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APPLICATION NUMBER:

20-584/S003

MEDICAL REVIEW

Lodine XL
(etodolac extended release tablets)

NDA 20-854 20-584

Medical Officer Review

Submission date:	November 11, 1997
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Drug Name:	Lodine™XL tablets
Generic name:	etodolac extended release tablets
Applicant:	Wyeth-Ayerst Research Division of American Home Products P.O. Box 8299 Philadelphia, PA 19101-8299
Pharmacologic category:	Nonsteroidal anti-inflammatory
Proposed Indication:	Osteoarthritis and Rheumatoid arthritis
Dosage Form and Route:	Oral tablet
Submission type:	Supplemental NDA (003)

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(James Witter, M.D., Ph.D. Medical Officer)

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HFD-550/Div File
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HFD-550/Biopharm/Bashaw
HFD-550/MO/Witter

Background and Overview:

Lodine XL (Lox), which is an extended-release formulation of Lodine (T_{max} for Lodine= 1.4 h; for Lodine XL= 6.7h), is indicated for the management of the signs and symptoms of osteoarthritis (**OA**) and rheumatoid arthritis (**RA**). Lodine, the trademark for etodolac, belongs to the pyranocarboxylic acid group of nonsteroidal anti-inflammatory drugs (NSAID). Etodolac is the USAN name for the chemical compound (±)1,8-diethyl-1,3,4,9-tetrahydropyrano-[3,4-b] indole-1-acetic acid. Etodolac is a racemic mixture of [+]S and [-]R-enantiomers.

According to the current labeling, Lodine (a conventional release formulation, **NDA 18-922)** is indicated for acute and long-term use in the management of signs and symptoms of OA and RA. Lodine (**Lod**) is also indicated for the management of pain. In analgesia, the recommended total daily dose for acute pain is 1000 mg. However, doses of Lodine may be increased to 1200 mg daily even though doses greater than 1000 mg/day have not been adequately evaluated in well-controlled trials. Similarly, for OA and RA, **the dose may be increased to 1200 mg/day when a higher level of therapeutic activity is required even though these higher doses have not been adequately evaluated in well-controlled trials.**

For Lox, the current maximum daily dose is 1000 mg/day. The Lox NDA (**NDA 20-584**, submitted on March 31, 1995, approved October 25, 1996), included draft labeling which reflected a maximum dose of 1200 mg/day to be consistent with the approved labeling for Lodine. However, the review of the Lodine Supplemental NDA (for adding the indication of RA, approved June 28, 1996) determined that the maximum approved dose for Lox would be the same dose accepted on October 21, 1996 for the revised Lodine labeling, i.e. 1000 mg/day, and not the dosing approved in the original NDA for Lodine (approved in January 1991) as noted above.

In a letter dated October 17, 1996 (just prior to the Lox NDA approval), Wyeth-Ayerst made a post-approval commitment to submit safety data from at least 300 patients receiving 1200 mg/day of Lox for at least 6 months. Therefore, **the purpose of this Supplemental New Drug Application (sNDA) is to provide the data necessary to support increasing the maximum daily dose recommended in the labeling of Lox to 1200 mg/day, and to fulfill the phase 4 commitments.** According to the cover letter, "these data show that, in general, the safety profile utilizing the 1200 mg dose is similar to the safety profile characterized in our current approved labeling." It is felt this would offer benefit to those arthritic patients who

may require a higher dose than the currently approved maximal dose for adequate control of their symptoms.

> ***Reviewer's comment: Protocol 654A-351-US-"Comparison of the Efficacy and Safety of Orally Administered Etodolac [to] Naproxen in Patients with Active Rheumatoid Arthritis" and Protocol 654A-426-US-"Placebo-Controlled Comparison of the Efficacy and Safety of Two Doses of Orally Administered Etodolac in Patients with Active Osteoarthritis of the Knee" as proposed in May, 1994 were not submitted in this sNDA. Per the Wyeth-Ayerst letter of April 8, 1997, these studies [redacted] were not conducted because of lack of feedback from the FDA on these protocols and Wyeth's belief these studies were superseded by studies with 1200 mg as included in this submission.***

The sponsor feels that the PK data support this dosage adjustment since administration of Lox results in etodolac plasma concentrations that are comparable to those of the immediate-release formulation at equivalent daily doses. Therefore, allowing an increase in the maximum daily dose to 1200 mg QD would result in etodolac plasma levels similar to that obtained with the immediate-release form at the same dose.

All the studies conducted in this sNDA were conducted in the U.S. Table 1, below, summarizes the important features of these studies.

