgesic meds for tooth and mouth pain (b) (6) *but were not listed in the rescue medication database. I also identified one subject who was incorrectly listed in the rescue medication database as taking analgesic medication for headache* (b) (6) *After my analysis, I concluded that 19 subjects (19.6%) rather than 18 subjects took rescue medication during the study.*

Regardless of the analgesic drug product used or the indication for use, about 30% of the study population used concomitant analgesic medication during the 2-day study period. Any analgesic medication administered during the 6-hour window post-DPSGC dosing when pain assessments were collected would have altered the accuracy of these assessments rendering it difficult to determine the efficacy of DPSGC. The Sponsor of this study attempted to address the potential for confounding from use of rescue medication by having subjects document their pain intensity at the time of rescue medication use. However, the Sponsor did not have the 10 subjects who took concomitant analgesic medications, not intended as rescue medications, document their pain intensity at the time of concomitant analgesic medication use.

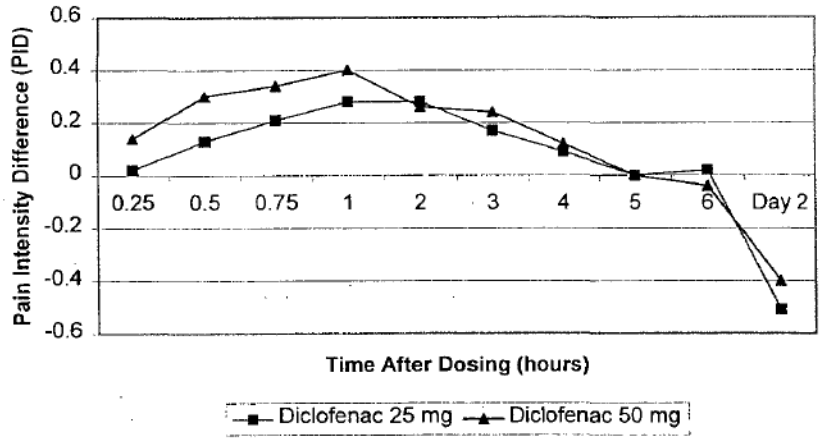
Efficacy Results

Of the 97 subjects enrolled in the study, all 97 were included in the FAS.

Pain Intensity and Pain Intensity Difference

Pain intensity was mostly none or mild throughout the study. About 14-18% of subjects had moderate pain at baseline, 4 hours, 5 hours, and 6 hours after DPSGC dosing. One subject in Group B had severe pain at 5 and 6 hours after dosing. The largest number of subjects (38 [40%]) had moderate or severe pain in the morning on Day 2. Mean PIDs over time were comparable between treatment groups. Mean PIDs were minimal at 15 minutes after dosing, improved at 30 minutes after dosing, peaked at about 1 hour after dosing, and then declined thereafter. There was no drug activity in either treatment group at 5 and 6 hours after dosing. PID over time is presented in the Figure 5.

Figure 5 Pain Intensity Difference (PID) Over Time (FAS)

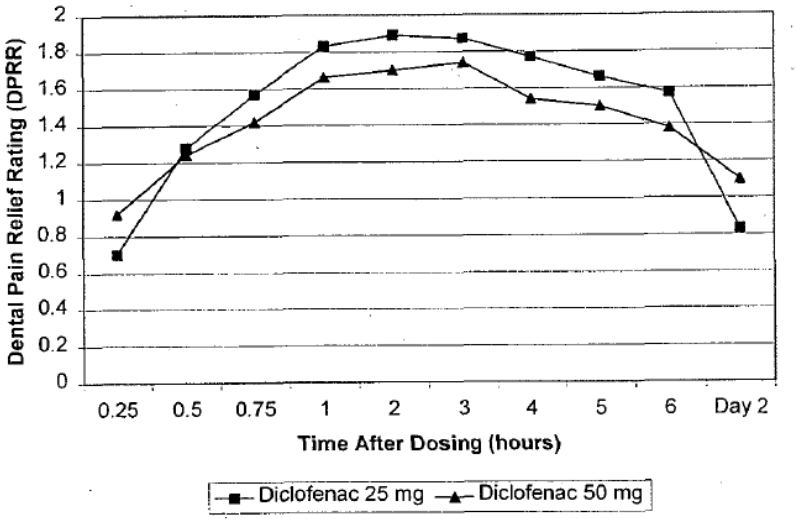


Source: CSR Study CL-000424, Figure 1, p.34.

Time-Weighted Sum of Pain Intensity Difference (PID) over 6 hours (SPID6)
There was no clinically relevant difference in SPID6 between treatment groups (Group A mean sum 0.71 ± 4.07 and Group B mean sum 0.88 ± 5.21).

Dental Pain Relief Rating (DPRR) Scores
For both treatment groups, DPRR scores increased within 15 to 30 minutes after DPSGC dosing, peaked at 1-2 hours after dosing, and then declined thereafter. Pain relief was still noted at 6 hours after dosing but was minimally improved over baseline pain by Day 2. There were no clinically relevant differences between treatment groups. DPRR scores over time are presented in Figure 6.

Figure 6 Dental Pain Relief Rating (DPRR) Scores Over Time (FAS)

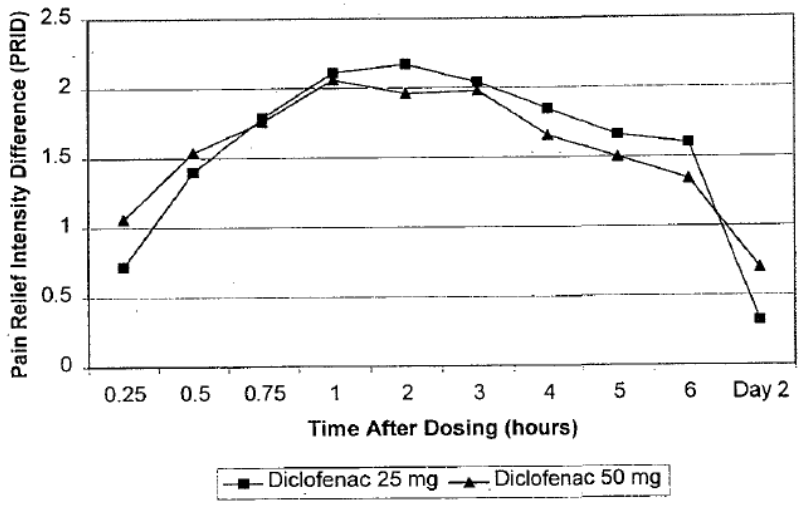


Source: CSR Study CL-000424, Figure 2, p. 35.

Time-Weighted Sum of Dental Pain Relief Rating (DPRR) over the Entire 6 hours (TOTPAR)
There was no clinically relevant difference in TOTPAR between the treatment groups (Group A mean TOTPAR 10.11 ± 9.12 and Group B TOTPAR 9.17 ± 9.10).

Pain Relief Intensity Difference (PRID) Over Time
PRIDs over time were comparable between treatment groups. Mean PRIDs improved within 30 minutes after dosing, peaked at 1-3 hours after dosing, and declined thereafter for both treatment groups. PRID over time is presented in Figure 7.

Figure 7 Pain Relief Intensity Difference (PRID) Over Time (FAS)



Source: CSR Study CL-000424, Figure 7, p. 40.

Discomfort Index Scores (DIS)
DIS for chewing over time, for biting over time, for fitting back teeth over time, and for fitting front teeth over time were comparable between treatment groups. Mean DIS values trended down within 30 minutes after dosing, peaked at approximately 1-3 hours, and then trended up in all DIS categories that were evaluated. There were no clinically relevant DIS differences in all categories between treatment groups.

Overall Global Evaluation Score
Mean Global Evaluation scores on Day 1 and Day 2 were similar and indicated that subjects rated DPSGC as good to very good for both treatment groups.

Time to Rescue Medication
Nine (9) subjects (2 in Group A and 7 in Group B) required rescue medication within the first 6 hours after DPSGC dosing. The median time to rescue medication was not possible to determine statistically given the small number of subjects who required rescue medication.

Safety Results
Discussed in detail in Section 8.2 of this review.

Conclusions

The following conclusions were made from Study CL-000424:

1. Efficacy parameters for pain intensity (PID and DIS for chewing, biting, and fitting) and pain relief (DPRR and PRID) demonstrated a gradual improvement in pain initially noted at 15 to 30 minutes after DPSGC dosing, peaking at 1-3 hours after dosing, and declining thereafter with no demonstrable effect noted by 6 hours after dosing.
2. Measurements of dental pain relief (DPRR and PRID) demonstrated an efficacy effect throughout 6 hours but not positive effect was seen by Day 2.
3. Both dosage strengths of DPSGC (25 mg and 50 mg) were safe and well-tolerated.

