CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-768
Submission Date: September 3, 2003
September 30, 2003
Drug Name and Formulation: Zomig (zolmitriptan) 5 mg tablet
Sponsor: Astra Zeneca Pharmaceuticals LP, Wilmington, DE 19803
Reviewer: Andre Jackson
Type of Submission: Response to Request for Information and Review of Studies in Healthy Adolescents and Healthy Adults Between Attacks

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I.Executive Summary

A. Recommendations:

The clinical pharmacology and biopharmaceutics information submitted to NDA 20-768 is acceptable. However discussions with the medical officer indicate that based upon the pediatric study decision tree the firm will have to conduct another efficacy study for Zolmitriptan in adolescents since the current study failed.

B. Phase IV Commitments

There are no phase IV commitments from OCPB.

C. Summary of Clinical Pharmacology and Biopharmaceutics Findings

The firm has submitted three studies to address issues from a pediatric written request issued by the Agency on March 26, 1999. Issues for the written request were:
1) a safety and tolerability study in adolescents and adults
2) pharmacokinetic study (in adolescents with a history of migraine)
3) one controlled efficacy trial and a long term safety trial in adolescents and adults

The PK studies submitted by the firm to address the PK issues were:

1) zolmitriptan tablets in healthy adolescents and healthy adults between attacks (Trial 311CIL/0092)
2) zolmitriptan tablets in adult migraineurs both during and between attacks (Trial 136-007)
3) zolmitriptan nasal spray in adolescent migraineurs and adult migraineurs between attacks (Trial D1221C000004).

(b) (4)

II. Question Based Review

A. BACKGROUND: The agency had issued a pediatric written request on March 26, 1999 for Zomig tablets to be evaluated in adolescents for the treatment of migraine. A safety and tolerability study, pharmacokinetic study (in adolescents with a history of migraine), one controlled efficacy trial and a long term safety trial were requested as part of this written request. The sponsor let the FDA know that the efficacy trial conducted in adolescents (in response to the written request) failed to show any efficacy. Therefore, in light of this data, the sponsor requested a meeting to ask the agency to consider dropping the PK and long term safety trial requirements from the written request.

During the discussion at the telecon on August 15, 2002, the sponsor stated that they had conducted a long term safety trial that has just been stopped. However, it appears that they do indeed have adequate number of subjects in this trial to meet the terms of the written request from the long term safety point of view.

From a PK perspective, however, the sponsor has not yet conducted the PK study in patients with a history of migraine (during or between migraines). However, they have one PK study (#92) conducted in healthy adolescents and adults at a dose of 5 mg, which they state has been submitted to the IND (s.no.079).

It was concluded from this meeting that from a PK perspective, since the PK study has already been conducted in healthy adolescents (b) (4) assuming the study was appropriately designed, another study in adolescent patients with a history of migraine may not be necessary.

(b) (4)

B. CURRENT REVIEW

The firm has conducted three studies to assess the pharmacokinetics of zolmitriptan (b) (4)

1) zolmitriptan tablets in healthy adolescents and healthy adults between attacks (Trial 311CIL/0092)
2) zolmitriptan tablets in adult migraineurs both during and between attacks (Trial 136-007)
3) zolmitriptan nasal spray in adolescent migraineurs and adult migraineurs between attacks (Trial D1221C000004).

The studies in healthy adolescents and healthy adults (Trial311CIL/0092 and Trial 136-007) between attacks have been submitted to the FDA and are reviewed below.

1. TRIAL D1221C00004 (Nasal Spray)

This study compared the pharmacokinetics of a 5-mg dose of zolmitriptan administered as a nasal spray in adolescents and adults with a history of migraine. Although this study assessed zolmitriptan as a nasal spray, approximately 70% of the bioavailable zolmitriptan is absorbed via the gastrointestinal tract according to the sponsor thus the firm claims provides data relevant to zolmitriptan oral pharmacokinetics in adolescents. **A full clinical study report is in preparation by the firm but has not been presented to the FDA although it was mentioned in the supplement.**

To date the firm has provided some rationale as to why they should not be required to conduct the studies in the written request from the FDA based upon Trial D1221C00004 but this can not be assessed since the data has not been formally submitted for review only a summary .