> ***Reviewer's comment: Data from patients in the crossover studies (369, 374, and 376) and 24 hour study (355) will not be used to support labeling changes. Also of note, Protocol 654D-375-US entitled "Comparison of the Safety and Efficacy of 1000 mg Daily Dosing of Etodolac ER and Etodolac followed by an Open Label Extension with Etodolac ER for up to One Year in Patients with Osteoarthritis of the Knee" has been discontinued [redacted] as of January 31, 1998.***

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Table 1: Characteristics of Lodine XL Studies

Study Id[a] (No. sites)	Total Daily Treatment (mg)[c]	Number of Patients	Indication	Length/Design of Study
323[b] (25)	Part 1:			
	Lox 800	106		24 week, DB
	Lox 1200	112		
	Lod 1200	113	knee OA	
	Part 2:			
	Lox 800	83		4 week, SB 242235
323-OL[d] (20)	Lox 800	40		Up to 2 yr. Open-label of study 323
	Lox 1200	39		
357	Lox 800	104		
	Lox 1200	102	knee OA	4 week, DB
	Naproxen 1000	106		
	placebo	108		
357-OL	Lox 800	46		Up to 2 yr. Open-label of study 357
	Lox 1200	37		
358	Lox 800	127		
	Lox 1200	132	knee OA	4 week, DB
	Nabumetone 1500	132		
	placebo	126		
358-OL	Lox 800	157		Up to 2 yr. open-label of study 358
	Lox 1200	185		
370	Lox 800	115		
	Lox 1200	114	knee OA	4 week, DB
	Naproxen 1000	113		
	placebo	114		
370-OL	Lox 800	158		Up to 2 yr. open-label of study 370
	Lox 1200	168	knee OA	
371	Lox 800	114		
	Lox 1200	116	knee OA	4 week, DB
	Nabumetone 1500	112		
	placebo	110		
371-OL	Lox 800	119		Up to 2 yr. open-label of study 371
	Lox 1200	170		
355	Lox 400	49	oral surgery	24 hour, DB
	Lox 1200	48		
	Lod 400	47		
	Lod 800	46		
	placebo	47		
369	Lox 800	157 total	knee OA	4 week (crossover with 1 week SB for placebo), DB
	Lod 800			
	placebo			
374	Lox 1000	166 total	knee OA	4 week (crossover with 1 week SB for placebo), DB
	Lod 1000			
	placebo			
376	Lox 1000 (3 weeks)	126 total	active RA	6 week (crossover with 1 week SB for placebo), DB
	Lod 1000 (3 weeks)			
	placebo (1 week)			

a) For cross-referencing, all protocols start with 654D (i.e. 654D-357-US).
b) Study 323 was previously submitted to the FDA in the original NDA (i.e. NDA 20-584).
c) Lox = Lodine XL; Lod = Lodine.
d) Dose in open-label study shown as predominant daily dose. Dose in double-blind = exact dose.

As can be seen in **Table 1**, regarding Lox 1200 mg/day , there were 112 patients studied in a double-blind, prospective, controlled fashion for 24 weeks (study 323) while there were an additional 599 patients potentially studied in an open-label fashion for up to 2 years (i.e., the LOX 1200 patients in study 323-OL, 357-OL, 358-OL, 370-OL, 371-OL; see also ***Table 3.1 appendix***). The open-label studies used predominantly 1200 mg/day. However, as discussed later, study 323 has previously been submitted to the original NDA for Lox.

Protocol 323-OL:

Protocol 323-OL is given as an example of the open-label studies listed in Table 1. This was a 2-year open-label, multicenter, outpatient extension of both the double- and single-blind parts of trial 323. Not all patients that participated in the these original protocols were eligible for this open-label extension because the appropriate protocol amendments were not available at the time that these patients completed the double-blind segment. The patients were given 800 mg of Lod for the first four weeks of the single-blind portion of study 323 (considered the first part of the open-label study). Thereafter, to maintain efficacy, the investigator could increase the dose to 1200 mg of Lox (3 x 400 mg QD) at any study visit. For safety reasons, the investigator could decrease the dose to 800 mg/d at any subsequent visit.

A category of **treatment-emergent study events (TESE)** was defined for the analysis of study event data in order to identify new events that may have been related to the administration of etodolac. Such study events were presented by **predominant dose.** To determine the patient's predominant dose, the number of days a patient took 800 mg or less was compared to the number of days that the patients took 1200 mg or more. The dose with the greater number of days determined the predominant dose. Therefore, study events did not necessarily occur when the patient was taking the predominant dose.

