Clinical Pharmacology Review

NDA	22307 Supplement 14 (SDN 900, eCTD 233)
Submission Date:	12 January 2016
Brand Name:	Effient®
Generic Name:	Prasugrel
Commercial Formulation:	5-mg and 10-mg tablets
DCPV Reviewers:	Elimika Pfuma Fletcher, Pharm.D., PhD Stacy S. Shord, Pharm.D. Brian Booth, PhD
OCP Division:	Division of Clinical Pharmacology V
OND Division:	Division of Hematology Products
Applicant:	Eli Lilly
Approved Dosing regimen:	A 60 mg dose, then 5 mg to 10 mg once daily with or without food.
Approved Indication:	Reduction of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) managed by percutaneous coronary intervention

1. EXECUTIVE SUMMARY

Prasugrel is a $P2Y_{12}$ platelet inhibitor approved for reduction of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) managed by percutaneous coronary intervention. The recommended dose is 60 mg followed by 5 mg (for patients < 60 kg) or 10 mg once daily with or without food.

A written request (WR) was issued in December 2012 and amended in July 2013 and July 2015 for assessment of prasugrel in the prevention of vaso-occlusive crises (VOC) in pediatric patients with sickle cell disease (SCD). The WR specified that a minimum of 10 patients in each age group of ≥ 2 to < 12 years and ≥ 12 to <18 years must be sampled for pharmacokinetics (PK) in studies TACX (dose finding trial) and TADO (efficacy trial). (b) (4)

(b) (4)

No new safety findings were identified. the Applicant is not seeking a pediatric indication.

1.1 RECOMMENDATIONS

The Applicant has fulfilled the clinical pharmacology aspects of the WR. The Pediatric Review Committee (PeRC) granted exclusivity on May 23, 2016.

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☐ Yes ☐ No ☒ NA	The Applicant is not seeking new indication.
Proposed dose for general population	☐ Yes ☐ No ☒ NA	The Applicant is not seeking new indication.
Proposed dose adjustment in specific patients or patients with co-medications	☐ Yes ☐ No ☒ NA	The Applicant is not seeking new indication.
Pivotal bioequivalence studies	☒ Yes ☐ No ☐ NA	(b) (4) [redacted]
Labeling	☒ Yes ☐ No ☐ NA	The approved Effient labeling will be not updated to include a summary of the pharmacokinetic (PK) data in accordance with the guidance document: Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling.

1.2 POST MARKETING REQUIREMENTS OR COMMITMENTS

None

SIGNATURES:

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2. QUESTION BASED REVIEW

Prasugrel is an adenosine diphosphate (ADP) receptor antagonist that inhibits platelet activation and aggregation mediated by the $P2Y_{12}$ ADP receptor. (b) (4)

Effient® was previously reviewed under NDA 22307 (approved 10 July 2009). This review only addresses questions related to this pediatric submission.

2.1 What are the clinical pharmacology and clinical trials submitted?

The Applicant conducted four clinical trials (b) (4) prasugrel to reduce the frequency and severity of vaso-occlusive crisis (VOC) in pediatric patients with sickle cell disease (SCD) (**Table 1**). The submission also included (b) (4) a population pharmacokinetic (PK) report that contained a summary of the final population PK model and exposure-response (E-R) analyses (data from Studies TACX and TADO) and two bioanalytical method validation reports (no. 03088VKJV-LI-R6 and 110886VRLC-EII). This review focuses on the PK data from Study TACX and Study TADO.

Table 1: Summary of Clinical and Clinical Pharmacology Trials

Trial	N	Trial Design
TAEJ	26	Pharmacokinetic-pharmacodynamic assessment in healthy adults (n=13) and adults with sickle cell disease at a dose of 10 mg on day 1 and then 5 mg or 7.5 mg once daily (depending on body weight) for 12 days
TAEK	60	Double-blind, randomized, placebo-controlled, multicenter trial in adult patients with sickle cell disease administered a dose of 5 mg once daily
TACX	33	Open-label, dose finding trial in pediatric patients (4 y to <18 y) with sickle cell disease
TADO	129	Double-blind, randomized, placebo-controlled, efficacy and safety trial in pediatric patients (2 y to < 18 y) with sickle cell disease administered an initial dose of 0.08 mg/kg that was titrated to a target range of platelet $P2Y_{12}$ receptor inhibition with a maximum daily dose of 0.12 mg/kg

2.2 What drug products were used in the clinical trials?

(b) (4)

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2.3 What are the characteristics of the dose-response?