2. CURRENT REVIEW-INDIVIDUAL PK STUDIES

The current review will review only the studies in healthy adolescents and healthy adults: Trial311CIL/0092; and Trial 136-007- adult migraineurs both during and between attacks.

a. STUDY : Trial 311CIL/0092

Objectives

The objectives of this trial were (a) to compare the pharmacokinetics of oral zolmitriptan 5 mg in adolescents and adults and (b) to compare the tolerability of oral zolmitriptan 5 mg in adolescents and adults.

Summary of trial design

This was a single-center, open-label, single-dose, parallel-group trial in 21 adolescent and 18 adults. A 5-mg dose of zolmitriptan was used in this trial because plasma levels of zolmitriptan

and 183C91 are more easily quantifiable at this dose than at a dose of 2.5 mg of zolmitriptan. In addition, a dosage recommendation of 5 mg will be made if the 2.5-mg dose is ineffective.

The total trial duration was approximately 40 hours. Subjects were admitted to the clinical research center (CRC) on the evening of Day 1 and received 2 tablets of 2.5 mg zolmitriptan orally on the morning of Day 2. Subsequently, plasma samples for assay of zolmitriptan and its metabolite, 183C91, were obtained at predetermined intervals for 15 hours, and safety assessments were made for 24 hours. Subjects were discharged from the CRC on the morning of Day 3 if clinically stable.

The protocol was amended once, on 18 November 1996. The original protocol called for enrollment of patients who were known to suffer migraine headaches. To facilitate recruitment, this was modified to specify the enrollment of subjects with normal histories (i.e., no history of migraines).

Methods:

Analytical : Summary of quality control results

Nominal concentration (ng/ml)	Mean (ng/ml)	SD (ng/ml)	CV %	bias %	n
0.300	0.291	0.021	7.1	-3.1	30
1.00	0.994	0.049	4.9	-0.6	30
12.0	11.9	0.56	4.7	-1.2	30

No analytical runs were rejected.

The limits of quantification for the assay method were 0.1 and 0.2 ng/ml for zolmitriptan and 183C91 respectively

Derivation of pharmacokinetic parameters

The plasma concentration-time profiles for zolmitriptan and 183C91 were subjected to pharmacokinetic analysis using the pharmacokinetic data analysis program PHASAR (a validated program written at Zeneca). Actual sample times were used for all calculations.

Terminal rate constants λz were calculated by log-linear regression of the terminal linear phase of the plasma concentration-time curves. Elimination half-lives ($t_{½}$) were calculated using the following equation; $\ln 2/\lambda z$. Cmax and tmax were determined by visual inspection of the data. AUC(0-t) was calculated using the linear trapezoidal rule. The AUC was determined by extrapolation of AUC(0-t) using λz

Statistical analysis and presentation of data

Pharmacokinetic parameters for zolmitriptan and 183C91 were log-transformed and analyzed by analysis of variance (ANOVA), using age group as the only factor, to calculate 90% confidence intervals (CI) of the geometric mean ratio of adolescent to adult for each parameter. Mean and standard error (SE), median, and range were determined for all parameters. Each summary parameter was derived for the following subgroups: adolescents, female adolescents, male adolescents, adults, female adults, male adults.

For each group, least-squares means using an ANOVA model on the log-transformed data were calculated, using age group as the only factor. A 90% confidence interval was then calculated on the basis of the ratio of least-squares means.

Results:

Demographic characteristic	Age group	
	Adolescents	Adults
Number of subjects exposed	21	18
Age (y)		
n	21	18
Mean	14.5	39.1
SD	1.5	12.9
Min	12	18
Max	17	65
Age distribution (number of subjects)		
12-15 (%)	15 (71)	0
16-17 (%)	6 (29)	0
18-30 (%)	0	5 (28)
31+ (%)	0	13 (72)
Sex (number of subjects)		
Female (%)	13 (62)	12 (67)
Male (%)	8 (38)	6 (33)
Weight (kg)		
n	21	18
Mean	61.2	73.9
SD	13.6	15.2
Min	37.3	51.7
Max	92.3	103.0
Race (number of subjects)		
White (%)	20 (95)	15 (83)
Black (%)	0	2 (11)
Other[a] (%)	1 (5)	1 (6)

[a] Other includes Asian, Hispanic.