> ***Reviewer's comment: Some of the limitations of attributing efficacy or adverse events to a "predominant dose" are discussed later in this review.***

The four primary efficacy variables were patient and investigator's global evaluation, walking pain and overall pain intensity. Change from baseline measured (before initiation of double-blind segment) at regular intervals was used to evaluate efficacy. Efficacy was evaluated using ANCOVA to compare mean change from baseline (compared to zero) at various timepoints while descriptive statistics were used to summarize changes from baseline for the safety variables.

> ***Reviewer's comment: It should be noted that inclusion criteria for this study included participants without a history of serious adverse reactions to NSAIDs. In other words, patients with a history of GI bleeding or ulcer in the past year or with a history of GI hemorrhage or ulcer associated with another NSAID were excluded.***

Integrated review of safety (ISS):

Although the sponsor claims in their ISS that "clinical studies in patients with OA or RA show that long-term once-daily administration of Lox at 1200 mg is well tolerated and has an acceptable safety profile", it is clear from Table 1 that **none of the studies in this sNDA involved patients with RA for a sufficient length of study to assess long-term safety**, they were all with patients with OA of the knee. The only study in RA was study 376 which was a crossover, 6 week trial with doses of 1000 mg each of Lod and Lox.

> ***Reviewer's comment:*** *Wyeth-Ayerst submitted (January 9, 1998/SN 094 and 095) amendments noting termination of the following two protocols: "Placebo Controlled Comparison of the Efficacy and Safety (of Two Doses) [protocol 654D-356-US] of Etodolac [protocol 654D-377-US] Extended Release with Nabumetone in Patients with Active Rheumatoid Arthritis Followed by a Long-Term Open Label Extension." These studies were closed on January 31, 1998. This termination, along with the fact that none of the studies listed in Table 1 are of sufficient duration in RA, argues that the Sponsor has not fulfilled their post-approval commitments for RA.*

Since there are no RA or OA studies of "adequate" length for review for efficacy (see Table 1, above), this review will focus on studies with doses of Lox at 1200 mg QD and will try to answer the following major questions:

- **Does use of 1200 mg of Lox daily pose increased risks over 800 mg Lox daily?**
- **Does use of 1200 mg of Lox daily pose increased risks over other NSAIDs (even though there were no comparator NSAIDs in the open-label portions)?**

The number of patients treated with Lox by dose is summarized in ***Tables 3.1, 3.2, 3.3, 3.4 (appendix)***. As can be seen from these tables (see description of tables, below), **there were sufficient numbers of patients exposed to 1200 mg Lox to address the phase 4 commitment.** The ISS study populations consist of four basic groups including:

> **Etodolac ER Exposure Population**: Includes all the patients in the double-blind and open label listed in Table 1 (i.e. study 323, 357, 358, 370, 371) and so the doses are either 800 or 1200 mg daily. Again, in the open-label extensions of these 5 studies, patients were reported as by predominant daily dose. It is **IMPORTANT TO NOTE** that this **INCLUDES** the patients in the 24-week, double-blind portion of **STUDY 323**; this is the only population that addresses their adverse events.
>
> **Double-blind, placebo-controlled OA studies**: Includes all the patients in the 4 week portions of studies 357, 358, 370 and 371. Note that this **EXCLUDES STUDY 323**. Doses here are exact and again either 800 or 1200 mg daily.
>
> **Open-Label OA studies**: Includes all the patients in the open-label extension of studies 323. 357, 358, 370, and 371. Patients are reported according to predominant daily dose.

Double-Blind Crossover Studies: Includes patients in studies 369, 374 and 376. Since the doses of Lox are ≤ 1000 mg daily, the results of these studies will not be used to support any potential labeling changes but rather as additional data regarding the safety of Lox.

Reviewer's comment: It needs to be reinforced that Study 323 has already been submitted to the FDA in the NDA application for Lox (i.e. NDA-584).

Additionally, safety data from the single-day, **oral surgery study (i.e. 355)** is included but this data **will not be used to support any labeling changes.**

The extent of exposure for Lox is shown in Tables 3.1, 3.2, and 3.3 (*appendix*). Table 3.1 represents the planned duration of exposure to Lox in the studies. Table 3.2 represents a cumulative tabulation of exposure and shows the number of patients who took the study drug for <u>at least</u> the time interval defined. Table 3.3 represents a non-cumulative tabulation of exposure and shows the number of patients who took the study drug for <u>exactly</u> the time interval defined.

