CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S003

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 20-584 (SE2003) SUBMISSION DATE: 11/12/97, 1/29/98
4/5/98

PRODUCT: Lodine™ XL, 1200 mg (Etodolac)

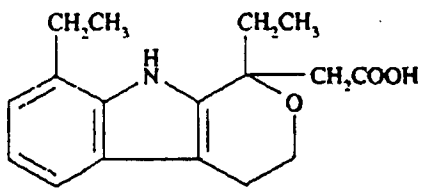
SPONSOR: Wyeth-Ayerst
Philadelphia, PA 19101 REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA Supplement

Background

Wyeth-Ayerst submits this supplement to the NDA 20-284 to gain approval to the change in the recommended daily dose of Lodine XL (etodolac extended release tablets) from 400-1000 mg daily to 400-1200 mg daily, similar to that allowed for the immediate release formulation. Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory and analgesic activities. Etodolac extended release has been available in 400 and 600 mg tablets since October 1996 under the trade name of Lodine XL. The immediate-release form of etodolac is marketed in the United States under the tradename Lodine® since 1991. It has been available in 200 and 300 mg capsules and 400 mg tablet forms. In June 1996, 500 mg tablets of Lodine was also approved. At the time of NDA approval, Wyeth-Ayerst agreed to provide the division as post-approval commitment with safety data from at least 300 patients treated with Lodine XL for at least 6 months at 1200 mg/day. This submission is their completion of the post-approval commitment.

The chemical name is (±) 1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b]indole-1-acetic acid and it has the following structural formula:



Etodolac is a racemic mixture of R- and S-etodolac. It has been demonstrated in animals that the S-form is biologically active and R- is not. Both enantiomers are stable and there is no R-to-S conversion in-vivo.

Lodine XL is indicated for the management of the signs and symptoms of Osteoarthritis.

