Office of Clinical Pharmacology Review

NDA or BLA Number	22202 S13
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Submission Date	11/09/2018, 5/31/2019
Submission Type	*[Standard review]*
Brand Name	Zipsor
Generic Name	Diclofenac Potassium
Dosage Form and Strength	Liquid Filled Capsules, 25 mg
Route of Administration	Oral
Proposed Indication	Relief of mild to moderate acute pain in adults (18 years of age or older).
Applicant	Assertio Therapeutics, Inc.
Associated IND	*[63,308]*
OCP Review Team	*[Srikanth C. Nallani, Ph.D.]*
OCP Final Signatory	*[Yun Xu, Ph.D.]*

Clinical Pharmacology Summary:

Xandodyne Pharmaceuticals transferred ownership of Zipsor NDA to Depomed Inc, who then transferred ownership to Assertio Therapeutics, Inc. This Post-Approval Supplement is intended to fulfill the requirements only under PMR 1053-1, and to support proposed labeling changes related to the treatment of pediatric patients ages ≥ 12 to 17 years (inclusive) with mild to moderate acute pain. Regulatory history on this NDA and discussions relevant to the supplement are in Appendix 1.

Two clinical studies were conducted by the Sponsor:

1. Study XP21L-402: Open-Label Study of the Pharmacokinetics and Safety of ZIPSOR (Diclofenac Potassium Soft Gel Capsules) in Pediatric Subjects (Ages 12-17) with Mild to Moderate Acute Pain; and
2. Study 81-0072: A Phase 4, Open-Label Study of the Safety and Efficacy of ZIPSOR (diclofenac potassium) Liquid Filled Capsules in Pediatric Subjects (Ages 12-17 years) with Mild to Moderate Acute Pain. This study is new and will be reviewed by medical officer. This study does not have any pharmacokinetic assessments.

Study XP21L-402 was submitted (b) (4) on 10/19/2012 and the study report and data were reviewed and documented in clinical pharmacology review dated 4/11/2013, which concluded that the submission is acceptable from a Clinical Pharmacology perspective provided that mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language in

the package insert. The Agency provided the written response to the 18 Nov 2013 meeting request. In this correspondence, the Agency clarified, "To allow extrapolation of efficacy from adults to pediatric patients 2 years and above, the pharmacokinetic profile and exposure in pediatrics should be comparable to that in adults". The sponsor submitted a Table comparing PK of diclofenac following Zipsor administration in adults and pediatrics (12-17 years). PK Data below 2 years of age is not available at this stage.

Table: Pharmacokinetic Parameters Following Oral Administration of Zipsor 25 mg in Adults and Pediatric Patients.

	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: Pharmacokinetic Analysis Report, Table 4

The numerical difference between table submitted by sponsor above and the proposed label are due to combining of single (Day 1) and multiple-dose (Day 2 following dose # 5) data in the table above from pediatric Study XP21L-402.

Labeling Changes Proposed: Underlined text indicates sponsor's proposed

The pharmacokinetics of ZIPSOR was assessed in 24 healthy, normal adult volunteers who received 25 mg ZIPSOR under fasting conditions. The mean pharmacokinetic parameters for ZIPSOR are shown in Table 4. The pharmacokinetics of ZIPSOR was also assessed in pediatric patients 12 to 17 years of age [see *Specific Populations: Pediatric*] and was found to be similar to adults.

Specific Populations

Pediatric: The pharmacokinetics of ZIPSOR was assessed in 24 pediatric patients ages 12 to 17 with mild to moderate acute pain who received 25 mg ZIPSOR **every six hours for up to four days**. The mean pharmacokinetic parameters of ZIPSOR **on Day 1** in pediatric patients ages 12 to 17 years are shown in Table 5. (b) (4) -Peak plasma levels were noted in 1 hour with an elimination half-life of less than 2 hours in pediatric patients ages 12 to 17. The pharmacokinetics of ZIPSOR in pediatric patients 12 to 17 years of age was similar to that in adults.