Figure 1. Mean adolescent and adult zolmitriptan plasma levels following the 5 mg oral dose. Table below figure contains the mean pharmacokinetic parameters.

Table 1. Pharmacokinetic parameters for zolmitriptan geometric mean ratio of values for adolescents and adults.

Conclusions:

b. STUDY: Trial 136-007 –Adults with history of migraine

OBJECTIVES

In male and female patients:

- to obtain a preliminary indication of the efficacy of an oral dose of 10 mg 311C90 as an acute treatment for migraine;
- to investigate the tolerability to an oral dose of 10 mg 311C90;
- to compare the absorption of oral 311C90 during and between migraine attacks;
- to explore the relationship between plasma concentrations of 311C90, the active metabolite 183C91, efficacy and adverse experiences.

Methods

General

This was an open, non–randomised, 2–period study in 20 male and female migraine patients aged 18–55 years. Following a medical screen at which the study was explained and written, informed consent was obtained, eligible patients were instructed to return to the clinic with their next migraine headache of moderate to severe intensity. The duration of headache and presence of preceding aura were recorded and patients received a single 10 mg dose of 311C90 with water.

The severity of the headache was assessed on a verbal 4 point scale: 0 = no headache, 1 = mild, 2 = moderate, 3 = severe. Headache severity along with the presence/absence of photophobia, phonophobia, nausea and vomiting were assessed predose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3 and 4 hours post–dose. Escape medication (not ergotamine or sumatriptan) was offered at 2 hours if the response was unsatisfactory.

3.2.1 ***Selection of Dose***

A single 25 mg dose of 311C90 had already proved efficacious in a previous open study. By comparison with plasma concentration data and information on the potency at 5HT receptors of sumatriptan, a 10 mg dose 311C90 was also expected to show efficacy. If after treating 5 patients there was no apparent efficacy, it was planned that the dose would be increased to 15 mg and then to 20 mg. However, this was not necessary and all 20 patients received a dose of 10 mg.

Special Inclusion Criteria:

At the study screen, patients must:

- have had a diagnosis of migraine with or without aura which met the criteria set by the International Headache Society (Cephalalgia 1988:8 (Suppl 7);1–98) (see Appendix A1);
- have been aged 18–55 years on the day the screen was performed;
- have had a frequency of migraine attacks averaging 1–6 per month for the 3 months prior to the screen;

Special Exclusion Criteria:

- could not distinguish interval headaches from migraine without aura;
- had interval headaches that were on average more frequent than 5 days per month in each of the past 3 months;
- had migraine which in the past had consistently failed to respond to treatment;
- had participated in more than two therapeutic trials for the treatment of migraine;
- regularly vomited early in the migraine attack;

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5.2 Drug Administration and Dosages

Patients received a 10 mg dose (2 x 5 mg tablets) 311C90 with 200 mL water on two occasions (during a migraine and outside a migraine).

Plasma samples were taken at :0, 0.25, 30, 0.75, 1, 1.5, 2, 3 and 4 hrs post dose

Pharmacokinetic
Analysis

Median values for plasma concentration and pharmacokinetic parameters were calculated as there was a wide spread of values with a large number of non-quantifiable concentrations at each time point. A summary was made for the parameters (0–2 hours and 0–4 hours) by compound and study occasion. Non-parametric techniques were used to compare study occasions 1 and 2. Individual differences between first and second study occasions were estimated and the median difference along with 95% confidence intervals were calculated using a method based on the Wilcoxon Signed-Rank test. Individual plasma concentration-time plots were produced for each patient for both occasions and median plasma concentration-time plots, with ranges, were produced for each analyte.

AUC_{0-2} and $C_{max\ 0-2}$ were summarised for those patients who did and did not have a reduction in headache severity within 2 hours.

Analytical:

Sample analysis was undertaken during 21 December 1993 – 17 June 1994, the analysis comprised of two batches of work (21 December 1993 – 19 January 1994 and 10 June 1994 – 17 June 1994). Hence the quality control data are summarised for each of these periods tables marked (i) and (ii) respectively. Calibration data for the period 21 December 1993 – 19 January 1994 were not summarised as there were insufficient data at one set of calibration weighings.