Reviewer Comment: Study CL-000424 was a R, DB, active-controlled safety and efficacy study demonstrating that a single dose of DPSGC 25 mg or 50 mg was safe and well-tolerated in the pediatric population ages 8 - 16 years when administered after an orthodontic procedure. Efficacy conclusions cannot be drawn from the study because it had no placebo control and was not statistically powered for efficacy as the primary endpoint. As stated earlier, Study CL-000424 does not meet the evidentiary standards for an adequate and well-controlled study to support the efficacy of DPSGC.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

One PK study, Study XP21L-402, was conducted to provide pediatric PK data following oral administration of DPSGC for comparison to adult PK data and to allow for extrapolation of DPSGC efficacy in adults to pediatric patients 12 years to 17 years of age. Efficacy data from two other studies, Study 81-0072 and CL-000424, were submitted to additionally support the efficacy of DPSGC in pediatric patients 12 years to 17 years of age; however, I concluded that these studies did not meet the evidentiary standards for adequate and well-controlled studies. Therefore, an assessment of efficacy across trials is not applicable to this review.

7.2. Additional Efficacy Considerations

The study population in Study CL-000424 consisted of healthy subjects undergoing an orthodontic procedure with about 62% of subjects reporting a medical condition. The study populations in Study XP21L-402 and Study 81-0072 consisted of subjects with medical histories who had mild to moderate acute pain from an acute painful condition or a painful surgical procedure. The medical histories for subjects in all three studies ranged from musculoskeletal and connective tissue disorders, HEENT disorders, prior surgical or medical procedures, and GI and GU disorders to neurological disorders, dermatologic disorders, infections and infestations, immune system disorders, and respiratory disorders. None of the subjects had significant laboratory abnormalities, renal disease, or hepatic disease. Subpopulations with renal

impairment or hepatic impairment were not represented in these studies. Nevertheless, we can use information from the Zipsor® prescribing information about use of DPSGC in adults with renal or hepatic impairment to inform use in pediatric subjects ages 12 – 17 years with renal or hepatic impairment.

The majority of subjects in all three studies were Caucasian. Other races were not adequately represented. However, I do not anticipate that the lack of racial diversity in the study population will have any impact on the generalizability of DPSGC's efficacy to pediatric subjects ages 12 years to 17 years of all races.

7.3. Integrated Assessment of Effectiveness

Study XP21L-402 is the PK study upon which the regulatory determination of the efficacy of Zipsor® in pediatric patients ages 12 – 17 years is being based. The clinical pharmacology team reviewed Study XP21L-402 and concluded that the systemic exposure of diclofenac following oral administration of DPSGC 25 mg in pediatric patients ages 12 – 17 is comparable to the systemic exposure of diclofenac following oral administration of DPSGC 25 mg in adults under fed conditions. Consequently, the efficacy of Zipsor® in pediatric patients 12years to 17 years of age can be extrapolated from prior data on the efficacy of Zipsor® in adults.

I contend that the efficacy results from Studies CL-000424 and 81-0072 are not clinically meaningful and do not support the efficacy of DPSGC in pediatric patients 12 years to 17 years of age. I do not agree with the Applicant's recommendation to include the efficacy results from Study CL-000424 and Study 81-0072 in the prescribing information. Neither study meets the evidentiary standards for efficacy as both studies had no placebo arm and were not statistically powered for efficacy as a primary endpoint. Additionally, Study CL-000424 had no minimum pain score requirement for subject inclusion in the study. Most subjects had no pain or minimal pain (pain severity score of 0 or 1) at baseline before administration of DPSGC. And most subjects had no more than mild pain throughout the study. Given the lack of pain severity experienced by subjects in Study CL-000424, the study has no ability to discriminate DPSGC from placebo in providing benefit for the management of pain following placement of either orthodontic separators or arch wires.

8. Review of Safety

8.1. Safety Review Approach

Safety data for this application consisted of pooled data from Studies XP21L-402 and 81-0072, individual data from Study CL-000424, post-market data with the diclofenac potassium moiety, and data from the literature on the safety of diclofenac in the pediatric population 12 years to 17 years of age.

I reviewed the integrated safety data from Studies XP21L-402 and 81-0072 and the individual

safety data from Study CL-000424. I reviewed the collected safety information and the cited articles from the Applicant's published literature search. I reviewed the Applicant's conclusions about the safety of diclofenac use in the adolescent population. Lastly, I reviewed the postmarket experience with DPSGC by looking at the Periodic Adverse Drug Experience Reports (PADERs) since approval of DPSGC in 2009.

I focused my safety review on the more common gastrointestinal (GI) and central nervous system (CNS) adverse reactions known with Zipsor® use in adults – abdominal pain, nausea, vomiting, dyspepsia, constipation, diarrhea, headache, dizziness, and somnolence. I closely reviewed the AE data and the clinical laboratory results data evaluating for any safety signals of cardiovascular effects, hepatotoxicity, renal toxicity, hematologic toxicity, serious skin reactions, or anaphylaxis, and the vital signs and physical examination data evaluating for any safety signal of hypertension or heart failure given the warnings and precautions in the Zipsor® prescribing information for use in adults. I also closely reviewed the safety data evaluating for any safety signal of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) as this AE was identified as an event of interest in the last three PADERs dating from 2015 to 2018.

Study Summaries

Study XP21L-402

Refer to Section 6.1 of this review for a summary of Study XP21L-402.

Study 81-0072

Refer to Section 6.2 of this review for a summary of Study 81-0072.

Study CL-000424

Refer to Section 6.3 of this review for a summary of Study CL-000424.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population for the pooled clinical trials, Studies XP21L-402 and 81-0072, was defined as subjects who received "any amount of the planned study drug (DPSGC 25 mg)" or "at least one dose of the study drug (DPSGC 25 mg)". The safety population for Study CL-000424 was defined similarly as "all patients that received study medication (DPSGC 25 mg or 50 mg). Therefore, the safety database for this application consisted of all pediatric subjects who took at least one dose of DPSGC.

Applicant's Pooling Strategy

The Applicant pooled and analyzed safety data from the PK and safety clinical trial, Study XP21L-402, and the most recent safety and efficacy clinical trial, Study 81-0072. The Applicant separately referenced the safety data from the older safety and efficacy clinical trial, Study CL-000424. The Applicant stated that the safety data from Studies XP21L-402 and 81-0072 were pooled because of the following trial similarities:

- Phase 4, OL study design

- Study population consisting of pediatric subjects ages 12 – 17 years
- Study population demographics (majority male and majority Caucasian)
- Study drug dose and duration (DPSGC 25 mg every 6 hours as needed for up to 4 days)
- Indication of mild to moderate pain resulting from an acute painful condition or a surgical procedure.

The safety data from Study CL-000424 were not pooled with the data from Studies XP21L-402 and 81-0072 because of the following trial differences:

- Study CL-000424 used a different study design (Phase 3, randomized, parallel-group, DB study design).
- Study CL-000424 used a different study drug dose and duration (a single-dose of DPSGC 25 mg or 50 mg).
- Study CL-000424 encompassed a different study population consisting of pediatric subjects ages 8 – 16 years undergoing a scheduled orthodontic procedure.

Given the number of commonalities between Study XP21L-402 and Study 81-0072 and the number of differences between Study CL-000424 and Studies XP21L-402 and 81-0072, I agree with the Applicant's approach to pooling and analyzing the safety data. Additionally, the Applicant discussed their pooling strategy with DAAAP at a Type C Meeting dated August 2017 and we agreed that the approach appeared acceptable.

Overall Exposure

The Applicant used the pooled data from Studies XP21L-402 and 81-0072 to determine the overall exposure to DPSGC. However, in my evaluation, I used the pooled data from Studies XP21L-402 and 81-0072 combined with the individual data from Study CL-000424 to determine the overall exposure to DPSGC. Twenty-one (21) of the pediatric subjects in Study CL-000424 were < 12 years of age. In total, 146 pediatric subjects were exposed to at least one dose of DPSGC. One hundred and twenty-five (125) of these pediatric subjects were 12 years to 17 years of age. This information is presented in Table 11.