Table 5

Mean Pharmacokinetics of ZIPSOR **(Day 1)** in Pediatric Patients 12 to 17 Years of Age

PK Parameter	Number of Subjects	Mean ± Standard Deviation
T_{max} (hr)	24	0.94 ± 0.42
Terminal Half-life (hr)	24	1.81 ± 0.92
C_{max} (ng/mL)	24	699 ± 464
AUC(0-∞) (ng·h/mL)	24	659 ± 208

Reviewer's comment: The submitted table is consistent with observations noted in clinical pharmacology review dated 4/11/2013. The proposed labeling is acceptable with a marking that the data is from Day 1 of the multiple dose PK study.

Conclusion: The submitted labeling supplement is acceptable from a clinical pharmacology perspective with the above noted labelling changes.

Appendix 1:

Table: Regulatory history of Zipsor.

Reference ID	Date	Activity
SN0000	21 Sept 2007	NDA 022202 submitted by Xanodyne (original sponsor) with a request for deferral of pediatric studies (SN0000, Section 1.9.2)
FDA approval letter dated 16 June 2009	16 June 2009	NDA 020202 approved • The Agency waived the pediatric study requirement for ages birth to 1 year. • Agency deferred submission of pediatric studies for ages 1 to 17 years as follows: o Treatment of relief of mild to moderate acute pain in pediatric patients ages ≥12 to 17 years o Treatment of relief of mild to moderate acute pain in pediatric patients ages ≥ 2 to 12 years o Treatment of relief of mild to moderate acute pain in pediatric patients ages ≥ 1 to 2 years
SN0023	04 May 2010	Sponsor submitted revised pediatric plan based on a teleconference with the Division (13 April 2010) in which FDA notified Xanodyne that it is scientifically valid to extrapolate efficacy data from adults to pediatrics down to 2 years of age for NSAIDs (SN0023, Section 1.9.6). The revised plan modified
FDA communication dated 07 July 2010	07 July 2010	• The Agency released the Sponsor from the PREA PMRs outlined in the NDA approval letter and replaced them with the following required studies: o PMR 1053-1: PK and safety study of Zipsor® in pediatric patients ages 12–17 years with mild to moderate acute pain o PMR 1053-2: PK and safety study of Zipsor in pediatric patients ages 2–12 years with mild to moderate acute pain* o PMR 1053-3: Efficacy, safety, and PK study of Zipsor in infants ages 1–2 years with mild to moderate acute pain* • The Agency determined that findings of efficacy for Zipsor (diclofenac potassium) Liquid Filled Capsules in adults can be extrapolated to pediatric patients ages 2 through 17 years.
SN0050	27 June 2012	Transfer of NDA 022202 to Depomed
[redacted]		(b) (4)
SN0057	24 Sept 2012	Sponsor requested a deferral extension for the pediatric subgroups ≥ 2 to 12 years of age and ≥ 1 to 2 years of age in order to develop an acceptable liquid or equivalent pediatric formulation for these age groups.
3292835	12 Apr 2013	"Deferral Extension Granted" received from the Agency. Revised PMR due dates: • PMR 1053-1: Final report submission date 15 December 2014 • PMR 1053-2: Final report submission date 30 June 2016* • PMR 1053-3: Final report submission date 30 September 2019*
SN0066/ SN0068	20 May 2013/ 24 June 2013	Sponsor submitted a Type C Meeting Request (20 May 2013) and briefing package (24 June 2013) to gain FDA input on the protocol 81-0072 for the age group 12–17 years (PMR 1053-1).

3350899	01 Aug 2013	The Agency provided written responses to the studies needed to fulfill PMR 1053-1. Advice included the following: • Safety data from a total of 50 adolescent patients treated for acute pain from Studies XP21L-402 and 81-0072, combined with safety data from the literature, could be sufficient to fulfill PMR 1053-1.
SN0071	18 Nov 2013	Sponsor submitted a Type C Meeting Request to gain FDA input on the protocol for the age group 2–12 years (PMR 1053-2).
3484833	07 Apr 2014	The Agency provided the written response to the 18 Nov 2013 meeting request • The Agency clarified, "To allow extrapolation of efficacy from adults to pediatric patients 2 years and above, the pharmacokinetic profile and exposure in pediatrics should be comparable to that in adults"

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