Exposure data to 1200 mg daily of Lox is further defined in ***Table 3.4 (appendix)***. Four hundred and twenty-four (424) patients took an actual dose of 1200 mg for at least 185 days of continuous dosing in studies 323, 357, 358, 370 and 371 (including extensions). It should be noted that the days on 1200 mg were counted forward from the first day on 1200 mg; the count does not include days on other doses of Lox. Of these, 237 patients took 1200 mg daily of Lox for more than 365 days. A list identifying these 424 patients and their individual duration of exposure is included in Supportive Table 3.A (volume 78, not included in this review).

Demographics:
The demographic profile for the 1654 patients in the Lox Exposure Population is listed in ***Table 4.1 (appendix)***. As can be seen, most of the patients were older, white females and there are no significant differences between the 800 and 1200 mg Lox groups with regards to sex, weight, height, and race. Although more patients in the 800 mg group tended to be ≥ 65 years, there were no significant differences in demographics when "elderly" patients (≥ 65 years) were compared to "non-elderly" (< 65 years) between the 800 and 1200 mg doses of Lox ***(Table 4.6, appendix)***. There did not appear to be any significant differences when patients were compared in the Placebo-Controlled, OA studies, and the Open-Label studies, separately.

Adverse events:
The main focus of the presentation of study events was according to treatment-emergent-study events (**TESE**). The description/definition of these events for the various study populations (noted above) was somewhat different but essentially TESEs were defined and counted as any event that started or worsened on or after the first

dose of medication. The attribution to responsible dose in the open-label studies was again by predominant dose. **It should be remembered that the only study that addressed TESE with immediate-release etodolac (i.e. Lod) was the double-blind portion of study 323.**

Statistical analysis for the Etodolac ER exposure population was by pairwise comparisons of elderly vs. non-elderly and men vs. women (0.05, no overall protection). Statistical testing was not performed across racial subgroups because of the small number of non-white patients. For the double-blind portions of the studies, pairwise comparisons of Lox 800 vs. Lox 1200 vs. naproxen vs. nabumetone vs. placebo (0.05 level, no overall protection) was done. There also was a relative risk analysis of Lox 800 vs. Lox 1200 for men and women as well as for Lox 800 vs. Lox 1200 for elderly and younger patients. Again, statistical testing was not performed across racial subgroups because of the small number of non-white patients.

Representative TESE are noted in **Table 2** below. Recalling that the double-blind population represented four weeks of observation, open-label up to 2 years of observation and the total population all the patients (including those in the 24 week study 323), there do not appear to be any unusual findings in these populations. In general, longer exposures (i.e. open-label) to Lox resulted in higher rates of adverse events in all the categories and the rates appeared generally similar for 800 mg and 1200 mg of Lox daily as well as between the open-label and etodolac ER total population. These same trends appear to hold when the TESE are analyzed for the 424 patients who received 1200 mg Lox for ≥ 6 months ***(Table 5.7, appendix)*** and the 237patients who received a continuous dose of 1200 mg Lox for ≥ 1 year ***(Table 5.8, appendix).***

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Table 2: Adverse events[a] for Etodolac ER

COSTART term	Etodolac ER Population		Double-Blind Population		Open-Label Population	
	800 mg (n=779)	1200 mg (n=875)	800 mg (n=460)	1200 mg (n=464)	800 mg (n=520)	1200 mg (n=599)
Any event	625 (80)[b]	726 (82)	267 (58)	273 (59)	440 (84)	514 (85)
Body as a Whole	204 (26)	252 (28)	54 (12)	37 (8)	155 (29)	193 (32)
Digestive	342 (43)	386 (44)	130 (28)	143 (31)	212 (40)	235 (39)
• Liver Function Test abnormal	16 (2)	30 (3)	6 (1)	8 (2)	11 (2)	18 (3)
Metabolic & Nutritional	84 (10)	127 (14)	22 (5)	27 (6)	61 (11)	84 (14)
• BUN increased	2 (< 1)	5 (< 1)	0	1 (< 1)	1 (< 1)	3 (< 1)
• Creatinine increased	8 (1)	10 (1)	1 (< 1)	1 (< 1)	5 (< 1)	6 (1)
• Generalized edema	7 (< 1)	16 (1)	4 (< 1)	5 (1)	4 (< 1)	11 (1)
Musculoskeletal system	179 (22)	243 (27)	35 (8)	31 (7)	144 (27)	197 (32)
Nervous system	209 (26)	250 (28)	72 (16)	81 (17)	128 (24)	168 (28)
• Headache	105 (13)	133 (15)	39 (8)	41 (9)	62 (11)	86 (14)

a) Events are from Tables 5.2 & 5.4 (vol. 77); Supportive Table 5.B (vol. 78)
b) Numbers in () are percentage of patients.