(b) (4)

No E-R relationship for major bleeding was identified.

Study TACX

Thirty-two pediatric patients (4.3 y to 17.9 y; 58% girls) participated in an open-label two-part study to characterize the relationship between prasugrel dose, exposure to prasugrel-AM, and platelet inhibition in pediatric patients with SCD. Patients were administered a dose of 0.03 mg/kg to 0.6 mg/kg on a maximum of three occasions (part A) or a dose of 0.06 mg/kg to 0.12 mg/kg (Part B) once daily for 20 days to 36 days using the ODT formulation. The Applicant stated that patients were instructed to place the tablet on the tongue and allow it to dissolve; patients were allowed to drink water and swallow if the tablet did not dissolve completely (Response to Information Request dated May 27, 1016). The ODT formulation was allowed to be taken with or without food.

(b) (4)

Study TADO

A total of 341 pediatric patients (2.1 y to 18.8 y; 51% girls) participated in a double-blind, placebo-controlled, randomized trial to assess the rate of VOC (a composite endpoint of painful crisis or acute chest syndrome). Patients were administered a dose of 0.06 mg/kg to 0.12 mg/kg once daily without food (defined as no eating one hour before or after taking prasugrel) for 9 months to 24 months using the ODT3 formulation; the dose was titrated based on platelet inhibition. The Applicant stated that patients were instructed to place the tablet on the tongue and allow it to dissolve; patients were allowed to drink of water and swallow if the tablet did not dissolve completely (Response to Information Request dated May 27, 1016). The E-R dataset used for VOC rate analysis contained 282 records comprised of 112 from prasugrel-treated patients and 170 from placebo-treated patients. The E-R relationships were explored using nonlinear mixed-effects modeling. (b) (4)

No discernible relationship between the risk of a bleeding event requiring medical intervention and prasugrel-AM exposure over the range of prasugrel-AM population model-predicted AUC estimates; however, the number of patients experiencing a bleeding event requiring medical intervention was relatively low. Eleven prasugrel-treated patients and eight placebo-treated patients experienced a bleeding event requiring medical intervention.

(b) (4)

Source: Population Pharmacokinetic Report, Figure 8.3

2.4 What are the single dose and multiple dose PK parameters in pediatric patients?

(b) (4)

No safety concern was identified in pediatric patients relative to adult patients.

Study TACX

Twenty-four pediatric patients (4.3 y to 17.6 y, median 10.9 y) were administered a dose of 0.03 mg/kg to 0.60 mg/kg (0.9 mg to 48 mg) without regard to food as the ODT formulation (Part A). Three patients were 2 y to <6 y, 12 patients were 6 y to <12 y and 9 patients were 12 y to < 18 y. Each patient received a single dose (separated by 14 ± 4 days) on up to three occasions, with the dose escalated based on platelet inhibition observed with the prior dose. PK samples were drawn for up to 4 hours after a dose.

(b) (4)

notable effect of weight on exposure and stated that there appeared to be less variability in exposure when dose was expressed as assigned dose (mg/kg) rather than actual dose (mg). The PK profile appears similar in pediatrics compared to adults, as the maximal concentrations (C_{max}) increased dose proportionally and the AUC_{0-4h} increased more than dose proportionally in adults and the median time to the maximal concentrations (t_{max}) was 0.5 h in adults.

Table 5: A Summary of pharmacokinetic parameters for the active metabolite of prasugrel after a single dose in part A of Study TACX

Dose (mg/kg)	N	C_{max} (ng/mL)	T_{max} (hr)	AUC_{0-last} (ng*hr/mL)
0.03	2	8.1 13.2	0.5 0.5	6.8 11.1
0.05	2	13.2 10.8	0.5 0.5	10.8 19.4
0.07	2	9.1 19.6	0.5 1.0	16.8 25.8
0.09	2	18.1 25.2	0.5 0.5	26.4 37.1
0.11	1	9.8	1.0	22.2
0.13	2	63.3 75.1	0.5 0.5	43.8 57.9
0.15	2	40.0 7.9	1.0 2.0	59.5 20.9
0.20	2	12.5 28.9	1.0 1.0	31.7 60.3
0.25	3	29.0 (132)	1.0 (0.5, 1.0)	60.7 (88)
0.30	3	63.3 (33)	1.0 (0.5, 1.5)	87.9 (52)
0.35	11	74.1 (92)	0.5 (0.5, 2.0)	111 (59)
0.40	15	61.0 (67)	1.0 (0.5, 2.1)	108 (55)
0.45	8	70.9 (83)	1.0 (0.5, 2.0)	136 (53)
0.50	7	133 (66)	0.5 (0.5, 1.0)	186 (36)
0.55	1	82.7	0.50	87.0
0.60	3	258 (25)	0.5 (0.5, 0.5)	299 (4)