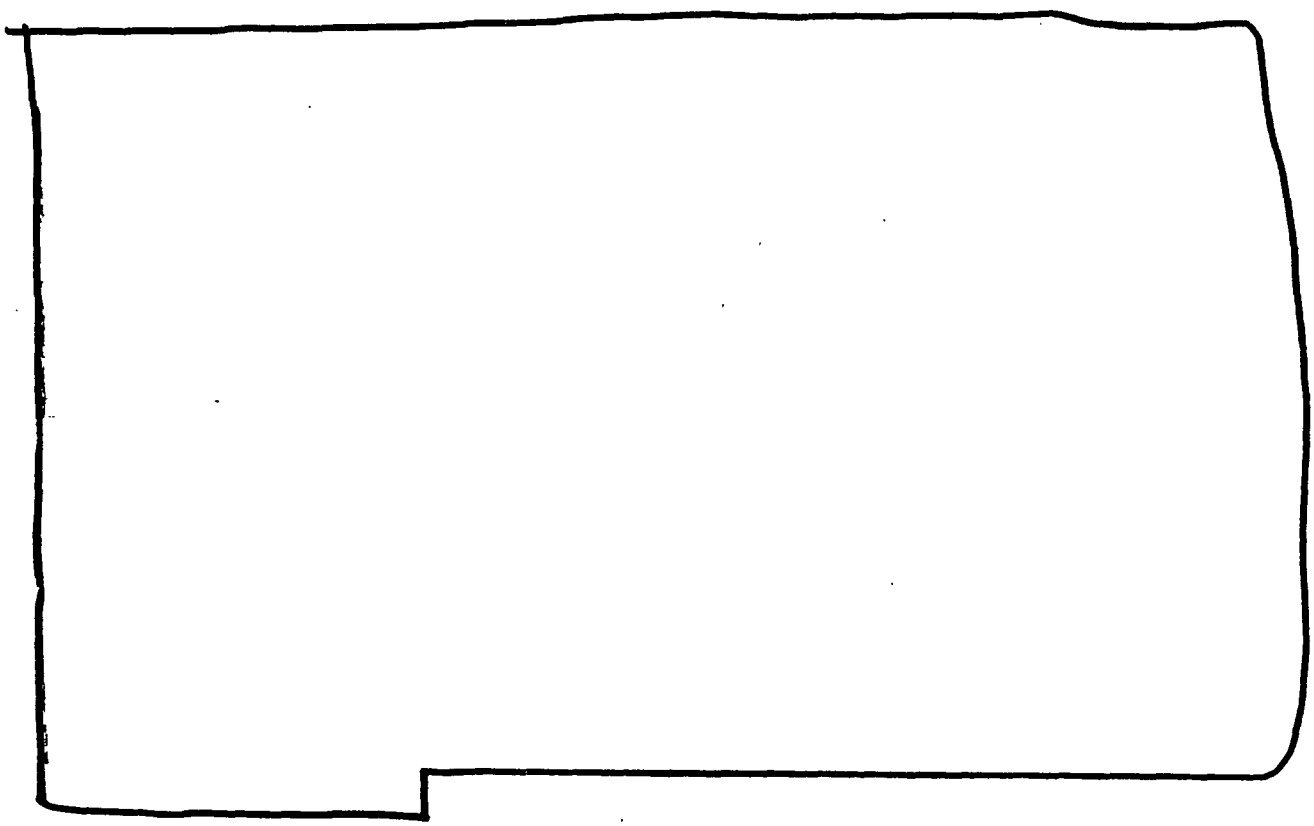
Recommendation

The bioavailability of etodolac given as Lodine XL results in etodolac plasma concentrations that are comparable to those of the immediate release formulation at equivalent daily dosing. This submission is the post approval commitment to demonstrate safety at the 1200 mg dose of Lodine-XL. There was a high drop out rate (86%) in the pharmacokinetic/pharmacodynamic study submitted. The appropriateness of the indirect response model in assessing the PK-PD relationship of etodolac cannot be evaluated due to the limited number of subjects. However, the analysis is not critical to the approvability of this submission. Hence, it is approvable from the standpoint of clinical pharmacology and biopharmaceutics.

Pharmacokinetics/Pharmacodynamics

The population pharmacokinetic analyses have been performed on data from 499 patients who received etodolac ER in two clinical studies (654D-355 and 654D-323). To investigate whether OA patients with more severe symptomology benefited from the increased daily dose of 1200 mg, two sub-grouped analyses of pooled data sets were performed.

Analytical Validation



Study Title

A double-blind comparison of the analgesic efficacy and safety of etodolac sustained release, etodolac conventional formulation and placebo in patients following oral surgery (Protocol No: 064D-355-US).

Objective

- The primary objective was to compare the analgesic efficacy and safety over a 24-hour period of an extended-release formulation of etodolac (etodolac ER), the conventional formulation of etodolac, and placebo in patients following oral surgery.

- The secondary objective was to evaluate the relationship between analgesia and plasma etodolac concentrations. Patients received a single dose of either 400 or 1200 mg of etodolac ER (given at baseline), or two doses of either 200 or 400 mg of conventional etodolac (given at baseline and at 8 hours), or placebo.

All treatments were administered in a double-blind fashion so that each patient would receive a dose at baseline and at 8 hours. Patients who took rescue medication (name not specified) before hour 8, did not receive the second dose of the study drug.

Duration of Treatment

The duration was ten hours of assessments on site. After on-site evaluations, patients used a diary card for evaluation at 11, 12, and 24 hours or just before administration of rescue medication.

Study Population

Planned 250 patients; enrolled and provided data for safety analysis, 237; Valid-for efficacy, 231; provided data for pharmacokinetic analysis, 187. The demographics is attached in the appendix on page 13. The number of patients who withdrew from the study is tabulated below.

Number(%) of patients who withdrew from study, all reasons[a]

Reason for Withdrawing	Etodolac ER 1200 mg (n = 48)	Etodolac ER 400 mg (n = 49)	Etodolac 400 mg (n = 46)	Etodolac 200 mg (n = 47)	Placebo (n = 47)	Total (n=237)
Any reason	39 (81)	43 (88)	39 (85)	39 (83)	43 (91)	203 (86)
Adverse reaction	0	1[b] (2)	0	1 (2)	1 (2)	3 (1)[b,c]
Lack of efficacy	38 (79)	40 (82)	39 (85)	39 (83)	42 (89)	198 (84)[d]
Protocol violation	1 (2)	3 (6)	0	0	1 (2)	5 (2)[e]

[a] Patients may have had more than one reason for withdrawal.

[b] Primary reason; this patient (No. 355-001-0250) also appears under Protocol Violation (secondary reason).
[c] Primary reason; this patient (No. 355-001-0212) also appears under Protocol Violation (secondary reason).
[d] For one of these patients, (No. 355-001-0204) this was the primary reason; this patient also appears under Adverse Reaction (secondary reason).
[e] For one of these patients, (No. 355-001-0090) this was the primary reason; this patient is also included under Lack of Efficacy (secondary reason).

Efficacy assessment methods

Efficacy as measured by pain intensity, pain relief (PR), and pain half-gone, was evaluated at 15, 30, 45, 60, 75, 90, and 105 minutes and 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, and 24 hours after ingestion of the study drug. Time to meaningful relief was measured from the first dose. Patients provided a global assessment at the time of study completion or withdrawal. Patients who took rescue medication before 2 hours were replaced or in other words all subjects had to provide pain ratings for the first 2 hours. The efficacy variables are attached in the Appendix on page 12.

The following extrapolation rules were used:
- After 10 hours, if the patient was missing one or more consecutive observations either before administration of rescue medication without the final observation or up to the end of the study without having taken rescue medication, the last observation was used to replace this missing value.