Table 11 Safety Database for DPSGC in the Pediatric Population Ages 8 – 17 Years

Total number of Pediatric Subjects exposed to DPSGC for the acute pain indication N=146			
Clinical Trial Groups	DPSGC (25 mg) (n=96)	DPSGC (50 mg) (n=50)	Total (n=146)
Study XP21L-402	24	0	24
Study 81-0072	25	0	25
Study CL-000424	47 36 (ages 12-16) 11 (ages 9-11)	50 40 (ages 12-16) 10 (ages 8-11)	97

Source: SCS/S-013, Table 2, p.18 and CSR Study CL-000424, Listing 16.2.3, p. 263.

Extent of Exposure

The Applicant analyzed the pooled data from Studies XP21L-402 and 81-0072 to determine the extent of exposure to DPSGC. In my review of the extent of pediatric exposure to DPSGC, I summarized not only the pooled data from the multiple dose studies but also the individual data from Study CL-000424 using single doses of DPSGC. On review of the pooled data, pediatric subjects received a mean of 11.8 doses of DPSGC 25 mg. Over half (55.1%) of subjects received at least 12 doses of DPSGC and over one-fourth (26.5%) of subjects received at least 16 doses of DPSGC. Approximately half (49%) of subjects received DPSGC for 4 days and about one-third (34.7%) of subjects received DPSGC for 5 days. On review of the data for Study CL-000424, all pediatric subjects (100%) received 1 dose of DPSGC. Fifty subjects received 1 dose of DPSGC 50 mg and 47 subjects received 1 dose of DPSGC 25 mg. This information is summarized in Table 12 below.

Table 12 Extent of Exposure to DPSGC in the Pediatric Population Ages 8 – 17 Years

Exposure to DPSGC	Study CL-000424 (N=97)	Study XP21L-402 (N=24)	Study 81-0072 (N=25)	Total from Pooled Studies XP21L-402 and 81-0072 (N=49)
DPSGC 25 mg # Doses received per subject, n (%)				
1 Dose	47 (48.5%)	0	0	0
4 Doses	0	1 (4.2%)	0	1 (2.0%)
5 Doses	0	0	3 (12.0%)	3 (6.1%)
6 Doses	0	0	1 (4.0%)	1 (2.0%)
7 Doses	0	1 (4.2%)	2 (8.0%)	3 (6.1%)
8 Doses	0	1 (4.2%)	1 (4.0%)	2 (4.1%)
9 Doses	0	3 (12.5%)	4 (16.0%)	7 (14.3%)
10 Doses	0	2 (8.3%)	0	2 (4.1%)
11 Doses	0	1 (4.2%)	2 (8.0%)	3 (6.1%)
12 Doses	0	1 (4.2%)	2 (8.0%)	3 (6.1%)
13 Doses	0	0	3 (12.0%)	3 (6.1%)
14 Doses	0	1 (4.2%)	3 (12.0%)	4 (8.2%)
15 Doses	0	3 (12.5%)	1 (4.0%)	4 (8.2%)
16 Doses	0	9 (37.5%)	3 (12.0%)	12 (24.5%)
>16 Doses	0	1 (4.2%)	0	1 (2.0%)
Total # of DPSGC 25 mg doses received per subject				
Mean (SD)	1 (N/A)	12.9 (3.75)	10.8 (3.65)	11.8 (3.81)
Minimum, Maximum	1, 1	4, 17	5, 16	4, 17

Exposure to DPSGC	**Study CL-000424 (N=97)**	**Study XP21L-402 (N=24)**	**Study 81-0072 (N=25)**	**Total from Pooled Studies XP21L-402 and 81-0072 (N=49)**
# of days on DPSGC 25 mg per subject, n (%)				
1 Day	N/A	0	0	0
2 Days		1 (4.2%)	3 (12.0%)	4 (8.2%)
3 Days		0	4 (16.0%)	4 (8.2%)
4 Days		6 (25.0%)	18 (72.0%)	24 (49.0%)
5 Days		17 (70.8%)	0	17 (34.7%)
Cumulative # of DPSGC 25 mg doses received per subject, n (%)				
≥ 4 doses	N/A	24 (100%)	25 (100%)	49 (100%)
≥ 5 doses		23 (95.8%)	25 (100%)	48 (98.0%)
≥ 6 doses		23 (95.8%)	22 (88.0%)	45 (91.8%)
≥ 7 doses		23 (95.8%)	21 (84.0%)	44 (89.8%)
≥ 8 doses		22 (91.7%)	19 (76.0%)	41 (83.7%)
≥ 9 doses		21 (87.5%)	18 (72.0%)	39 (79.6%)
≥ 10 doses		18 (75.0%)	14 (56.0%)	32 (65.3%)
≥ 11 doses		16 (66.7%)	14 (56.0%)	30 (61.2%)
≥ 12 doses		15 (62.5%)	12 (48.0%)	27 (55.1%)
Cumulative # of DPSGC 25 mg doses received per subject, n (%)				
≥ 13 doses	N/A	14 (58.3%)	10 (40.0%)	24 (49.0%)
≥ 14 doses		14 (58.3%)	7 (28.0%)	21 (42.9%)
≥ 15 doses		13 (54.2%)	4 (16.0%)	17 34.7%)
≥ 16 doses		10 (41.7%)	3 (12.0%)	13 (26.5%)
Cumulative # of Days on DPSGC 25 mg per subject, n (%)				
≥ 1 Day	N/A	24 (100%)	25 (100%)	49 (100%)
≥ 2 Days		24 (100%)	25 (100%)	49 (100%)
≥ 3 Days		23 (95.8%)	22 (88.0%)	45 (91.8%)
≥ 4 Days		23 (95.8%)	18 (72.0%)	41 (83.7%)
≥ 5 Days		17 (70.8%)	0	17 (34.7%)
DPSGC 50 mg # Doses received per subject, n (%)				
1 Dose	50 (51.5%)	0	0	0

Exposure to DPSGC	Study CL-000424 (N=97)	Study XP21L-402 (N=24)	Study 81-0072 (N=25)	Total from Pooled Studies XP21L-402 and 81-0072 (N=49)
Total # of DPSGC 50 mg doses received per subject Mean (SD)	1 (N/A)	0	0	0

Source: SCS/S-013, Table 3, pp. 20 – 21 and CSR Study CL-000424, p.31.

Disposition

For Study XP21L-402, 24 subjects entered the study and 23 subjects completed the study. One subject was discontinued from the study because he was unable to provide a PK sample as scheduled on Day 2. He was not administered a fifth dose of study drug. For Study 81-0072, 25 subjects entered the study and 25 subjects completed the study. For Study CL-000424, 97 subjects entered the study and 96 subjects completed the study. One subject in Group B (DPSGC 50 mg) took acetaminophen for a headache before the 6-hour pain assessment and did not record pain assessments at 6 hours post-DPSGC dosing and at Day 2.

Reviewer Comment: The majority of study participants completed the studies.

8.2.2. Relevant characteristics of the safety population:

The Applicant analyzed the pooled data from Studies XP21L-402 and 81-0072 to make conclusions about the demographics and other characteristics of the safety database. During my review of demographics, I evaluated not only the pooled data from studies XP21L-402 and 81-0072 but also the individual data from Study CL-000424 to incorporate a broader picture of the safety database.

Pooled Studies

Most subjects were Caucasian (77.6%), the mean age of subjects was 15.1 years (range: 12 – 17 years), and the mean weight was 71.2 kg (range: 26.2 – 143 kg). More males than females were included in the studies (61.2% and 38.8%, respectively). Looking at other races and ethnicities, 1 subject (2.0%) was a Native Hawaiian/Pacific Islander, 3 subjects (6.1%) were multiple races, 7 subjects (14.3%) were African-American, and 8 subjects (16.3%) were Hispanic or Latino.

Study CL-000424

Most subjects were Caucasian (93.8%), the mean age of subjects was 13.3 years (range: 9 – 16 years), and the mean weight was 52.4 kg (range: 23 – 106 kg). In the group administered DPSGC 25 mg, there were equal numbers of males and females (51.1% males and 48.9% females). In the group administered DPSGC 50 mg, there were more females than males (66% and 34%). Looking at other races and ethnicities, one (1) subject (1.0%) was an Asian/Pacific Islander, three (3) subjects (3.1%) were African-American, and no subjects were Hispanic or Latino.

The demographic data from all three studies are presented in Table 13.