Table 2.Quality control data for the determination of 311C90 in human plasma.

Assay No.	Actual Concentration (ng/ml).					
	16.56		82.8		165.6	
		% Difference		% Difference		% Difference
LC2696B	17.8	7.5	BI	_	195.3	18.7
	18.7	12.9	76.5	–7.6	163.3	–0.6
LC2722B	16.9	2.1	89.8	8.5	180.2	–8.9
	16.7	0.8	83.8	1.2	168.7	2.7
LC2728B	14.9	–10.0	88.1	6.4	167.8	2.1
	16.2	–2.2	85.1	2.8	167.6	2.0
LC2734B	14.5	–12.4	86.8	4.8	155.8	–5.2
	17.3	4.5	90.4	9.2	174.6	6.3
Mean	16.6		85.8		171.7	
Std Dev	1.41		4.73		11.96	
%CV	8.5		5.5		7.0	
%Bias	0.4		3.6		3.7	

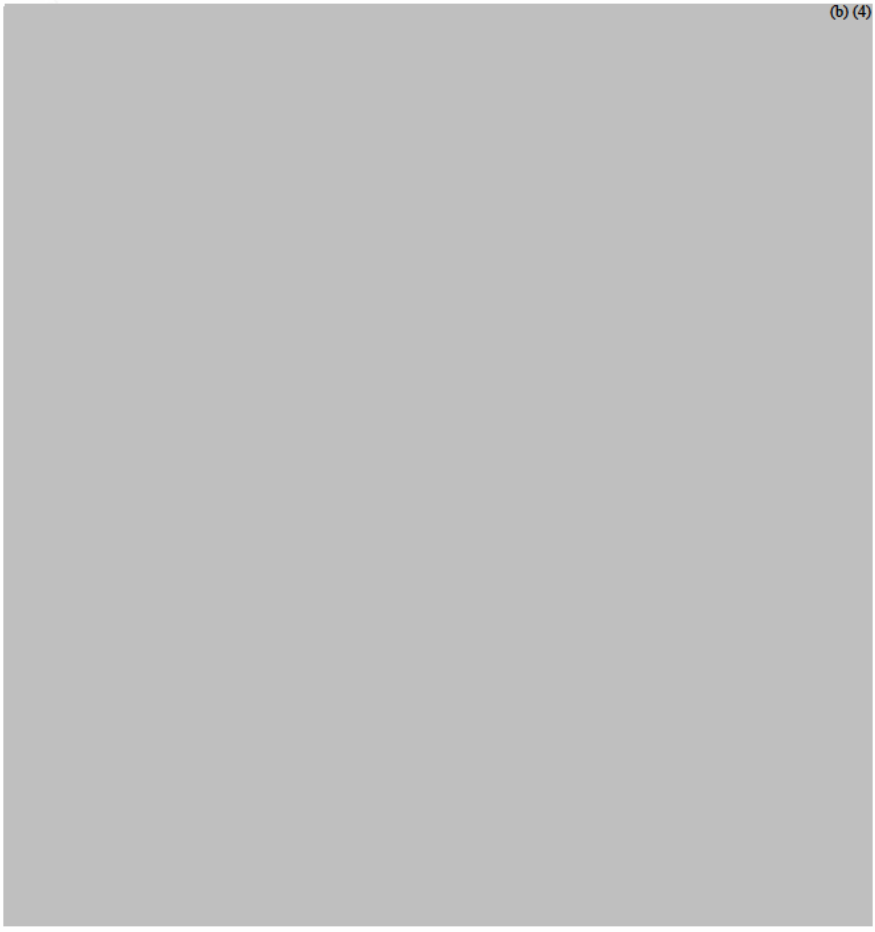
The limits of quantification for 311C90 is 2 ng/ml.