C_{max} and AUC shown as geometric mean (CV%) and T_{max} is shown as median (min, max) when appropriate.
Source: Study Report TACX, Table TACX.14.60 (corrected, May 26, 2016)

Eighteen pediatric patients aged 4.3 y to 17.9 y (median 11 y) received multiple doses of prasugrel (Part B) at doses ranging from 0.04 mg/kg to 0.12 mg/kg (0.9 mg to 9.0 mg) once daily for up to 36 days without regard to food (as ODT). The initial dose was 0.08 mg/kg dose; the dose was subsequently titrated to achieve platelet inhibition in the target range of 30% to 50%. Five patients were 2 y to <6 y, five patients were 6 y to <12 y and eight patients were 12 y to <18 y. PK samples were drawn for up to 4 hours postdose 10 to 14 days after the initial dose and 10 to 14 days after the titrated dose. (b) (4)

(b) (4)

A total of 341 pediatric patients (2.0 y to 17.8 y) were randomized into the trial: 171 to prasugrel and 170 to placebo. The median age was 10.6 years, with 67 patients 2 y to <6 y, 132 patients 6 to <12 y, 141 patients 12 to <18 y, and 1 patient 18 y. The PK analysis was conducted using 530 samples from 111 patients. **Table 7** provides a summary of the PK parameters for prasugrel-AM.

(b) (4)

(b) (4)

hours; AUC(0-4) = area under the plasma concentration versus time curve from time 0 to 4 hours postdose; C_{max} = maximum observed concentration; CV = coefficient of variation; N= number of patients; Pras-AM = prasugrel active metabolite; t_{max} = time of maximum observed concentration.

[a] Individual results reported because N=2.

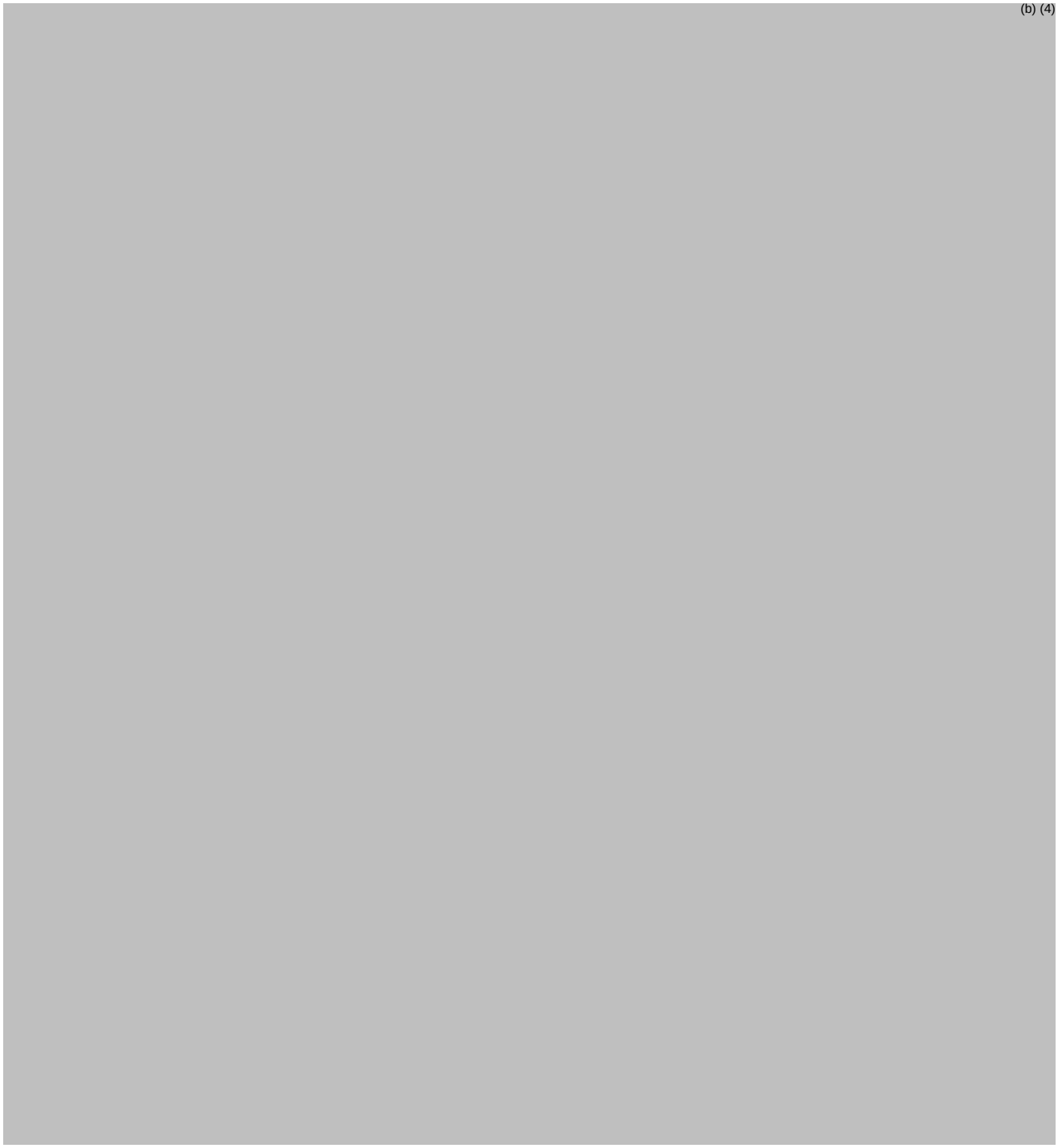
[b] Population model was simplified from a 4-compartment model.