Table 13 Demographics for the Pediatric Population Ages 8 – 17 Years

	Study CL-000424 (N=97)			Study XP21L-402 (N=24)	Study 81-0072 (N=25)	Pooled Data from Studies 81-0072 and XP21L-402
	DPSGC 25 mg (N=47)	DPSGC 50 mg (N=50)	Total			
Race						
Caucasian	44 (93.6%)	47 (94%)	91 (93.8%)	15 (62.5%)	23 (92%)	38 (77.6%)
African-American	1 (2.1%)	2 (4.0%)	3 (3.1%)	6 (25%)	1 (4.0%)	7 (14.3%)
Native Hawaiian/ Pacific Islander	0	1 (2.0%)	1 (1.0%)	0	1 (4.0%)	1 (2.0%)
Multiple Races	0	0	0	3 (12.5%)	0	3 (6.1%)
Ethnicity						
Hispanic/Latino	0	0	0	0	8 (32%)	8 (16.3%)
Age (years)						
Mean	13.4	13.2	13.3	15.3	14.9	15.1
Range	(9.1, 16.9)	(8.1, 16.7)	(8.1, 16.9)	(12, 17)	(12, 17)	(12, 17)
Weight (kg)						
Mean	53.8	51.0	52.4	67.3	75.13	71.2
Range	(29.3, 93.2)	(23.0, 105.7)	(23.0, 105.7)	(47.7, 88.4)	(26.2, 143)	(26.2, 143)
Gender						
Male	24 (51.1%)	17 (34.0%)	41 (42.3%)	14 (58.3%)	16 (64.0%)	30 (61.2%)
Female	23 (48.9%)	33 (66.0%)	56 (57.7%)	10 (41.7%)	9 (36.0%)	19 (38.8%)

Source: SCS/S-013, Table 4, p. 22 and CSR Study CL-000424, Table 2, p. 32.

Other baseline characteristics –
For Study XP21L-402, all subjects included in the study had mild or moderate pain severity at baseline. For Study 81-0072, all but one subject included in the study had mild or moderate pain severity at baseline. For Study CL-000424, about half of the subjects had mild or moderate pain intensity at baseline. All subjects in studies XP21L-402 and 81-0072 had medical histories upon study entry. About 62% of subjects in Study CL-000424 reported a medical condition. The more common medical histories included musculoskeletal and connective tissue disorders, HEENT disorders, prior surgical or medical procedures, GI disorders, neurological disorders, dermatological disorders, infections and infestations, and immune system disorders. Prior medications were used by all subjects in Study XP21L-402 and by almost half of the subjects in Study 81-0072. Concomitant medications were used by about half of the subjects in Study CL-000424. Mostly anesthetics, analgesics, and anti-nausea drugs were used prior to DPSGC administration in Study XP21L-402. Mostly analgesics were used prior to DPSGC administration in Study 81-0072. A combination of non-analgesic and analgesic medications were used during Study CL-000424.

Reviewer Comment: As expected for clinical trials in the United States, most study participants were of Caucasian race. The sex distribution between males and females was fairly equal.

8.2.3. Adequacy of the safety database:

The total number of pediatric subjects in the Applicant's safety database was 146 of which 125 subjects were ages 12 - 17. Studies XP21L-402 and 81-0072 enrolled 49 pediatric subjects and Study CL-000424 enrolled 97 pediatric subjects of which 76 subjects were 12 years to 16 years of age. As recommended by the Division, the Applicant augmented the safety database of this pediatric efficacy supplement by providing a literature review of published articles on diclofenac use in the pediatric population. Overall, the safety database is small but, when supplemented with a literature review, provides sufficient data to evaluate the safety of DPSGC for the pediatric population 12 years to 17 years of age.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

This sNDA was submitted in Electronic Common Technical Document (eCTD) format. The datasets were submitted in SAS format. I calculated a different number than the Applicant for the total number of pediatric subjects exposed to DPSGC (125 vs. 146) because I subtracted out any subjects in Study CL-000424 who were less than 12 years of age. This difference was negligible and did not have any impact on the safety findings. I also identified two other numerical discrepancies when reviewing the AE and laboratory data; however, these numerical discrepancies were small and did not change my conclusions about the safety of DPSGC in the adolescent population. I did not identify any other issues concerning the quality or integrity of the submission. There are no outstanding clinical information requests to date.

8.3.2. Categorization of Adverse Events

Pooled Studies

In the CSRs for Study XP21L-402 and Study 81-0072, treatment-emergent AEs (TEAEs) were defined as events with onset at the time of or following the start of treatment with study drug up to 30 days after the last treatment, or AEs starting before the start of treatment but increasing or worsening in severity or relationship at the time of or following the start of treatment with study drug up to 30 days after the last treatment. This definition of TEAEs with safety monitoring for events up to 30 days after the last treatment was appropriate given the known half-life of 12 hours for DPSGC. TEAEs were coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 14.0. In the ISS, the Applicant summarized TEAEs by each study and by overall subject number.

Study CL-000424

In the CSR for Study CL-000424, AEs were defined as any signs, symptoms, syndromes, or illnesses that occurred or worsened during the use of study drug and for 15 days after the use of study drug regardless of causality. This definition of AEs with safety monitoring for events up to 15 days after use of study drug was appropriate given the known half-life of 12 hours for DPSGC. AEs were summarized by treatment group and subject number and coded by SOC and

PT. Verbatim terms were included in the data and correctly translated to appropriate PTs. There was no documentation as to which version of MedDRA was used for coding AEs in Study CL-000424.

Reviewer Comment: The approach to categorization of TEAEs in studies XP21L-402 and 81-0072 was acceptable. The overall approach to categorization of AEs in Study CL-000424 was reasonable; however, the Sponsor should have clearly documented the version of MedDRA used for coding AEs.

8.3.3. Routine Clinical Tests

Pooled Studies

The clinical laboratory assessments in Study XP21L-402 and Study 81-0072 consisted of blood and urine samples for hematology, chemistry, and urinalysis in all subjects, and pregnancy testing in females of childbearing potential, at screening, baseline, and final study visits. Blood samples for PK analysis were also collected in Study XP21L-402 only.

Study CL-000424

The clinical tests in Study CL-000424 consisted of urine pregnancy testing in females of childbearing potential before the orthodontic procedure.

Reviewer Comment: The clinical laboratory testing in the pooled studies was acceptable and provided some information to support the safety of using DPSGC in the pediatric population 12 years to 17 years of age. The clinical laboratory testing in Study CL-000424, however, was lacking and provided no information to support the safety of using DPSGC in the pediatric population 8 years to 16 years of age. Of note, Study CL-000424 is a single-dose study of two DPSGC dosage strengths and contributes little to the overall exposure of DPSGC in the adolescent population. The lack of adequate laboratory data from the single-dose study does not impede my ability to make a safety determination about DPSGC in pediatric patients 12 years to 17 years of age.

8.4. Safety Results

8.4.1. Deaths

No deaths occurred during Studies XP21L-402, 81-0072, and CL-000424.

8.4.2. Serious Adverse Events

No serious adverse events (SAEs) occurred during studies XP21L-402 and CL-000424. One SAE occurred in Study 81-0072 – Subject (b) (6) experienced a post-procedural bile leak. I reviewed the safety narrative for Subject (b) (6) A summary of the SAE is provided below.

Subject Number: (b) (6)
Study Number: 81-0072

PT: Post-procedural bile leak

Subject (b) (6) is a 16-year old, Caucasian, female with a past medical history of biliary colic, gastroesophageal reflux disease (GERD), abdominal pain, diarrhea, and anemia who had a laparoscopic cholecystectomy on (b) (6) Prior medications included iron 325 mg by mouth daily for anemia and Prilosec 20 mg by mouth daily for GERD. She received numerous medications preoperatively and intraoperatively for sedation, for induction and maintenance of anesthesia, for pain management, for neuromuscular blockade reversal, and as prophylaxis for nausea, acid reflux, and infection. She had intraoperative hypotension that was managed with phenylephrine IV.

She took her first dose of DPSGC 25 mg at 0908 on (b) (6) and continued taking DPSGC every 6 hours as needed for pain. She took her last dose of DPSGC at 2220 on (b) (6) In total, she took nine doses of DPSGC from (b) (6) (b) (6)

On (b) (6) 2 days after her last dose of DPSGC, Subject (b) (6) presented to the ER with right upper quadrant abdominal pain. She received a single dose of morphine IV with no pain relief. Blood work revealed an elevated white blood cell (WBC) count (16.6 x 1000; reference range 4.6-10.6 x 1000). A computed tomography (CT) scan of the abdomen and pelvis demonstrated a trace amount of free fluid in the gallbladder fossa later determined to be a bile leak on a hepatobiliary scan. The subject was hospitalized for further management.