Results: Demographic data

Sex:	Female	16
	Male	4
Age (years):	N	20
	Mean	38
	SD	9.2
	Median	40
	Min	22
	Max	50
Height (cm):	N	19
	Mean	171
	SD	8.9
	Median	170
	Min	152
	Max	186
Weight (Kg):	N	20
	Mean	69
	SD	13.5
	Median	70
	Min	50
	Max	102

Figure 1. Zolmitriptan plasma concentrations

Table Summary of Cmax and AUC values


(b) (4)

7.3 Pharmacokinetics

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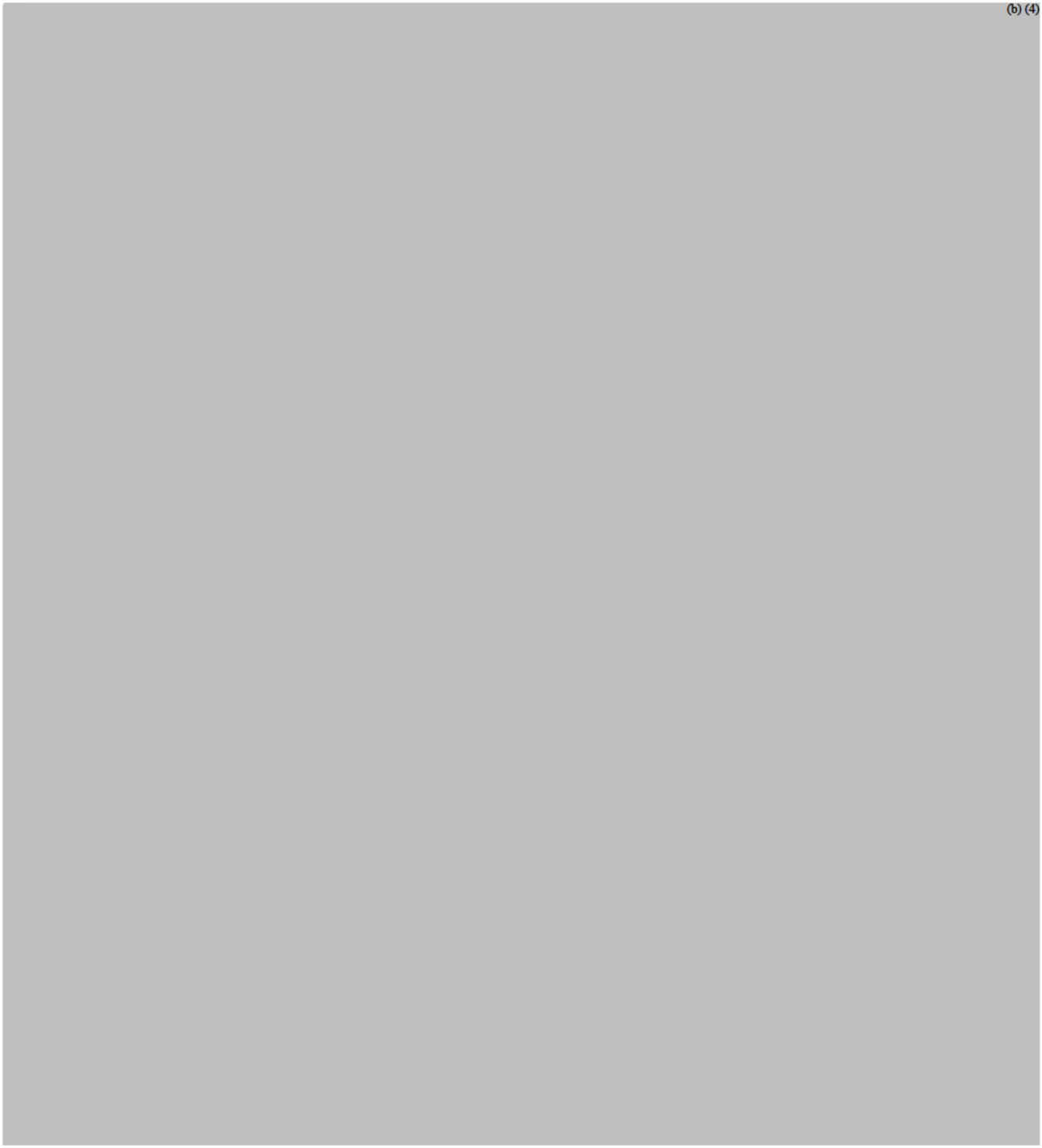

Conclusions;

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Comments:

1. (b) (4) OCPB is providing labeling text below..

