CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Summary of Pharmacometrics Review

NDA 20-584
Drug Name: Lodine® XL (etodolac capsules and tablets)
Sponsor: Wyeth-Ayerst
Submission Date: Oct. 11, 1999
Primary Reviewer: Dennis Bashaw, Pharm.D.
Pharmacometrics Scientist: Dan Wang, Ph.D.

The sponsor requested a "Written Request" for the conduct of a clinical trial of Lodine® XL in pediatric patients with juvenile rheumatoid arthritis (JRA) on July 15, 1998. Based upon the "Written Request" letter, the following two studies were submitted:

> "A 12-week, open-label study of etodolac administration in patients with juvenile rheumatoid arthritis, including an optional 8-week extension."
> (Clinical study report-CSR 37670 of protocol 0654D1-386-US)

The pharmacokinetic (PK) parameters for the JRA patients treated in this open-label trial were compared with the PK results from adult RA patients as follows:

> "Population pharmacokinetic analyses of etodolac in patients with active rheumatoid arthritis and in patients following oral surgery."

The clinical aspect of the studies has been reviewed by the Medical Officer. This review will focus on the pharmacokinetic aspect of the studies.

Study 37670 of protocol 0654D1-386-US

Objectives

The primary objective of this protocol was to examine the safety profile in pediatric patients with JRA after treatment with Lox for the initial 12-week open-label portion. The secondary objective was to evaluate the efficacy and PK of Lox in these same patients as well as characterize the safety and efficacy of Lox in JRA patients who participated in the 8-week open-label extension.

Study design

This was an open-label, multicenter, 2-segment outpatient study with pediatric patients who had JRA. Segment I included a ***12-week*** open-label treatment period and segment II was an optional, up to ***8-week extension*** of the open-label treatment, for those patients who had completed segment I. See detailed study design in medical review. Patient demographic information is summarized in Table 1. The age distribution is shown in Figure 8 in appendix.

Table 1: Demographic and Baseline Characteristics of Patients by Age Group

Characteristic	Age < 12 yr. (n=31)	Age ≥ 12 yr. (n=41)	Total N=72
Age (mean ± SD)	8.6± 1.5	13.8± 1.4	11.5± 2.9
Sex, n (%)			
Female	22 (71)	27 (66)	49 (68)
Male	9 (29)	14 (34)	23 (32)
Race, n (%)			
Black/Hispanic/Asian/Other	9 (29)	14 (34)	23 (31)
White	22 (71)	27 (66)	49 (68)
JRA diagnosis, n (%)			
Pauciarticular	17 (55)	15 (37)	32 (44)
Polyarticular	11 (35)	23 (56)	34 (47)
Systemic	3 (10)	3 (7)	6 (8)
Asthma history			
No	28 (90)	34 (83)	62 (86)
Yes	3 (10)	7 (17)	10 (14)

Lodine® XL was administered orally at a dosage based on body weight, 13.3-21.3 mg/kg, once daily as follows:

400 mg tablet x 1 (white label)	**20-30 kg**
600 mg tablet x 1 (yellow label)	**31-45 kg**
400 mg tablet x 2	**46-60 kg**
500 mg tablet x 2 (green label)	**>60 kg**

There were 41 patients that received Lodine® XL for more than 84 days.

Pharmacokinetic samples (***consisting of one 3-mL blood sample***) were collected at baseline and during the week 2, 4, 8 and 12 (or final) study visits for analysis of etodolac concentrations utilizing [redacted] It was noted that since patients did not always attend visits as scheduled, blood samples were also not always obtained as scheduled. For example, plasma samples for PK analysis were obtained from only 4 patients at week 12.