[c] N=61. Patients 5106 and 8751 are not included in calculation of summary statistics.

Population Pharmacokinetic Analysis

A population PK model was constructed using data from Study TADO and Study TACX that included 145 patients (mean 11 y and 30 kg) and 1029 observations.

- The population model was simplified from a 4-compartment model to 3-compartment model. The Applicant states that the model developed in adults (4-compartment model) was (b) (4)
- The base model included body weight (13 kg to 81 kg) as a covariate of clearance and volume of distribution. (b) (4) (*Refer to the clinical pharmacology review of the original NDA submission*).
- Age, race, sex and concomitant hydroxyurea were evaluated as covariates in the final model. (b) (4)



2.5 What bioanalytical methods were used to assess prasugrel-AM concentrations?

Prasugrel-AM concentrations were analyzed using an LC/MS/MS method. The derivatized plasma samples were analyzed using the validated method 110886, "Determination of R138727_MP, R106583, and R119251 in Human Plasma by Turbo Ion Spray LC/MS/MS." The analytical method was described in report no. 110886VRLC_EII. It appears to be the same method used in the original NDA (*Please refer to the Clinical Pharmacology Review of the original NDA submission*).

The analytical range was 0.500 ng/mL to 250 ng/mL. Samples above the limit of quantification were diluted to yield results within the calibrated range. A 10-fold dilution was validated, extending the range to 2500 ng/mL. A linear model and $1/x^2$ weighting factor was used to estimate prasugrel-AM plasma concentrations. The calibration curves met all acceptance criteria. The stability of prasugrel-AM in human plasma under multiple conditions was adequately characterized to support the estimation of prasugrel-AM concentrations in samples collected from these two trials. The precision and accuracy of the calibrators and quality controls were within the typical prespecified range of ±15%. The assay appears acceptable to estimate prasugrel-AM plasma concentrations for these trials.

3. DETAILED LABELING RECOMMENDATIONS

The Applicant proposed to modify sections 8.4 (b) (4). The Applicant's proposed changes are noted by an underline and proposed deletions are noted by a strikethrough line. FDA agrees with the proposed changes to these sections with the exception of the inclusion of the trial name.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

<u>In a randomized, placebo-controlled trial (b) (4), the primary objective of reducing the rate of vaso-occlusive crisis (painful crisis or acute chest syndrome) in pediatric patients, aged 2 to less than 18 years, with sickle cell anemia was not met.</u>

(b) (4)

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/s/

STACY S SHORD
07/12/2016

BRIAN P BOOTH
07/13/2016

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I agree with the team's recommendation.