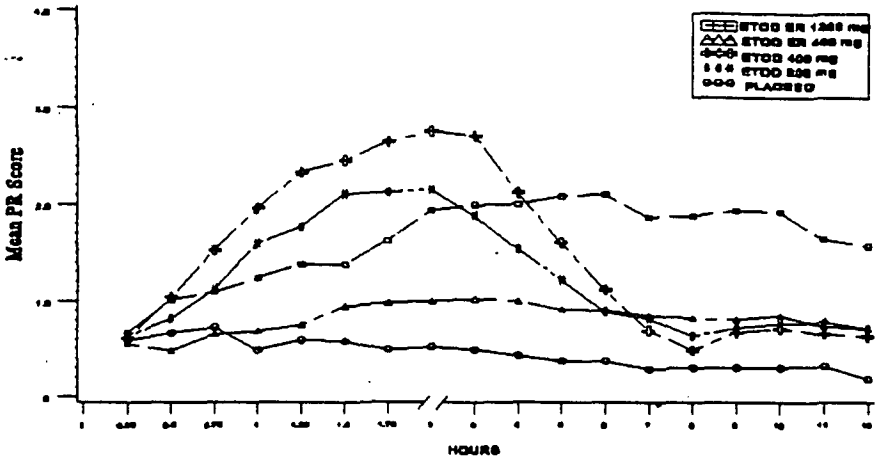
- Data missing between two observations were replaced with linear interpolations.

- If a patient took rescue medication before the end of the timed rating period, the baseline-observation-carried-forward (BOCF) method was used to extrapolate the remaining data.

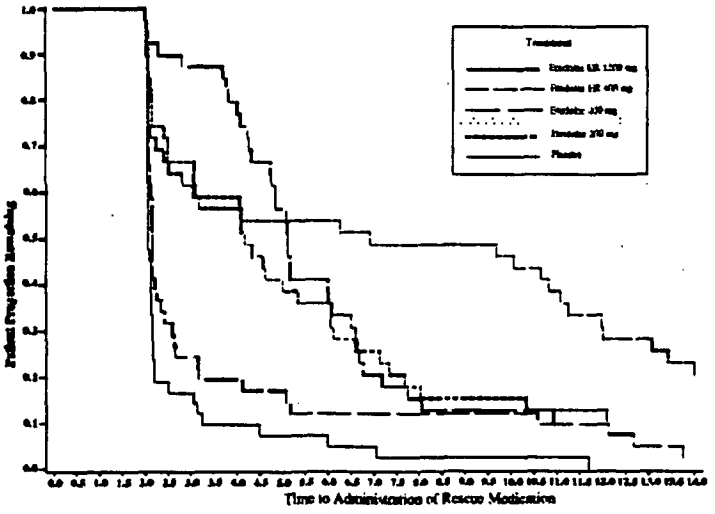
Statistical methods

The clinical efficacy variables included PR, pain intensity difference (PID), and a combined score of PR + PID (PRID). Summed PID (SPID), total pain relief (TOPAR), and PRID (SPRID) scores were computed at various time points (i.e., 3, 8, 12, and 24 hours) by using the trapezoidal rule. Treatment comparisons for each variable were assessed by using analysis of variance (ANOVA), nonparametric analysis, or categorical analysis as appropriate. Occurrence rates for study events were analyzed by using Fisher's exact test to assess and compare the relative safety of the study treatments. The hourly pain relief from different regimens and the duration of analgesia is shown in the following figures.

HOURLY MEAN PR
(Extrapolated)



ESTIMATED DURATION OF ANALGESIA
(Time in hours to administration of rescue medication)



The duration of analgesia has been determined from the time (hours) to administer rescue medication.

Population Pharmacokinetic analysis

A population pharmacokinetic approach was used to evaluate the concentrations of etodolac in patients experiencing post-surgical dental pain in study 654D-355-US, and in patients with osteoarthritis in study 654D-323-US. The latter study was submitted in the

full NDA for Lodine-XL. Details have not been provided in this submission. The data from this study has been re-evaluated in this submission using the indirect response model. The population pharmacokinetic analysis of Lodine was performed using a one compartment pharmacokinetic model with first order absorption.

$$C(t)=\frac{F\cdot Dose\cdot k_a}{V\cdot(k_a-K)}\cdot\frac{1-e^{-n\cdot K\cdot\tau}}{1-e^{-K\cdot\tau}}\cdot e^{-K\cdot t'}-\frac{1-e^{-n\cdot k_a\cdot\tau}}{1-e^{-k_a\cdot\tau}}+\varepsilon$$

In this equation, C(t) is concentration as a function of time, V is the apparent volume of distribution, F is the unknown absolute bioavailability, k is the first-order elimination rate constant, k_a is the first-order absorption rate constant, t' is elapsed time since the n^{th} dose was given, and τ is the dosing interval of 8 hours. The term ε is the random variable describing residual error in the model.

For patients receiving Lodine XL, the simplified version of this equation describing first-order absorption and one compartment disposition was used:

$$C(t)=\frac{F\cdot Dose\cdot k_a}{V\cdot(k_a-K)}\cdot\left[e^{-K\cdot t}-e^{-k_a\cdot t}\right]+\varepsilon$$

The population pharmacokinetic data resulting from this analysis is shown in the table below.