Assay

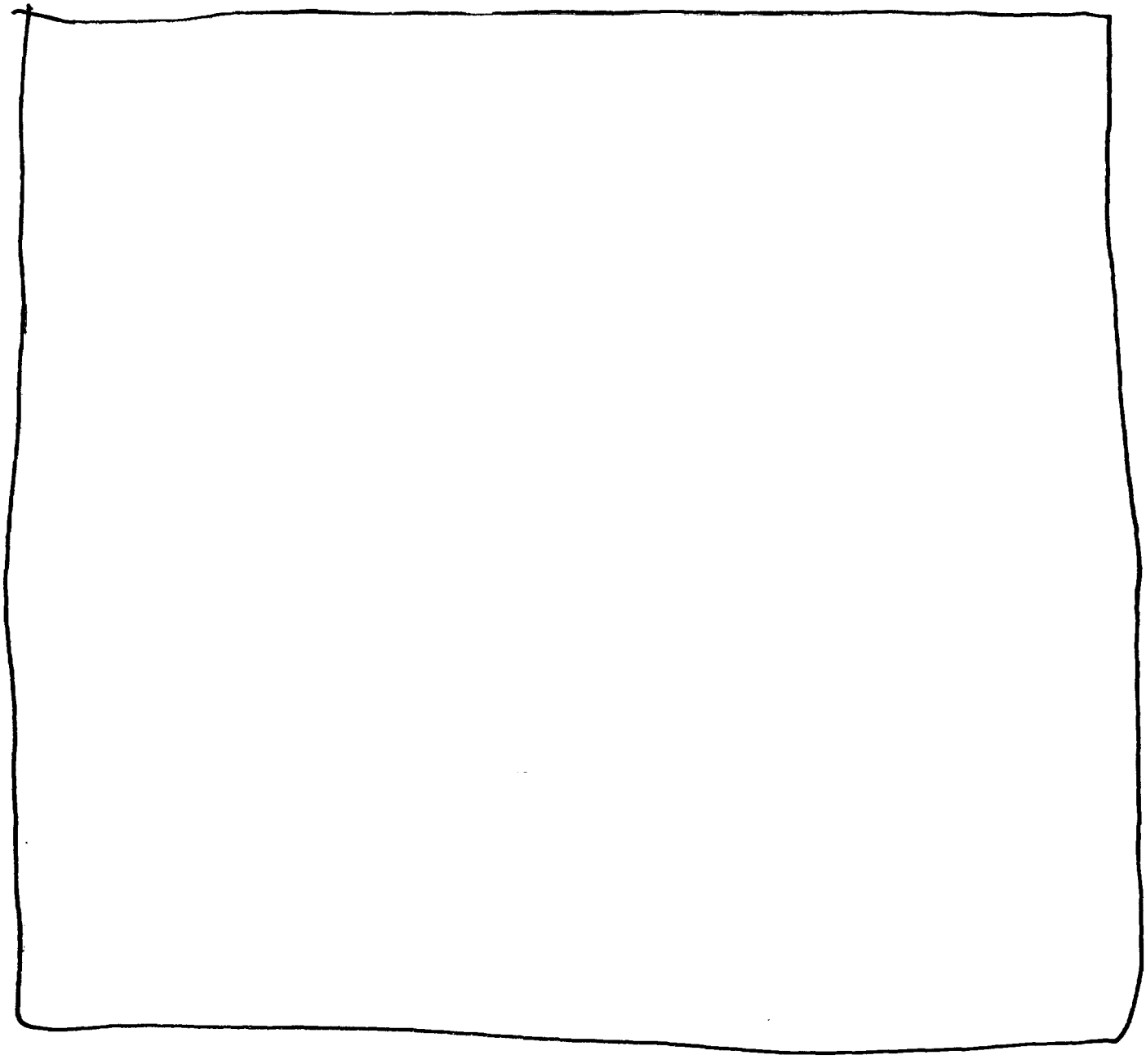
[redacted]

Results

Seventy-two (72) patients were enrolled into segment I and 59 completed. There were then 13 patients that subsequently enrolled in segment II and 6 completed. A total of 139 observations of study drug concentration in plasma obtained from 59 patients were

included in the analysis. Plasma concentrations below the limit of quantitation were not included in the data set. Therefore, on average there were 2.4 samples from each subject and they were taken on different visits. All the data were treated as steady-state levels during the analysis.