Hepatic events, listed as above as "Liver function test abnormal" included the following: hepatitis, gamma glutamyl transpeptidase increased, liver function tests abnormal, alkaline phosphatase increased, bilirubinemia, SGOT increased, SGPT increased. There were discrepancies between the total numbers listed in **Table 2** (above) and Table 5.11 (vol. 77) with 19 TESE categorized as hepatic events for 800 mg Lox versus 34 TESE for 1200 mg Lox in either the open-label or double-blind portions of these studies; these discrepancies are presumed secondary to "Reclassification of selected COSTART terms" listed in Table 5.1 (vol. 77, not included in review). Four and six of these TESE in the 800 and 1200 mg Lox groups (respectively) resulted in discontinuation from the study because of liver enzyme abnormalities; none were serious.

Renal events, classified under COSTART as albuminuria, BUN increased (>30 mg/dl, ≥ 65 years; >25 mg/dl, < 65 years), creatinine increased (>1.9 mg/dl ≥ 65 years; >1.5 mg/dl < 65 years), hematuria, bladder calculus, or kidney calculus were listed in Table 5.12 (vol. 77). During the open-label, single-blind, or double-blind studies, there were 21 TESE noted in the 800 mg Lox group and 22 TESE in the 1200 mg Lox group. Five and two of these TESE in the 800 and 1200 mg Lox groups (respectively) resulted in discontinuation from the study because of these renal

abnormalities; none were serious. There were no episodes of flank pain syndrome described as flank pain, hematuria, and decreased renal function. It should be noted that two of the "renal calculi" cases were discussed in the Wyeth-Ayerst letter (April 8, 1997) noted above.

Hematologic events, classified as anemia, hemolytic anemia, hypochromic anemia, leukopenia, neutropenia, or thrombocytopenia were listed in Table 5.13 (vol. 77). During the open-label or double-blind studies, there were 11 TESE in the 800 mg Lox group and 29 TESE in the 1200 mg Lox group, it was noted that these differences were not statistically significant. Two and six of these TESE in the 800 and 1200 mg Lox groups (respectively) resulted in discontinuation from the study. One patient in the 1200 mg group (patient 35809-0019) withdrew from the study because of a stomach ulcer noted with a drop in hematocrit (41 to 32%) and hemoglobin (14 to 10 g/dL) at week 19. Other patients in both groups were suspicious for GI bleeds but were not listed as such.

As can be seen in **Table 3** which addresses the TESE associated with "clinically important" GI outcomes associated with Lox (not Lod, see study 323), the number of events are is small. Since the Etodolac ER population contains more patients than the other two populations, it would not be unexpected that this population would have more events than in the other populations; in many instances the numbers are the same (i.e. GI hemorrhage). On the other hand, there are discrepancies that are difficult to explain such as the reversal of numbers for duodenal ulceration. However, when all these events are artificially pooled (i.e. Total; Table 3), **it appears that the overall incidence of PUBs is not worsened by increasing Lox doses from 800 to 1200 mg/day or by increasing exposure times to these higher doses of Lox.** The Life Table Analysis of PUBs ***(Figure 5.1, appendix)*** for Lox suggests the same general conclusion but this figure is difficult to understand since there were the same number of patients with events in both the 800 and 1200 mg groups with 10 and 13 events, respectively (yet the data suggests that 800 mg has a higher incidence). Overall, as seen in Figure 5.1 and ***Table 5.9C (appendix)***, the incidence of upper gastrointestinal events for the 1200 mg treatment group at 6 months was less than 1%, and less than 2% at 1 year. **These rates are clearly within the range noted in the current NSAID class label.**

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Table 3 : Upper gastrointestinal PUBs[a] associated with Lox

COSTART term	Etodolac ER Population[b]		Double-Blind Population		Open-Label Population	
	800 mg (n=779)	1200 mg (n=875)	800 mg (n=460)	1200 mg (n=464)	800 mg (n=520)	1200 mg (n=599)
Duodenal ulcer	2	1	0	0	1	2
Esophageal ulcer	4	0	0	0	1	1
GI hemorrhage	4	2	0	1	4	1
Intest. Obstruction	0	1	0	1	0	0
Intest. Perforation	0	1	0	0	0	1
Intest. Ulcer	1	1	0	0	1	1
Melena	4	4	1	2	2	1
Stomach ulcer	2	3	0	1	1	3
Total	17	13	1	5	10	10

a) PUBs: Defined to include perforations, obstructions, ulcerations and bleeding. Number of events taken from Supportive Tables 5 A, B and C (vol. 78).

b) Populations are as defined above and as noted in Table 1. Essentially, the Etodolac population contains the patients in the active comparitor portion of study 323. The double-blind population was studied for 4 weeks while the open-label exposures were up to 2 years in some patients.