Study	Doasge Form	N	Cl/F (L/h)	V/F (L)	Ka (hr-1)	ηcl (L/h)	ηv (L)	ε
654D-335	ER	95	3.36(13)	18.6 (55.4)	0.134 (54.62)	-	0.559(23)	0.513[a] (13)
	IR	92	3.01(12	14 (6.8)	2.3 (34)	0.10 (32)	0.28 (53)	0.14 (37)
654D-323	ER	314[c]	2.52 (30)	27 (-)	0.19 (71)	0.10 (32)	-	5.0[a]

a: intra-individual residual error estimated using a proportional error model
b: intra-individual residual error estimated using a combined additive and proportional residual error model.
Cannot be directly compared to ε from proportional error model.
c: average weight = 90 kg; average age = 64 years
Values in parentheses represent % coefficient of variation.
--not determined

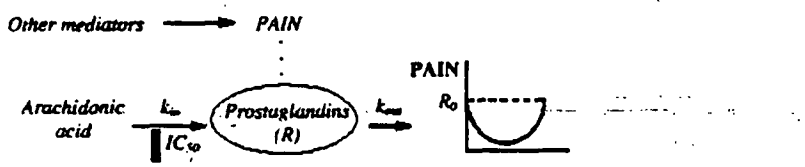
Reviewers' Comments

The parameters for study 654D-355 have been reported from a reanalysis of the pharmacokinetic and pharmacodynamic results by the sponsor on the reviewers' request. Upon looking at the raw data set the reviewer had observed that the data set had several patients who had apparently received a second dose of Lodine XL eight hours after the first dose. There were no provisions in the protocol for a second dose of extended-release etodolac, which called into question the results of the analysis. Without admitting responsibility the sponsor indicated that this was due to the SAS program used to prepare the NONMEM data set. The program contained an error that inadvertently input a dose for all patients that received Lodine-XL who remained in the study until the 10 hour observation point. The sponsor looked into the error in the data set and

performed a reanalysis. Most parameters from the reanalysis remained the same, with the exception of volume of distribution, which decreased from 24.3 L/hr to 18.6 L/hr. The table comparing the results from the old and new analysis is attached in the Appendix on page 16.

It is interesting to note here that there were only 12 subjects that had data until the 10 hour observation point and in the original data set all these 12 subjects showed a dose at 8 hours. It was also pointed out to the sponsor that some of these subjects has a very significant rise in the plasma concentrations at the 10 hour observation point, which could be very consistent with a second dose. However, some of these subjects showed a rise at 2 hours, followed by a decrease in 6 hours and again arise at 10 hours. The sponsors explanation to this was that the Tmax for Lodine-XL is typically 6.9±3.3 hours. It should be kept in mind that had these 12 subjects not been there, the entire PK-PD analysis for sustained pain relief up to 10 hours (50% of Imax) and pain relief up to approximately 20 hours (20% of Imax) would not be valid (see analysis on page 9)

Population PK-derived C(t) values shown in the Appendix on pages 17 and 18 (Figures B.1 and B.2) from the oral surgery pain study were coupled with mean, placebo-corrected transformed PID (PAIN) scores to evaluate the PK/PD relationship using an indirect response model which will now be described briefly. The basic premise of the indirect response model is that a measured response (R) to a drug is not caused by an immediate action of the drug but by some indirect mechanism. Factors controlling the onset or offset of R may be either inhibited or stimulated. The schematic model describing the inhibition of k_{in} (indirect response) is shown in the graphic below.



For etodolac, the amelioration of pain is thought to involve the inhibition of prostaglandin synthesis. The onset of response (k_{in}) is assumed to be a zero-order rate process while the dissipation of response (k_{out}) is assumed to be a first-order rate process. R_0 denotes the baseline response, which was assumed to be 3, consistent with the maximum PAIN score possible. Mathematically, these parameters contribute to the rate of change in R by the relation:

$$\frac{dR}{dt} = k_{in} \cdot I(t) - k_{out} \cdot R_0$$

and I(t) denotes the classical inhibitory function:

$$PAIN = 1 - \frac{FR \cdot C_p(t)^{\gamma}}{C_p(t)^{\gamma} + IC_{50}^{\gamma}}$$

FR denotes the fraction of maximum possible inhibition of I_{max}, γ is the coefficient describing sigmoidicity (also known as Hill ccefficient), and IC_{50} represents the concentration of drug providing 50 % of maximum inhibition. Partial inhibition can be accommodated in the model by setting FR to a value less than 1.

The results of the PK/PD analysis using the indirect response model are shown in the Table below. The data from Lodine administration could not be adequately described by the model, as estimates of the parameters were highly correlated.