Data Analysis Methods



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Objectives

The primary objective of this analysis is to characterize the pharmacokinetics of etodolac in patients with rheumatoid arthritis (RA). The secondary objective is to determine whether patients with RA have the same pharmacokinetic disposition for etodolac as patients without RA who receive etodolac after oral surgery.

Dosage and Administration

Study 0654D1-376-US was a 2 period, randomized, crossover, double-blind, multicenter study. Etodolac extended release (ER) (1000 mg once a day) or etodolac immediate release (IR) (500 mg twice a day) was administered for 3 weeks to patients with RA who were either male or female and at least 18 years of age. A crossover design was used to reduce the influence of interpatient variability. After the crossover segment there was a 1-week period of single-blind treatment with placebo. Next, the patients entered an open-label phase and took 1000 to 1200 mg of etodolac ER once a day for up to 1 year. Plasma samples taken in this study are all steady-state levels.

Study 0654D1-355-US was a double-blind comparison study of etodolac ER and etodolac (200 or 400 mg) in patients who had had oral surgery. Patients received a single dose of either 400 or 1200 mg of etodolac ER (given at baseline), or 2 doses of either 200 or 400 mg of conventional etodolac (given at baseline and at 8 hours), or placebo (given at baseline and at 8 hours). Patients were either male or female and at least 18 years of age.

Patients included in the population pharmacokinetics analysis in study 0654D1-355-US received either 2 doses of etodolac IR (200 mg or 400 mg), or a single dose of etodolac ER (400 mg or 1200 mg). When combined with the data from study 0654D1-376-US, the data set collectively contained 535 observations derived from 240 patients, of which 97 observations were derived from 53 patients with RA. On average, there are 2.2 samples per subject. Of this combined data set, an INDEX data set was formed by randomly selecting 80% of all observations. The INDEX data set was used for all model development activity. The remaining 20% of observations comprised the VALIDATION data set utilized in validation of the model.

Data Analysis

The population pharmacokinetics analysis was conducted in 2 steps by the sponsor. Step 1 involved model development by using data from study 0654D1-376-US (P376, RA patients alone). Step 2 involved model development by using combined data from studies P376 and 0654D1-355-US (P355, patients following oral surgery), as well as the final model validation procedure. A flow scheme of the steps taken during analysis follows:

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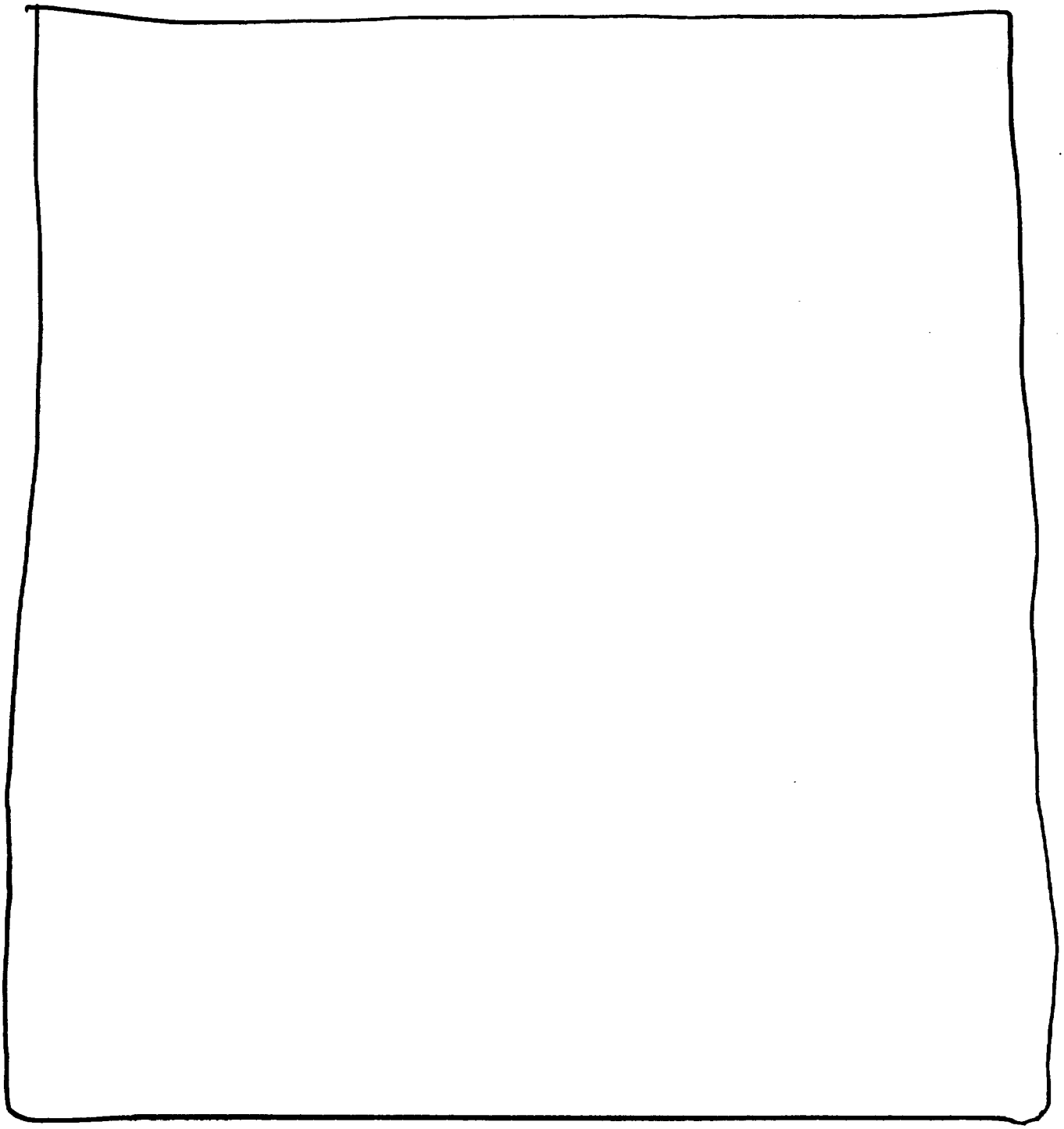

These plots showed the high variability of the data. The same variability has been seen in oral surgical patients. It should also be noted that the samples taken are very sparse (2.2 per subject) and obtained after different doses, and some after single dose (oral surgical patients), some after multiple doses (RA patients). All these factors raise the concern about the quality of the population PK parameter estimate in this population. Same concern applies to pediatric population PK analysis. The reviewer therefore requested

the sponsor to provide CL and V values obtained from intensively sampled healthy subjects (oral surgical patients can be considered healthy subjects from PK point of view). The following is the comparison of PK parameters.

	CL (ml/h/kg)	V (ml/kg)
Health subject (dense data)	46.8 (CV= 37%)	566 (CV= 26%)
Current analysis (sparse data)	38.2 (CV = 5.4%)	244 (CV = 3.1%)

As seen in the comparison, CL from current analysis is about 20% less and V is less than half of what obtained from dense data. This suggests that population PK parameters obtained from this analysis may not be reliable.

In the pediatric study, similar sampling scheme was used with even much fewer patients in the study. The reviewer believes that no statistical comparison can be made on pediatric and adult PK based on the studies submitted.

Conclusions

1. The sponsor indicated that adjustment of doses based on body weight adjustment might not be necessary for patients with JRA. However, based on reviewer's analysis, body weight was a significant covariate of clearance for those whose body weight is less than 50 kg in JRA patients (6 to 16 years). Therefore, dosing of Lodine® XL for children less than 50 kg should be based on body weight as it has been done in the pediatric clinical trial.

2. Pharmacokinetics of etodolac in RA adult patients is similar to that in healthy adult subjects.

3. Comparison of pharmacokinetics of etodolac in children and adults can not be made based on the studies submitted.

/S/ 8/8/2000

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