During the hospitalization, Subject (b) (6) was treated with hydromorphone IV as needed for abdominal pain, potassium chloride 40 mEq IV for hypokalemia, a single dose of ondansetron IV for nausea, ketorolac IV four times daily and APAP IV every 8 hours for two days for abdominal pain, pantoprazole IV daily for two days for acid reflux, ampicillin sodium/sulbactam sodium IV four times daily and vancomycin IV two times daily for 3 days as prophylaxis for infection.

On (b) (6) the subject had an endoscopic retrograde cholangiopancreatography with sphincterotomy. The procedure identified a peripheral bile leak in the right lobe of the liver. She received numerous medications preoperatively, intraoperatively, and postoperatively for sedation, for induction and maintenance of anesthesia, for pain management, for relaxation of the Sphincter of Oddi, for neuromuscular blockade reversal, and as prophylaxis for nausea. She again received phenylephrine IV for intraoperative hypotension. The SAE of post-procedural bile leak was considered resolved on (b) (6)

On (b) (6), Subject (b) (6) was discharged from the hospital with five days of oral antibiotics.

Impression
Subject (b) (6) is a teenage girl with a past medical history significant for GERD, abdominal pain, biliary colic, and anemia who experienced a post-procedural bile leak on post-operative day #6, two days after completing the last dose of DPSG. The Applicant considered the SAE of post-procedural bile leak not related to DPSGC but rather to the subject's surgical procedure. A

post-procedural bile leak is a known complication of a cholecystectomy. Subject (b) (6) SAE is not related to DPSGC.

Reviewer Comment: I agree with the Applicant's conclusion that the SAE of post-procedural bile leak is related to the subject's post-surgical status and not related to DPSGC.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No discontinuations due to AEs occurred during Study XP21L-402 and Study 81-0072. One discontinuation due to AE occurred during Study CL-000424 - Subject 81-013 discontinued from the study due to a headache and use of rescue medication. I reviewed the case report form (CRF) for Subject (b) (6) A summary of the discontinuation due to AE is provided below.

Subject Number: (b) (6)
Study Number: CL-000424
PT: Headache

Subject (b) (6) is a 15-year old, Caucasian, female with a past medical history of left-sided Legg Calvé Perthes disease status post leg brace placement and removal who completed her orthodontic procedure at 1355 on (b) (6) Her procedure was scored as mild on the trauma rating scale. She rated her pain as "none" on the pain severity rating scale at 1402 and took a 50-mg dose of DPSGC at 1403 pm on (b) (6) Her pain rating remained "none" for the first hour after DPSGC administration and increased slightly to "mild" at 2 hours after DPSGC administration. Her pain rating decreased to "none" at 3, 4, and 5 hours after DPSGC administration. Before the 6 hours post-DPSGC pain assessment, the subject reported a headache that was moderate in severity. The subject took acetaminophen 500 mg by mouth at 2000 for the headache. She rated her pain as "none" on the pain severity scale at 2000. The headache lasted for about one and one-half hours. The headache was documented as resolved in the CRF.

Impression
Subject (b) (6) is a teenage girl with no significant past medical history who experienced a headache during the study after taking a single 50-mg dose of DPSGC. The Sponsor of Study CL-000424 considered the AE of headache possibly related to DPSGC. Headache is listed as a common adverse reaction in the Zipsor® prescribing information. The AE of headache is possibly related to DPSGC.

Reviewer Comment: The CSR for Study CL-000424 states that Subject (b) (6) had a history of using paracetamol daily for headaches (p.31/96). However, I reviewed both the CRF for Subject (b) (6) and the datasets for Study CL-000424 and found no documentation of headaches in the medical history for this subject. It appears the statement that Subject (b) (6) had a history of using paracetamol daily for headaches may have been erroneous. I did not pursue further clarification of this discrepancy with the Applicant because accuracy regarding one subject's past medical history in Study CL-000424 is minor and does not impact my conclusions about the safety profile of DPSGC.

8.4.4. Significant Adverse Events

Other than the above-mentioned SAE and discontinuation due to AE, no significant AEs occurred during studies XP21L-402, 81-0072, and 81-0074.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Pooled Studies

The total number of TEAEs in the pooled studies was 47 with 19 TEAEs in Study XP21L-402 and 28 TEAEs in Study 81-0072. The total number of treatment-emergent SAEs (TESAEs) was one. The TESAE occurred in Study 81-0072 and is discussed in more detail in Section 8.4.2 of this review. The total number of subjects reporting at least one TEAE was 21 (42.9%) with 9 subjects in Study XP21L-402 and 12 subjects in Study 81-0072.

When looking at TEAEs by severity, the total number of subjects who had TEAEs of mild severity was 7 (14.3%) with 2 subjects in Study XP21L-402 and 5 subjects in Study 81-0072. The total number of subjects who had TEAEs of moderate severity was 14 (28.6%) with 7 subjects in Study XP21L-402 and 7 subjects in Study 81-0072. There were no subjects who had TEAEs in the severe category.

The incidence of TEAEs, the incidence of TESAEs, and the incidence of TEAEs by severity for the pooled studies are summarized in Table 14.

Table 14 Overall Summary of TEAEs in Studies XP21L-402 and 81-0072

	Study XP21L-402 (N = 24) n (%)	Study 81-0072 (N = 25) n (%)	Total (N = 49) n (%)
Total Number of TEAEs	19	28	47
Total Number of TESAEs	0	1	1
Number (%) of Subjects Reporting at Least One:			
TEAE	9 (37.5%)	12 (48.0%)	21 (42.9%)
TEAE by Severity[1]			
Mild	2 (8.3%)	5 (20.0%)	7 (14.3%)
Moderate	7 (29.2%)	7 (28.0%)	14 (28.6%)
Severe	0	0	0

TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event

[1] Subjects reporting more than one adverse event were counted only once using the highest severity.

[2] Subjects reporting more than one adverse event were counted only once using the closest relationship to study drug. Not related events include those reported as "Unlikely" or "Not Related" to study drug; related events include those reported as "Certain," "Probable," "Possible," "Probably Related," or "Possibly Related" to study drug.

Source: CSS, S-013 PAS Efficacy, Table 5, p. 24.

When summarizing TEAEs by System Organ Class, the most common TEAEs from the pooled studies occurred in the following SOCs:

- Gastrointestinal (GI) disorders (26.5%)
- Nervous system disorders (16.3%)
- Musculoskeletal and connective tissue disorders

The most common AEs in the GI disorders SOC were nausea (14.3%), constipation (8.2%), upper abdominal pain (4.1%), and vomiting (4.1%). The most common AEs in the nervous system disorders SOC were headache (10.2%) and dizziness (4.1%). The most common AEs in the musculoskeletal and connective tissue disorders were back pain (4.1%) and musculoskeletal pain (4.1%).

When summarizing TEAEs by preferred term (PT), the most commonly reported AEs in descending order were as follows:

- Nausea (14.3%)
- Headache (10.2%)
- Constipation (8.2%)
- Abdominal Pain (4.1%)
- Back Pain (4.1%)
- Dizziness (4.1%)
- Musculoskeletal Pain (4.1%)
- Vomiting (4.1%)

The incidence of TEAES by SOC and PT in the pooled studies is presented in Table 15.

Table 15 Incidence of TEAEs by SOC and PT in Studies XP21L-402 and 81-0072

MedDRA System Organ Class Preferred Term[1]	Study XP21L-402 (N = 24) n (%)	Study 81-0072 (N = 25) n (%)	Total (N = 49) n (%)
Any TEAE	9 (37.5%)	12 (48.0%)	21 (42.9%)
Gastrointestinal disorders	7 (29.2%)	6 (24.0%)	13 (26.5%)
Nausea	3 (12.5%)	4 (16.0%)	7 (14.3%)
Constipation	2 (8.3%)	2 (8.0%)	4 (8.2%)
Abdominal pain upper	2 (8.3%)	0	2 (4.1%)
Vomiting	1 (4.2%)	1 (4.0%)	2 (4.1%)
Nervous system disorders	4 (16.7%)	4 (16.0%)	8 (16.3%)
Headache	3 (12.5%)	2 (8.0%)	5 (10.2%)
Dizziness	1 (4.2%)	1 (4.0%)	2 (4.1%)
Musculoskeletal and connective tissue disorders	1 (4.2%)	1 (4.0%)	2 (4.1%)
Back pain	1 (4.2%)	1 (4.0%)	2 (4.1%)
Musculoskeletal pain	1 (4.2%)	1 (4.0%)	2 (4.1%)

MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event
Note: At each level of summarization (any event, system organ class, and preferred term), subjects reporting more than one adverse event were counted only once.
[1] Adverse events were coded to system organ class and preferred term using MedDRA, version 14.0.