	I_{max} [a] (PID units)	k_{in} (h^{-1})	IC_{50} (mg/L)	k_{out} (h^{-1})	γ
FR = 1.0					
200mg etodolac	3.0	5.7 (19)	14.7 (21)	1.6 (22)	1 <fixed>
400mg etodolac	3.0	7.1 (8.0)	11.5 (12)	1.5 (2.8)	1 <fixed>
400mg etodolac ER	3.0	35 (12)	43.1 (17)	12 (10)	1 <fixed>
1200mg etodolac ER	3.0	7.7 (7.8)	40.9 (19)	2.6 (5.9)	1 <fixed>
FR = 0.63					
200 and 400mg etodolac	-	-	-	-	-
400 and 1200mg etodolac ER	1.89[b]	-[c]	18.4 (4.6)	4.3 (44)	1.3 (6.7)
Lodine meta analysis[d]					
100, 200 and 400mg etodolac	1.89[b]	-[c]	9.74 (8.5)	1.25 (21.3)	1 <fixed>

Data in parentheses denote the percent coefficient of variation.
a: Constant describing the magnitude of maximum possible inhibitory effect.
b: Assumes that maximal response for NSAIDs is 63% of maximum possible response.
c: Parameterized as the product of k_{out} and R_0.
d: Fitting yielded FR = 0.63 (9.2).
-: not determined

Values originally reported in study 0654D-355-US, where it was assumed FR = 1, are shown in the Table. As can be observed, parameters differ for IC_{50}, k_{in} and k_{out} between dosage forms. Assuming that etodolac causes analgesia independently of presentation to the body, a single value for each parameter would make more sense. The analysis was also limited in that a ceiling effect for NSAID-mediated analgesia was not considered, thereby assuming a maximal possible inhibitory effect of pain (I_{max}) of 3 PID units.

A supplemental evaluation (meta-analysis) of previously submitted pharmacokinetic and efficacy data for Lodine (study 654D-323-US) provided pharmacodynamic parameter estimates of: FR =0.63; k_{out} = 1.25 and IC_{50} = 9.7 mg/L. The meta-analysis in the table refers to analysis from the data from single dose of 100, 200 and 400 mg, combined with the pain intensity difference (PID) scores derived from 8 dental pain studies, none of which had concentration measurements. A population approach was used to predict the concentrations using the following polyexponential model.

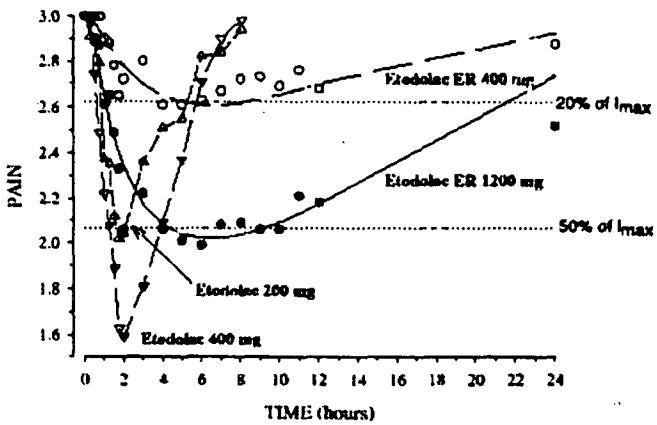
$$C_p(t) = 0.228 \cdot D \cdot e^{-0.97 \cdot t} + 0.022 \cdot D \cdot e^{-0.095 \cdot t} - 0.25 \cdot D \cdot e^{-1.58 \cdot t}$$

Where Cp is the predicted etodolac concentration, D is Lodine dose and t is time after dosing.

It is recognized clinically that NSAIDs are associated with a ceiling of analgesic response of less than 3 PID. Therefore, an I_{max} of 1.89 PID (= 0.63*3) was assumed.

FR could not be estimated reliably and therefore was fixed as 0.63, making the assumption that the fraction of maximum possible response to etodolac would be independent of dosage form. In addition, γ was defined as a parameter. Attempts to simultaneously fit a model to single 200 and 400 mg doses of Lodine were unsuccessful, and yielded fits that largely underestimated the observed responses. Simultaneous fitting of the 400 and 1200 mg doses of Lodine XL yielded the following pharmacodynamic parameter estimates: IC_{50} = 18.4 mg/L, k_{out} = 4.9 hr^{-1} and γ = 1.3. The PCNONLIN code for Lodine XL used in this analysis is attached in the Appendix on page 14 and 15.

To allow modeling with an indirect response model, PID scores were transformed as follows: 1) mean placebo PID scores were subtracted from mean PID scores for each group, 2) PAIN scores were calculated by subtracting each placebo-correct mean PID score from 3, which is the maximum PID score that could be obtained.
The observed and predicted plasma concentrations after administration of two doses of Lodine and a single dose of Lodine XL is attached in the Appendix on pages 17 and 18. The pharmacodynamic response for Lodine and Lodine XL is shown in the figure below.



Symbols are observed; lines are model predicted for Lodine XL and observed for Lodine.

Based on this figure and the analysis the applicant claims that a dose of 1200 mg may provides pain relief up to approximately 20 hours (see 20% of Imax), and substantial pain relief up to approximately 10 hours (as shown by 50% of Imax) and a more sustained profile as compared to the IR dosage form.