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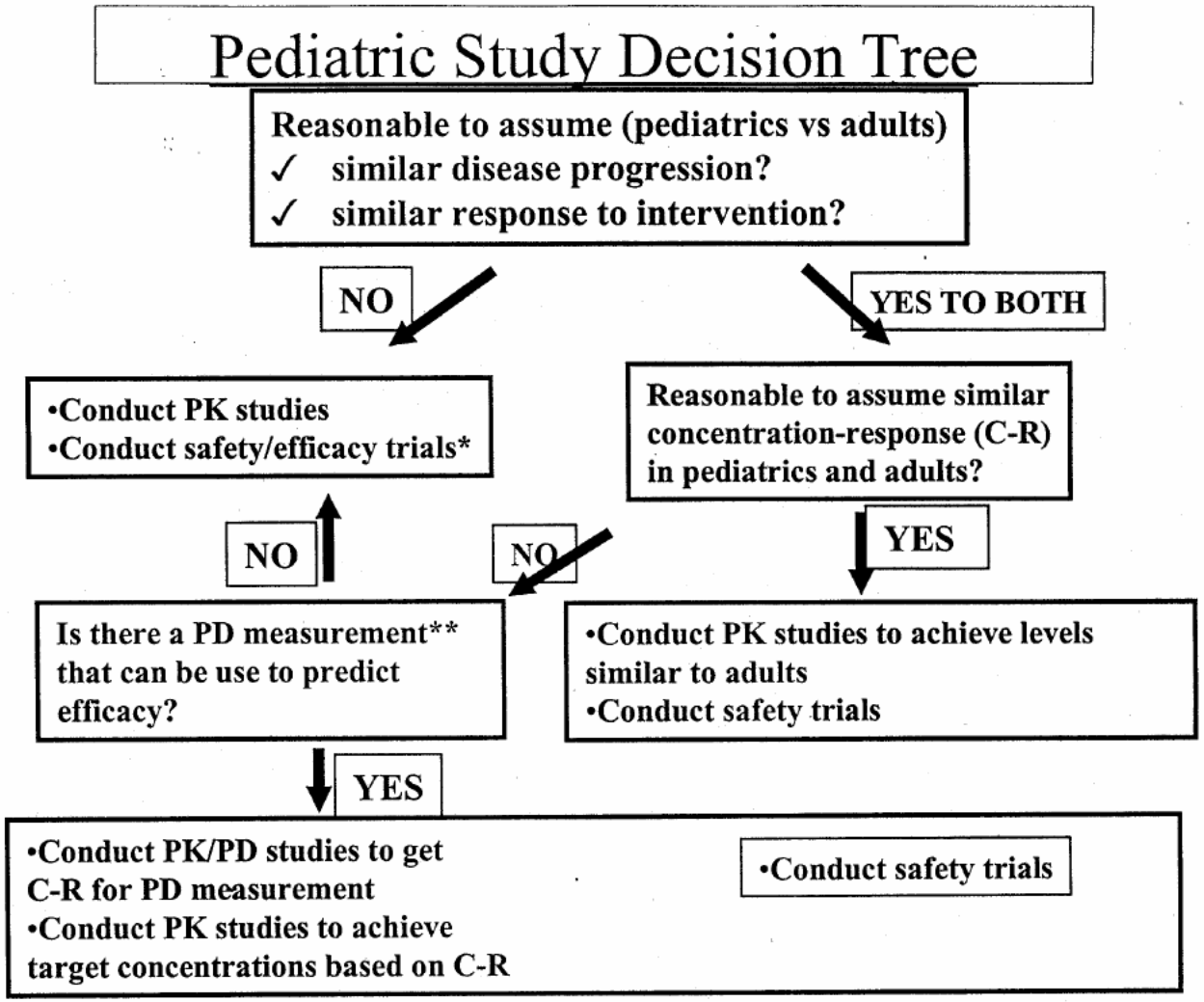
III. Decision Tree

Pediatric Study Decision Tree



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IV. OCPB LABEL RECOMMENDATION:

Please include the following in the Clinical Pharmacology/Pharmacokinetics, Special Populations/Age section of labeling.

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Andre Jackson_____

RD/FT Initialed by Raman Baweja, Ph.D._____

Cc-NDA 20768, HFD-860(Jackson, Baweja, Sahajwalla, Mehta), Central Documents Room(Biopharm-CDR)

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