Source: CSS, S-013 PAS Efficacy, Table 6, p. 26.

Study CL-000424

The total number of AEs in Study CL-000424 was 26 with 15 AEs in the DPSGC 25 mg group and 11 AEs in the DPSGC 50 mg group. There were no SAEs in Study CL-000424. The total number of subjects reporting any AE was 23 (23.7%) with 13 subjects in the DPSGC 25 mg group and 10 subjects in the DPSGC 50 mg group.

When looking at AEs by severity, there was a total of 20 AEs of mild severity with 13 AEs occurring in the DPSGC 25 mg group and 7 AEs occurring in the DPSGC 50 mg group. There was a total of 6 AEs of moderate severity with 2 AEs occurring in the DPSGC 25 mg group and 4 AEs occurring in the DPSGC 50 mg group. There were no AEs in the severe category.

The incidence of AEs and SAEs and the incidence of AEs by severity for Study CL-000424 are summarized in the Table 16.

Table 16 Overall Summary of AEs in Study CL-000424

	DPSGC 25 mg Group (N=47) n (%)	DPSGC 50 mg Group (N=50) n (%)	Total (N=97) n (%)
Total # of AEs	15*	11	26*
Total # of SAEs	0	0	0
# of Subjects Reporting Any AE	13 (27.7%)	10 (20%)	23 (23.7%)
AEs by Severity			
Mild	13 (27.7%)*	7 (14%)	20 (20.6%)*
Moderate	2 (4.3%)	4 (8%)	6 (6.2%)
Severe	0	0	0

Source: CSR Study CL-000424, Table 5, p. 42, Tables 14.3.2, 14.3.3, and 14.3.4, pp. 82 – 84, and Listing 16.2.7, p. 336.

When summarizing AEs by SOC, the most common AEs from Study CL-000424 occurred in the following SOCs:

- Nervous system disorders (17.5%)*
- GI disorders (7.2%)

The most common AEs in the nervous system disorders SOC were headache (10.3%), somnolence (4.1%), and dizziness (3.1%). The most common AEs in the GI disorders SOC were upper abdominal pain (4.1%) and pharyngolaryngeal pain (1.0%).

When summarizing AEs by PT, the most commonly reported AEs in descending order were as follows:

- Headache
- Somnolence
- Abdominal Pain
- Dizziness

- Fatigue
- Urticaria

The incidence of AEs by SOC and PT in Study CL-000424 is presented in Table 17 below.

Table 17 Incidence of AEs by SOC and PT in Study CL-000424

MedDRA System Organ Class Preferred Term	DPSGC 25 mg Group (N=47) n (%)	DPSGC 50 mg Group (N=50) n (%)	Total (N=97) n (%)
Any AE	15*	11	26*
Nervous System Disorders			
Headache NOS	6 (12.8%)	4 (8%)	10 (10.3%)
Somnolence	2 (4.3%)	2 (4%)	4 (4.1%)
Dizziness	2 (4.3%)	1 (2%)	3 (3.1%)
GI Disorders			
Abdominal Pain	3 (6.4%)	1 (2%)	4 (4.1%)
General Disorders and Administration Site Conditions			
Fatigue	1 (2.1%)	0	1 (1.0%)
Skin and Subcutaneous Tissue Disorders			
Urticaria NOS	0	1 (2%)	1 (1.0%)

Source: CSR Study CL-000424, Table 5, p. 42 and Listing 16.2.7, p. 336.

Reviewer Comment: My analysis of the AE data for Study CL-000424 yielded slightly different numerical results than those stated in the CSR. I presented my numerical results in this review and noted the values that differed from those stated in the CSR with an asterisk. The CSR displayed a total of 27 AEs with 16 AEs in the DPSGC 25 mg group and 11 AEs in the DPSGC 50 mg group; however, I calculated only 15 AEs in the DPSGC 25 mg group. I verified my calculations by reviewing Tables 14.3.2, 14.3.3, and 14.3.4 as well as the line listing of AEs (Listing 16.2.7). I did not pursue further clarification of these AE discrepancies with the Applicant because the numerical differences were minimal and did not impact my conclusions about the safety profile of DPSGC.

8.4.6. Laboratory Findings

Pooled Studies

As described in Section 8.3.3, laboratory evaluations were measured at multiple time points during the pooled studies. There were no clinically significant individual laboratory abnormalities and no clinically significant changes from baseline in laboratory values during

these studies.

The Applicant noted that four subjects had a shift in alanine aminotransferase (ALT) values from the normal range at baseline to the abnormal range at the final study visit with the abnormal ALT values ranging from 1.25 times to 1.5 times the upper limit of normal (1.25x to 1.5x ULN). Additionally, the Applicant stated that no subjects had aspartate aminotransferase (AST) values greater than 1.2x ULN at baseline or at the final study visit. To verify the Applicant's analyses, I looked at the laboratory results for studies XP21L-402 and 81-0072 in more detail. I focused on AST, ALT, alkaline phosphatase (alk phos), and bilirubin results.

On review of the laboratory data for Study 81-0072, I identified the following:

1. Two subjects had AST values > 1.2x ULN at baseline –
   a) Subject (b) (6) had a baseline AST value of 51 U/L (1.3x ULN) and a normal AST value at the final study visit.
   b) Subject (b) (6) had a baseline AST value of 52 U/L (1.3x ULN) and no AST value documented at the final study visit.
2. Four subjects had alk phos values greater than 1.2 times ULN at baseline –
   a) Subject (b) (6) had a baseline alk phos value of 178 U/L (1.4x ULN) and a final study visit alk phos value of 189 U/L (1.5x ULN).
   b) Subject (b) (6) had a baseline alk phos value of 193 U/L (1.5x ULN) and a final study visit alk phos value of 147 U/L (1.2x ULN).
   c) Subject (b) (6) had a baseline alk phos value of 179 U/L (1.7x ULN) and a final study visit alk phos value of 171 U/L (1.6x ULN).
   d) Subject (b) (6) had a baseline alk phos value of 196 U/L (1.6x ULN) and a final study visit alk phos value of 193 U/L (1.5x ULN).
3. There were no subjects with ALT values >1.2x ULN at baseline or at the final study visit.
4. There were no subjects with bilirubin values >1.2x ULN at baseline or at the final study visit.

On review of the laboratory data for Study XP21L-402, I identified the following:

1. One subject had an AST value = 1.2x ULN at baseline –
   a) Subject (b) (6) had a screening AST value of 45 U/L (1.2x ULN) and a normal AST value at the final study visit.
2. Two subjects had ALT values >1.2x ULN and one subject had an ALT value = 1.2x ULN at baseline –
   a) Subject (b) (6) had a screening ALT value of 27 U/L (1.4x ULN) and a normal ALT value at the final study visit.
   b) Subject (b) (6) had a screening ALT value of 39 U/L (1.3x ULN) and a normal ALT value at the final study visit.
   c) Subject (b) (6) had a screening ALT value of 35 U/L (1.2x ULN) and a normal ALT value at the final study visit.
3. Four subjects had normal ALT values at baseline but abnormal ALT values at the final study visit –

   a) Subject (b) (6) had a final study visit ALT value of 30 U/L (1.5x ULN).
   b) Subject (b) (6) had a final study visit ALT value of 43 U/L (1.4x ULN).
   c) Subject (b) (6) had a final study visit ALT value of 25 U/L (1.25x ULN).
   d) Subject (b) (6) had a final study visit ALT value of 40 U/L (1.3x ULN).
4. One subject had an alk phos value >1.2x ULN at baseline –
   a) Subject (b) (6) had a screening alk phos value of 541 U/L (1.5x ULN) and a final study visit alk phos value of 489 U/L (1.4x ULN).
5. Two subjects had bilirubin values >1.2x ULN at baseline –
   a) Subject (b) (6) 5 had a screening bilirubin value of 30.8 µmol/L (1.5x ULN) and a final study visit bilirubin value of 29.1 µmol/L (1.4x ULN).
   b) Subject (b) (6) had a screening bilirubin value of 25.7 µmol/L (1.25x ULN) and a normal bilirubin value at the final study visit.

Study CL-000424

No laboratory data other than urine pregnancy testing in females of childbearing potential before the orthodontic procedure was collected in Study CL-000424.