Reviewers' Comments (not for the sponsor)

- *Upon consultation with Dr. Raymond Miller (Pharmacometrics), it was felt that the indirect response model does not adequately describe the PK-PD relationship for Lodine-XL dosage form since the pain scores can only be treated as a continuous variable in this model, which is inappropriate. They should be treated as categorical variable.*
- *The applicant has not modeled placebo, however, has corrected the pain scores for placebo response.*

- *There were only 12 patients out of 237 patients that lasted for more than 10 hours in the trial for the 1200 mg Lodine-XL treatment regimen. The applicant's claim that 1200 mg ER provides pain relief up to 20 hours is based on a total of 12 subjects from study 064D-335. About 79% of the patients dropped out from the trial due to lack of efficacy.*
- *It is the understanding of the reviewer based on discussion with the medical officer, that this submission is the completion of the post approval commitment to demonstrate safety at the 1200 mg dose of Lodine-XL. As per the statistical review the 1200 mg daily dose of etodolac ER appears to be comparable to the 800 mg daily dose with regard to discontinuation rates and incidence of adverse reactions. Therefore the reviewer did not feel the need to re-analyze the PK-PD relationship using categorical pain scores. (other comments on page 6).*
  No comments need to be conveyed to the applicant.

/S/ 9/16/98

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation III

Team Leader: E. Dennis Bashaw, Pharm. D. /S/ 9/16/98

CC: NDA 20-584(SE2003)
HFD-550/Div File
HFD-550/CSO/Koener)
HFD-880(Bashaw/Tandon)
HFD-880(Lazor)
HFD-344(Viswanathan)
CDR ATTN: B.Murphy

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APPENDIX I

NDA/IND#: Volume 3-12

Study Type: Bioavailability and PK-PD *Study* # 064D-355-US

Study Title: A double-blind comparison of the analgesic efficacy and safety of etodolac sustained release, etodolac conventional formulation and placebo in patients following oral surgery

Study Site	
Clinical Site	Analytical Site
[redacted]	

Study Design							
Single Dose	Multiple Dose	Randomized	Parallel	Other Design	Fasted/ Fed	FDA Diet	No. of fasted hrs.
For ER	2 doses IR	X	X	Double Blind			

Subject Category					
Normal	Patients	Young	Elderly	Renal	Hepatic
	post-oral surgery				

Subject Type			
Males		Females	
Age	Weight	Age	Weight
See page13			

Subject Treatment Group			
Group No.	Total No.	Males	Females
400 ER	50		
1200 ER	50		
200 IR	50		
400 IR	50		
Placebo	50		

Treatment Groups	Dose	Dosage Form	Strength	Lot #
	one	ER	400 mg	3WCZ
	one	ER	1200 mg (3x400)	
	two (0 &8 hrs)	IR capsules	200 mg	2 WFP
	two (0 &8 hrs)	IR capsules	400 mg (2x200)	
	placebo	ER	400 mg	2 WKP
	placebo	IR	200 mg	2 WFR

Sampling Times

Plasma: 0, 1, 2, 4, 6, 8 and 10 hrs (1,4,8 hr at site 1 and 2, 6, 10 hr at site 2)
Pain Intensity: 0.25,0.5,0.75,1,1.25,1.5,1.75,2,3,4,5,6,7,8,9, 10,11,12,24 hrs
Pain Relief: 0.25,0.5,0.75,1,1.25,1.5,1.75,2,3,4,5,6,7,8,9, 10,11,12,24 hrs
Pain half gone: 0.25,0.5,0.75,1,1.25,1.5,1.75,2,3,4,5,6,7,8,9,10,11,12,24 hrs.

Observed efficacy variables and rating scales

Pain Intensity[a]: 0=None, 1=Mild, 2=Moderate, 3=Severe
Pain relief: 0=None, 1=A Little, 2=Some, 3=A Lot, 4=Complete
Pain half gone[b]: 1=Yes, 2=No
Patient's global assessment[c] : 1=poor, 2=fair, 3=good, 4=very good, 5=excellent

a Also assessed at time of remedication, drop out or at end of study
b "No" was interpreted as 0 to calculate the sum of pain half gone
c Assessed at time of completion or patient withdrawal.

Variable	Description/Definition
PID	Pain intensity (t=0) minus pain intensity (t=0.25, 0.5, 0.75,...2, 3, 4,...12, 24)
PR	Pain relief (t=0.25, 0.5, 0.75,...2, 3, 4,...12, 24)
PRID	PID (t) + PR (t=0.25, 0.5, 0.75,...2, 3, 4,...12, 24)
Peak PR	Maximum PR
Peak PID	Maximum PID
Peak PRID	Maximum PRID
SPID	Area under PID-time curve (h 0-3, 0-8, 0-12, 0-24), trapezoidal rule
TOPAR	Area under PR-time curve (h 0-3, 0-8, 0-12, 0-24), trapezoidal rule
SPRID	Area under PRID-time curve (h 0-3, 0-8, 0-12, 0-24), trapezoidal rule
Sum of pain half-gone	Area under the pain half-gone curve, (h 0-24), trapezoidal rule
Global assessment	Patient's overall evaluation
Percent of patients taking rescue medication	Patients taking rescue medication within 24 hours (% of total number per treatment group)
Onset of pain relief (on-PR)	Unextrapolated PRID at 30 minutes
Duration of pain relief (dur-PR)	Estimated duration of pain relief, mean survival time

Sample size/power

The sample size and power calculations done for this study were based on the variability estimates from earlier analgesic studies with Lodine®. These calculations indicated that 50 patients per group would provide 90% power to detect a mean difference between groups of 2.9 in 3-hour SPID. A sufficient number of patients were to be enrolled to achieve a total of approximately 250 evaluable patients.