Lower intestinal events attributed to such events as "colitis", diverticulitis, cecal ulcer, bowel perforation, etc. were not different between the two groups of Lox (i.e. 6 with 800 mg, 7 with 1200 mg).

There did not appear to be significant differences between any of the groups in terms of the occurrence of **neoplastic** events, **hematologic** events, **skin disorder** events, or **allergic** events.

While there were statistically significant differences between the different doses of Lox and placebo, or Lox and **comparitor NSAIDs** (Naproxen, Nabumetone, see ***Table 5.3, appendix)***; none of these differences accorded for a reason for discontinuation between any of the treatments.

Demographic influence on TESE

Some differences were seen between elderly and non-elderly patients. There were 14 TESE in the 1200 mg group and 8 TESE in the 800 mg group that were different statistically ***(Table 5.5; appendix)***. However, none of the differences in the 1200 mg group for hypotension, melena, or arrhythmia TESEs were attributed to study drug. Some of events in the 1200 mg group, such as melena, seem to reinforce what is already known that elderly patients are at a greater risk for GI events with higher doses of NSAIDs. Other events, such as dizziness, seem to suggest that age has more of an effect than dose. As seen in ***Table 5.6 (appendix),*** in both Lox groups, more women than men reported TESE; this is not an unusual observation in a clinical trial.

As with age, some of these events (such as headache) appear unrelated to an increasing dose of Lox while other events (such as dyspepsia) do appear related to an increasing dose of Lox. Overall, the rates and types of TESE reported for patients in the Etodolac exposure population in each of the demographic subgroups mentioned above, were similar whether the patients received 1200 mg or 800 mg of Lox.

Premature Discontinuations:
Treatment could be stopped and patients could have been prematurely discontinued from the studies for the following reasons:

- **Adverse Reaction**
- **Failure to Return**
- **Other Medical Event**
- **Other Non-Medical Event**
- **Patient Request (unrelated to study)**
- **Protocol Violation**
- **Unsatisfactory Response (efficacy)**
- **Administrative Reason**

Table 6.1 (appendix) depicts the number of patients and reason for discontinuations in the major patient populations studied. Of note, the major reasons for discontinuations were Adverse Reactions and Unsatisfactory Response (efficacy). In the latter category, it should be noted that **more patients discontinued for Unsatisfactory Response in the 1200 vs. 800 mg Lox groups** in the long-term, open-label experience which is also then reflected in the Pooled Exposure. On the other hand, it is interesting to note that **more patients discontinued for Adverse Reactions 800 mg vs. 1200 mg Lox groups** in the long-term, open-label experience which was again reflected in Pooled Exposure; about half of these events were due to Digestive complaints Table 6.8, not included in review). Neither of these trends is suggested in the Double-Blind portion of these studies. The explanation offered is that of the titration design of the open-label studies. Patients could be titrated to 1200 mg (from 800 mg) of Lox to improve efficacy, while they could be titrated to 800 mg (from 1200 mg) of Lox to minimize side effects. However, it should be remembered that the event was attributed to the predominant dose, as previously described (and listed in Table 6.1, appendix).

Table 6.4 (appendix) lists the Discontinuations for Adverse Reaction and Other Medical Event combined. Not unexpectedly, most of the reasons for discontinuation related to the digestive system. However, there are no apparent differences in the number and type events which led to discontinuation between the 800 and 1200 mg Lox groups.

Table 6.5A (appendix) lists the Premature Discontinuations for the two doses of Lox as compared to comparator NSAIDs (Nabumetone 1500 mg QD, Naproxen 500 mg BID) in the double-blind segments of the OA studies. Again, not unexpectedly, there

are significant differences between discontinuations between placebo and all other NSAIDs; this difference is driven by discontinuations for Unsatisfactory Response. There are also no clinically obvious differences for reasons for discontinuations across the two doses of Lox and the comparator NSAIDs ***(Table 6.6, appendix)***.