Reviewer Comment: My review of the laboratory data identified some subjects who had abnormal AST, ALT, alk phos, and bilirubin values at baseline. Most subjects with abnormal AST and ALT values at baseline had normalization of these values by the final study visit. Subjects with abnormal alk phos values at baseline had elevated, but stable, alk phos values at the final study visit. There were two subjects with abnormal bilirubin values at baseline. One subject's bilirubin value remained abnormal and the other subject's bilirubin value normalized.

I confirmed the Applicant's determination that four subjects in Study XP21L-402 had an ALT shift from normal at baseline to abnormal at the final study visit. I looked at the medical history for the four subjects with ALT values >1.2x ULN at the final study visit to better understand if another etiology other than exposure to study drug might explain the shift from normal to abnormal in ALT values. All four subjects underwent surgical procedures before entering the study. Two subjects had a tonsillectomy and adenoidectomy, one subject had a closed reduction of a displaced nasal fracture, and one subject had right shoulder arthroscopy with labral repair. None of the subjects had surgical procedures involving the GI tract or liver. None of the subjects had any medical history of GI or hepatic disorders. Given that these subjects received multiple other medications preoperatively and intraoperatively for anesthetic induction, anesthetic management, and pain management, it is plausible that the shift in ALT values was related to a medication other than DPSGC or related to combined use of another medication with DPSGC. However, this ALT shift was not seen in all subjects who had surgical procedures and received multiple other medications preoperatively and intraoperatively.

I did not identify any other factors besides exposure to other medications that may have contributed to ALT elevation in the four subjects from Study XP21L-402. I cannot rule out the possibility that DPSGC may have caused a mild elevation in ALT values for a small percentage of subjects. However, I believe that these abnormal ALT values are not clinically significant because the values did not exceed 1.5x ULN, did not meet the criteria for adverse events, did not

result in significant shifts of other laboratory values, and did not lead to any symptomatology or physical examination findings for the involved subjects.

8.4.7. Vital Signs

Pooled Studies

In the pooled studies, vital signs assessment consisted of systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and weight at screening, baseline, and final study visits. There were no clinically significant changes from baseline in any of the vital signs during the pooled studies.

The Applicant noted that there were small mean decreases in systolic and diastolic blood pressure at 1 and 2 hours after DPSGC administration and small mean increases in systolic and diastolic blood pressure at the final study visit. I verified the Applicant's analyses by examining the Integrated Summary of Safety (ISS) datasets. I identified 15 out of 49 subjects who had slight decreases in either systolic or diastolic blood pressure after administration of DPSGC. I identified 4 out of 49 subjects who had slight increases in either systolic or diastolic blood pressure at the final study visit.

Study CL-000424

No vital signs assessments were performed in Study CL-000424.

Reviewer Comment: My review of the vital signs data for the pooled studies confirmed the conclusions made by the Applicant. About 30% of the study population had a small blood pressure decrease at 1 and 2 hours after DPSGC administration affected. However, when looking at the blood pressure values in mmHg, the mean decreases of -3.2 mmHg for systolic blood pressure and -1.7 mmHg for diastolic blood pressure are negligible and not clinically significant. About 8% of the study population had a small blood pressure increase at the final study visit. Again, when looking at the blood pressure values in mmHg, the mean increases of 3.5 mmHg for systolic blood pressure and 4.4 mmHg for diastolic blood pressure are negligible and not clinically significant.

8.4.8. Electrocardiograms (ECGs)

Not applicable

8.4.9. QT

Not applicable

8.4.10. Immunogenicity

Not applicable

8.5. Analysis of Submission-Specific Safety Issues

Not applicable

8.6. Safety Analyses by Demographic Subgroups

The Applicant conducted subgroup analyses by sex and race for the pooled studies. From the analysis by sex, the Applicant concluded that there were no differences between males and females in the incidence of any TEAEs, that females had more AEs in the SOC of GI disorders, and that males had more AEs in the SOC of nervous system disorders. From the analysis by race, the Applicant concluded that the incidence of TEAEs was higher in other races than in Caucasians, that other races had more TEAEs in the SOC of GI disorders and nervous system disorders than Caucasians, and that Caucasians had TEAEs in the SOC of musculoskeletal and connective tissue disorders while other races did not.

Reviewer Comment: The race and sex subgroup analyses conducted by the Applicant are not clinically meaningful as the sample size of 49 subjects from the pooled studies was too small.

8.7. Specific Safety Studies/Clinical Trials

The Applicant conducted a review of the published literature evaluating the safety of diclofenac in adolescents to augment the safety database. The Applicant's literature review had some limitations. Only seven literature references were submitted. This number seems low given the length of time that the diclofenac moiety has been FDA approved in adults and potentially used off-label in adolescents. One citation (Swanepoel, 1999) was an editorial rather than a scientific article. Two articles (Krishna, 2003 and Litalien, 2001) were about the NSAID class in general, not diclofenac in specific. Another article (Boric, 2017) was about pharmacologic and non-pharmacologic interventions, not diclofenac in specific, for post-operative pain management. The remaining three articles (Courtney, 2001, Romsing, 2000 and Romsing 2001) provided slightly more meaningful data. All three were prospective studies analyzing the analgesic efficacy of different doses of diclofenac or of diclofenac compared to an active-control in patients undergoing tonsillectomy ± adenoidectomy. Sixty subjects were exposed to either a single-dose of diclofenac, diclofenac twice per day for 3 days, or diclofenac twice per day for 14 days. Efficacy results were variable. There was no increased risk of bleeding after tonsillectomy ± adenoidectomy in the subjects treated with diclofenac. Vital signs and laboratory results were not presented. Overall, these three articles provided more information about diclofenac's efficacy rather than diclofenac's safety. I identified no new safety signals for diclofenac after review of the referenced literature.

Table 18 below provides a summary of the study design, study population, diclofenac exposure, efficacy data, and safety data from the above-mentioned prospective studies referenced by the Applicant.

Table 18 Summary of Data from Prospective Trials Referenced by the Applicant

Article	Study Design	Study Population	Dose/Regimen	Objective	Efficacy Data	Safety Data
Courtney, MJ, 2001	R, SB	Total = 49 (25 diclofenac; 24 tramadol) Ages 11-36 years Tonsillectomy ± adenoidectomy	<50 kg, diclofenac 50 mg BID for 14 days ≥50 kg, diclofenac 50 mg TID for 14 days OR < 50 kg, tramadol 50 mg TID for 14 days ≥50 kg, tramadol 100 mg in am, 50 mg in afternoon, 50 mg in pm for 14 days	Analgesic efficacy of oral tramadol vs. oral diclofenac for management of post-tonsillectomy pain	No statistically significant difference in average VAS pain scores between tramadol and diclofenac	No significant difference in post-tonsillectomy hemorrhage incidence, cyclizine use, and hospital readmission. No significant difference in use of study drug or acetaminophen. Higher incidence of vomiting in tramadol group. No discussion of vital signs or labs.
Romsing, J, 2000	R, DB	Total = 48 (24/arm) Ages 5-15 years Tonsillectomy ± adenoidectomy	Diclofenac 2-3mg/kg/day for 3 days (starting day after surgery) [25 mg or 50 mg BID] OR APAP 90 mg/kg/day for 3 days (starting day after surgery)	Analgesic efficacy of diclofenac vs. APAP for the first three days at home after tonsillectomy.	1. Pain scores at rest in diclofenac group lower at 12 hours on Day 1-3 compared to APAP group. 2. # with severe pain at rest and during drinking in diclofenac group lower at 12 hours on Day 2 compared to APAP group. 3. # with severe pain in diclofenac group lower at rest at 7 hours on Day 3 compared to APAP group.	No children experienced any episodes of bleeding during the 3-day study period. No N/V in the diclofenac group for first 2 days after surgery compared to the APAP group. No discussion of vital signs or labs.
Romsing, J, 2001	R, DB	Total = 24 (11 diclofenac; 13 APAP) Ages 5-15 years Tonsillectomy ± adenoidectomy	Diclofenac 1-2 mg/kg single dose and PBO APAP (given the morning after surgery) OR APAP 22.5 mg/kg single dose and PBO diclofenac (given the morning after surgery)	Study the PK and pain scores following administration of single oral doses of either diclofenac or high-dose APAP	1. Diclofenac PK profile - mean lag time 1±0.6 hrs; mean tmax 2±0.5 hrs; mean Cmax 2.4±1.3 hrs. 2. APAP PK profile - mean tabs 0.7±0.3 hrs; tmax 1.4±0.5 hrs; mean Cmax 12.7±3.8 µg/ml. 3. No significant reduction in pain score seen at 1 hr or at any other assessments during the 5 hr study period for either group.	None of the subjects experienced any adverse effects related to either diclofenac or APAP. No discussion of vital signs or labs.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No studies to address human carcinogenicity or tumor development were conducted by the Applicant for this submission.