TABLE B.3 DEMOGRAPHIC CHARACTERISTICS FOR PATIENTS INCLUDED IN POPULATION PHARMACOKINETIC ANALYSIS FOR STUDY 654D-355-US

Dose	N	Gender	Weight [a]	Age [b]	Race [c]
Etodolac ER 1200 mg	47	26 men 21 women	71.9 ± 16.1	23 ± 4	9 B 5 O 33 W
Etodolac ER 400 mg	48	18 men 30 women	66.9 ± 13	23 ± 4	2 B 7 O 39 W
Etodolac 400 mg	46	21 men 25 women	71.5 ± 16.7	23 ± 4	2 B 7 O 37 W
Etodolac 200 mg	47	17 men 29 women	68.0 ± 16.1	23 ± 3	5 B 11 O 30 W
TOTAL Etodolac ER	95	44 men 51 women	69.4 ± 14.8	23 ± 4	11 B 12 O 72 W
TOTAL Etodolac	92	38 men 54 women	69.9 ± 16.4	23 ± 4	7 B 18 O 67 W
TOTAL	187	82 men 105 women	69.6 ± 15.6	23 ± 4	18 B 30 O 139 W

a: mean ± S.D., in kilograms b: mean ± S.D., in years c: B = black, O = other, W = white

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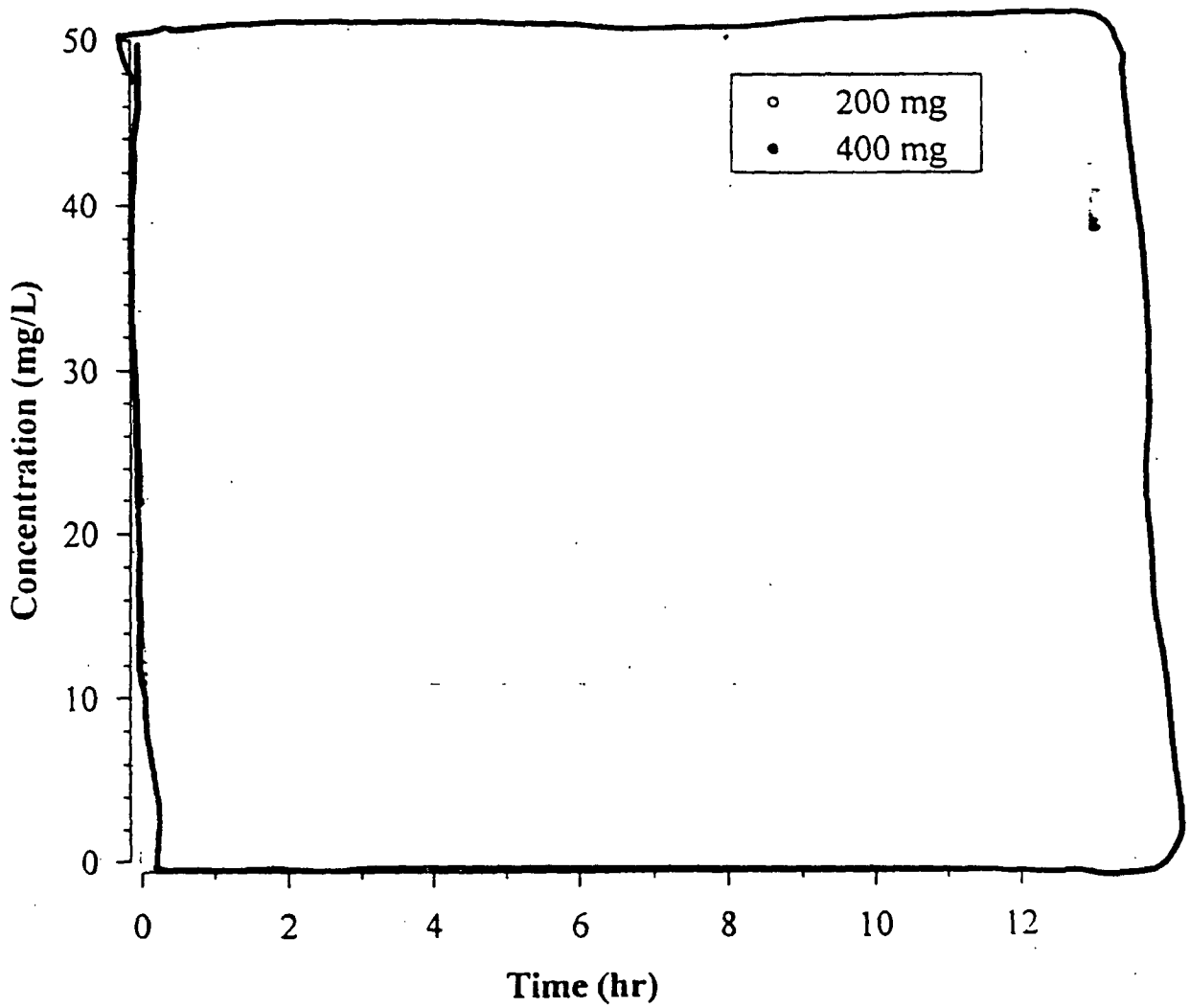
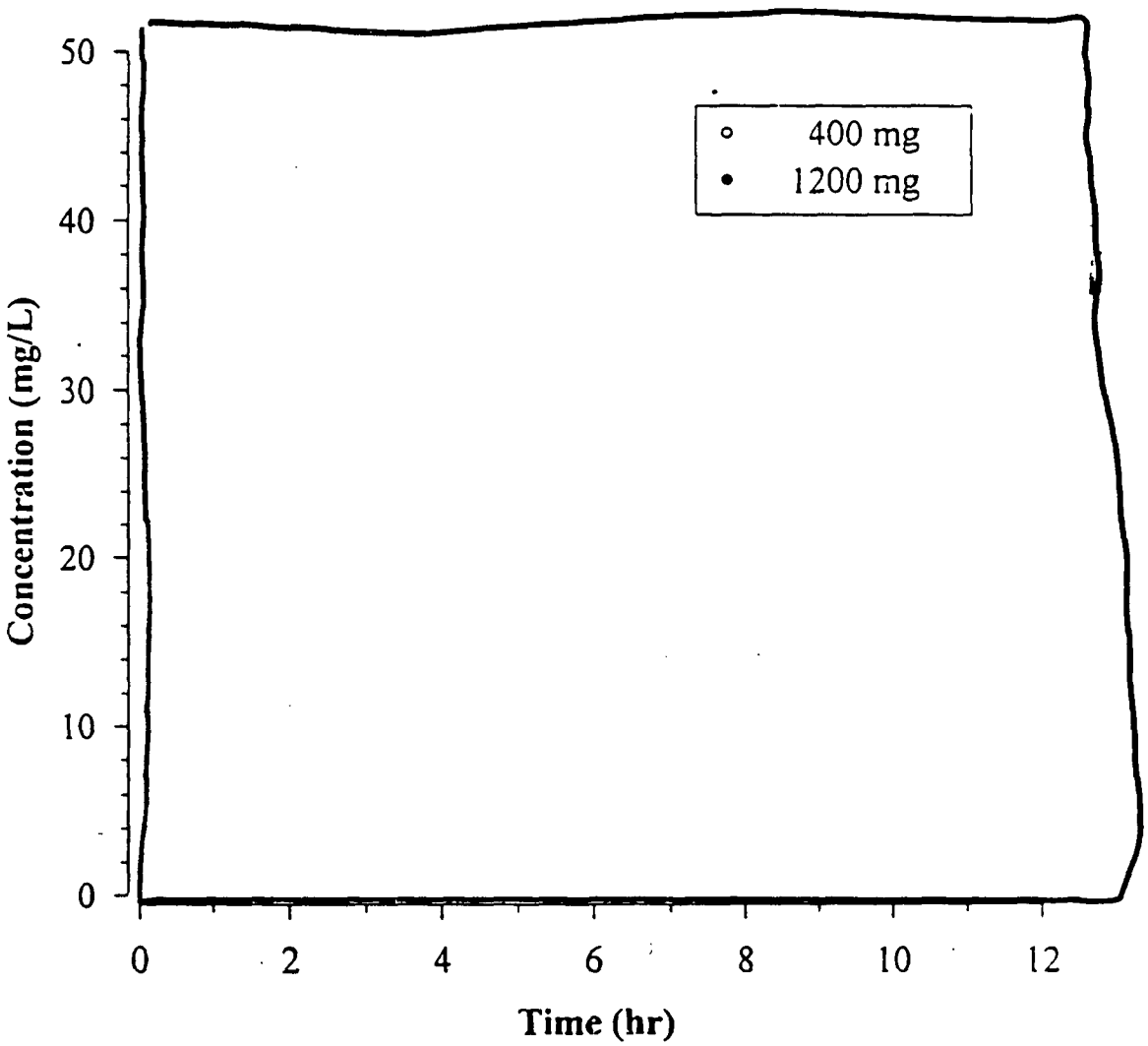
3 *pages have been removed here because they contain confidential information that will not be included in the redacted portion of the document for the public to obtain.*

FIGURE B.1
OBSERVED AND PREDICTED ETODOLAC CONCENTRATIONS IN PLASMA
AFTER ADMINISTRATION OF TWO DOSES OF LODINE
Observed versus Population-Predicted Data



Symbols are observed, lines are predicted.
Concentrations normalized to a 400 mg dose.

FIGURE B.2
OBSERVED AND PREDICTED ETODOLAC CONCENTRATIONS IN PLASMA AFTER ADMINISTRATION OF A SINGLE DOSE OF LODINE XL
Observed versus Population-Predicted Data



Symbols are observed, lines are predicted.
Concentrations normalized to a 400 mg dose.