Table 6.9 (appendix) lists discontinuations for the two doses of Lox according to whether patients were elderly (≥ 65 years) or younger (open-label studies). As can be see, the number of discontinuations due to Adverse Reaction were significantly higher for elderly patients compared to non-elderly for 1200 mg of Lox but not 800 mg Lox daily. There were no trends noted between men and women or across racial groups (again, most patients-88%- studied were white).

Laboratory results:

All laboratory tests were performed in a central laboratory for all sites.

Hepatic test results revealed that there were comparable numbers of discontinuations (Table 7.2, not included) between Lox 800 (6 patients) and Lox 1200 mg (9 patients) in all studies. Contingency table analysis of > than or = to three-fold elevations of SGPT x SGOT in the double-blind and open-label studies revealed comparable elevations between patients receiving Lox 800 mg and 1200 mg of < 1%. Of interest, there were more Potentially Clinically Important hepatic laboratory test results with both doses of Lox vs. comparator NSAIDs in the double-blind studies ***(Table 7.4A, appendix)***. No long-term consequences were noted in any patients.

Renal test results (increases of BUN and creatinine) revealed there were comparable numbers of discontinuations (Table 7.6, not included) between Lox 800 (4 patients) and 1200 mg (2 patients) in all studies. Contingency table analysis of BUN ≥ 40 mg/dL x creatinine ≥ 2 mg/dL in the double-blind and open-label studies revealed comparable elevations between patients receiving Lox 800 and 1200 mg of < 1%. Again, there were more Potentially Clinically Important renal laboratory test results with both doses of Lox vs. comparator NSAIDs in the double-blind studies ***(Table 7.8A, appendix)*** but not between the two doses of Lox (Table 7.8C, not included). No long-term consequences were noted in any patients.

Hematologic results revealed there were comparable numbers of discontinuations (Table 7.10, not included) between Lox 800 (2 patients) and 1200 mg (5 patients) in all studies; two patients discontinued for thrombocytopenia and one for changes in neutrophils. Contingency table analysis of decreases of hemoglobin (baseline - 2 g/dL) x hematocrit (baseline-10%) in the double-blind and open-label studies revealed

comparable decreases between patients receiving Lox 800 and 1200 mg of < 1% (Supportive Tables 7.O and 7.P, not included). Once again, there were more Potentially Clinically Important decreases in hemoglobin and hematocrit between both doses of Lox vs. comparator NSAIDs (Table 7.12A, not included); white blood cells counts (Table 7.17A, not included); and platelets (Table 7.18A, not included). No long-term consequences were noted in any of the patients.

Deaths

There were seven deaths noted during the course of the studies presented in this sNDA. None were attributable to the study drug since they involved other etiologies (i.e. sepsis, myocardial infarction, congestive heart failure, liver cancer, etc.). There were two additional deaths noted from postmarketing experience which again, did not appear to be the result of Lox (pancytopenia from Hodgkin's disease and renal failure).

Post-marketing surveillance:

It is noteworthy that two recent reports of a rare adverse event (colonic strictures) associated with other NSAIDs (especially sustained release formulations) have resulted in publications. One paper (preprint, written by Weinstock) noted the development of strictures in a 73 year-old who had taken 1000 mg Lox for 18 months (MedWatch; May 6, 1998, Mfr. # 8-981119-016N). The other report by Eis et. Al (AJG-vol.93, No. 1, 1998) noted the stricture in a 69 year-old who had been taking Lodine (? Formulation, dosage) for four years; she had a history of RA (MedWatch June 1, 1998, Mfr # 8-98141-006A).

Discussion:

This is a particularly difficult phase 4 commitment to evaluate. The discussion as to the exact nature of this commitment has been ongoing for a number of years (since approval of Lodine in 1991) and has had often conflicting input (see April 8, 1997 letter.

As has been discussed earlier in this review, it is difficult to adequately address efficacy of 1200 mg daily of Lox in this sNDA since the submission itself did not include patient populations that were originally intended (i.e. lack of patients with RA at doses of 1200 mg daily) or includes information previously submitted to the FDA (i.e. the 24-week, double-blind portion of study 323). The other OA studies that were submitted consisted of 4-week studies which are not of adequate duration to properly assess efficacy. Nonetheless, from the data that was presented, it does NOT appear that higher doses of Lox in patients with OA offers any significant avantages in

treatment responses. This would not be unexpected in patients with OA (vs. patients with RA). The discontinuation data for "lack of treatment effect" , in fact, suggest that higher doses of Lox are less efficacious than 800 mg Lox. Attributing this discrepancy to the "titration" design effect seems to be an inadequate explanation. **Therefore, it seems there is no support for labeling that would suggest greater efficacy (in either RA or OA) for Lox at 1200 mg daily.**

In addition, a more acceptable comparison of safety would have been possible if the open-label studies included comparator NSAIDs (vs. only during the randomized portions of these trials). Therefore, comparisons were really only made to different formulations and doses of etodolac against each other and against trends generally seen with other NSAIDs; this is especially true for the GI events.