8.8.2. Human Reproduction and Pregnancy

DPSGC has not been studied in pregnancy and lactation. There were no reported pregnancies during Study XP21L-402, Study 81-0072, or Study CL-000424.

8.8.3. Pediatrics and Assessment of Effects on Growth

DPSGC has not been studied in long-term pain models for either the adult or pediatric population. Zipsor® was approved for treatment of acute pain only. Therefore, the Applicant did not submit any AE data or assessment of effects on growth related to chronic use of DPSGC in the pediatric population.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There were no reported overdoses during Study XP21L-402, Study 81-0072, or Study CL-000424. The Applicant stated that no information is available on the potential for abuse, withdrawal, or rebound with DPSGC.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Applicant referenced Study XP21L-402, Study 81-0072, and two Periodic Adverse Drug Experience Reports (PADERs) covering the reporting periods of June 2016 to June 2017 and June 2017 to June 2018 when providing information on the postmarket experience with Zipsor®. The Applicant summarized the PADER data and stated there were no new safety findings from the postmarket experience that would alter the safety profile of Zipsor® when used for the approved indication at the recommended dose in the approved population. The Applicant also stated that no changes to the current approved label are warranted based on the safety data in the PADERs.

I reviewed four PADERs covering the reporting periods of June 2012 to June 2013, June 2015 to June 2016, June 2016 to June 2017, and June 2017 to June 2018. I could not locate the PADERs covering the reporting periods of June 2013 to June 2014 and June 2014 to June 2015. Vanishing Bile Duct Syndrome (VBDS) was an event of interest in the PADER from 2015 to 2016 but has not been an event of interest since that time. DRESS was an event of interest in the last

three PADERs, from 2015 to 2018. Other AEs listed in the most recent PADER that were reported in more than one patient were erosive esophagitis, erosive duodenitis, gastric ulcer, anemia, melena, Kounis syndrome, embolia cutis medicamentosa (Nicolau syndrome), hypersensitivity vasculitis, and drug interaction.

I also reviewed the postmarket experience with the NSAID class in general since approval of Zipsor® in 2009. In July 2015, the FDA required holders of approved drugs in the NSAID class to comply with a safety labeling change based upon new safety information that became available in the postmarket setting. New safety information about the risks of cardiovascular thrombotic events and GI bleeding, ulceration, and perforation were added to the prescribing information in a boxed warning. Additionally, new safety information about cardiovascular thrombotic events and heart failure and edema were added to the Warnings and Precautions section of the prescribing information.

Reviewer Comment: I agree with the Applicant's conclusion that safety concerns identified through the postmarket experience do not change the risk-benefit balance of Zipsor®.

8.9.2. Expectations on Safety in the Postmarket Setting

There are no anticipated safety concerns for pediatric subpopulations that were not well represented in the safety database. There are no important differences in the administration and use of Zipsor® in the conducted pediatric studies versus its expected use in the postmarket setting. As with all drug products in the NSAID class, the potential for common side effects such as abdominal pain, constipation, dyspepsia, nausea, vomiting, dizziness, headache, and somnolence exists with Zipsor®.

Zipsor has not been studied in long-term pain models in children. Therefore, safety concerns may be anticipated if Zipsor® is used off-label in the pediatric population with chronic pain. Known long-term adverse effects of the NSAID class in the adult population include cardiovascular thrombotic events, hypertension, congestive heart failure, GI inflammation, bleeding, ulceration, and perforation, renal papillary necrosis and other renal injury, serious skin reactions, hepatotoxicity, and anemia. The inclusion of the pediatric population 12 years to 17 years of age to the approved indication in the prescribing information is not expected to change off-label use of Zipsor®. Monitoring in the postmarket setting for long-term adverse effects in the pediatric population is warranted. The FDA Adverse Event Reporting System (FAERS) should be adequate to monitor for any long-term AEs with off-label use of Zipsor® for chronic rather than acute painful conditions.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues were identified from other disciplines.

8.10. Integrated Assessment of Safety

Review of the safety data from studies XP21L-402, 81-0072, and CL-000424 yielded no new safety signals with use of Zipsor® in adolescents. The most common adverse reactions from the multiple-dose, uncontrolled studies in pediatric subjects 12 years to 17 years of age were nausea (14.3%), headache (10.2%), constipation (8.2%), and abdominal pain (4.1%). Review of the collected safety information and cited articles from the Applicant's published literature search as well as the available postmarket safety data for Zipsor® did not raise any new safety concerns regarding use of Zipsor® in the adult and pediatric populations. Any anticipated long-term adverse effects with use of Zipsor® off-label for chronic pain in the pediatric population can be adequately monitored with FAERS. Based on review of the available data, Zipsor® has a safety profile in the pediatric population 12 years of age and older that is comparable to the adult population.

9. Advisory Committee Meeting and Other External Consultations

Not applicable

10. Labeling Recommendations

10.1. Prescription Drug Labeling

DAAAP consulted the Division of Pediatric and Maternal Health (DPMH) to review this supplement, the proposed prescribing information, and the literature referenced by the Applicant in support of any labeling changes in accordance with the Pregnancy and Lactation Labeling Rule (PLLR). The labeling review consultation from the pediatric team is complete; however, the labeling review consultation from the maternal health team is pending. The pediatric team recommends rewording the indication to include pediatric patients 12 years of age and older; including safety data from the studies in adolescents ages 12 years to 17 years in Section 6.1; adding language in Section 8.4 to inform prescribers that efficacy in pediatric patients 12 years of age and older has been established based on extrapolation of adult data and supported by pediatric data and that safety and efficacy in pediatric patients less than 12 years of age have not been established; and removing the uncontrolled, open-label pediatric study data from Section 14. Please see the review of Carolyn L. Yancey, MD with concurrence form Hari Cheryl Sachs, MD, and John J. Alexander, MD, MPH, for more details.

Based on the pediatric team labeling recommendations and discussion with other disciplines at the first labeling meeting on July 25, 2019, I recommend the following major changes to the prescribing information:

1. Section 2 Dosage and Administration
   a) Include a statement to inform prescribers that the Zipsor® dosage is the same in the adult population and in the pediatric population 12 years of age and older.
2. Section 6.1 Clinical Trials Experience
   a) Revise the wording to accurately describe the number of patients who were 12 years to 17 years of age, the different study populations, and the different Zipsor® dosages and dosing frequency in studies XP21L-402, 81-0072, and CL-000424.
   b) List the common AEs from the multiple-dose studies (Study XP21L-402 and 81-0072) in descending order of frequency with incidence as a percentage in parentheses.
   c) Delete Table 2 Incidence of Treatment Emergent Adverse Reactions with Incidence ≥4% of Zipsor® Treated Pediatric Patients (12-17 Years of Age) in Multiple-Dose Studies.
3. Section 8.4 Pediatric Use
   a) Add language to inform prescribers that efficacy in the pediatric population 12 years of age and older is based on extrapolation from adult data and supported by pediatric data.
   b) Add language to inform prescribers that safety and effectiveness in the pediatric population less than 12 years of age have not been established.
   c) Accurately summarize the different study populations, the trial designs, and the number of patients who were 12 years to 17 years of age in studies XP21L-402, 81-0072, and CL-000424.
4. Section 14 Clinical Studies
   a) Delete the uncontrolled, OL and active-controlled, DB study data because the efficacy in pediatric patients 12 years and older is based on extrapolation from adult data and the conducted studies do not meet the evidentiary standards for efficacy.

I also recommend the following minor change to the prescribing information:

1. Section 1 Indications and Usage
   a) Revise the word “adults” to “adult” such that the indicated population is “adult and pediatric patients 12 years and older.”

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

Not applicable

12. Postmarketing Requirements and Commitments

Not applicable

13. Appendices

13.1. References

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13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study XP21L-402

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not Applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		

Not applicable		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study 81-0072

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ Not applicable		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): Study CL-000424

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 2		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): None		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Not applicable Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements: Not applicable	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided: Not applicable	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____ Not applicable		
Is an attachment provided with the reason: Not applicable	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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08/02/2019 01:46:49 PM

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