Conclusions:

1. **It does not appear that long-term treatment with Lox 1200 mg results in any increase in the occurrence of upper or lower intestinal gastrointestinal events (e.g. PUBs). These rates are within those noted in the current NSAID class label.**

2. **There does not appear to be any substantially increased risk for clinically significant study events occurring for patients with OA treated with 1200 mg Lox compared to patients with OA receiving 800 mg Lox daily. Similarly, there did not appear to be any unexpected increased risk in demographic subgroups such as elderly patients, men, women, or ethnic subgroups (although this was a limited evaluation).**

3. **While there was no apparent increase in risk of premature study discontinuation (overall) for patients treated with 1200 mg compared to 800 mg Lox, there were interesting exceptions such as for lack of efficacy in the 1200 mg Lox daily population in the open-label OA studies.**

4. **No statements of efficacy of 800 vs. 1200 mg Lox (or comparisons to other NSAIDs) can be made from the double-blind sections of studies 357, 358, 370, and 371 because of their inadequate duration (i.e. 4 weeks) or because this information was already submitted in the original NDA (i.e. study 323).**

5. **There does not appear to be any significant differences between the rates of discontinuations because of laboratory test results, and the incidence of potentially important laboratory tests in the Lox 1200 vs. 800 mg groups.**

6. Overall, Lox 1200 mg appears to have a safety profile similar to that of Lox 800 mg but generally not as favorable to comparitor NSAIDs (during the double-blind treatment period) in these studies.

7. The Sponsor has fulfilled their phase 4 commitment to address the issue of safety of doses of Lox at 1200 mg daily.

8. There should be no changes made to the existing label (Indications and Usage section; Dosage and Administration) for Lox.

9. Further consideration of any label changes should be supported by adequate safety and efficacy information.

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Appendix Tables

TABLE 3.1. NUMBER OF PATIENTS TREATED WITH ETODOLAC ER, BY DOSE, BY ISS POPULATION

		Etodolac ER			
Population	Planned Duration[e]	Total	800 mg QD	1000 mg QD	1200 mg QD
Etodolac ER Exposure Population[a]	4 weeks in DB (4 studies), 24 week DB + 4 week SB (1 study), 3-10 day washout, up to 2-year OL extension	1654	779[f]	N/A	875[f]
DB, Placebo-Controlled OA Studies[b]	4 weeks in DB	924	460	N/A	464
OL Studies in OA[c]	Up to 2 years	1119	520[f]	N/A	599[f]
Crossover Studies[d]	2 or 3 weeks in first treatment period	223[g]	78[g]	145[g]	N/A

N/A = not applicable; dose not used in these studies.
a: Includes double-blind and open-label segments of studies 0654D-323-US, -357-US, -358-US, -370-US, and -371-US.
b: Includes double-blind segments of studies 0654D-357-US, -358-US, -370-US, and -371-US.
c: Includes open-label segments of studies 0654D-323-US, 357-US, -358-US, -370-US, and -371-US.
d: Includes studies 0654D-369-US, -374-US, and -376-US.
e: As per the protocol design.
f: Reported by predominant dose.
g: Reported by study drug received in the first treatment period.

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TABLE 3.2: CUMULATIVE DURATION OF EXPOSURE FOR THE POOLED ETODOLAC ER PATIENT POPULATION

Treatment	Week 1 (Days 0-7)	Month 1 (Days 8-30)	Month 2 (Days 31-60)	Month 3 (Days 61-90)	Month 4 (Days 90-120)	Month 5 (Days 121-150)	Week 24 (Days 151-168)	Month 6 (Days 169-180)	Month 9 (Days 181-270)
Etodolac ER 800 mg QD	779	750	577	509	474	444	412	393	372
etodolac ER 1200 mg QD	875	856	680	616	587	557	527	509	475
Total	1654	1606	1257	1125	1061	1001	939	902	847

	Month 12 (Days 271-360)	Month 15 (Days 361-450)	Month 18 (Days 451-540)	Month 21 (Days 541-630)	Year 2 (Days 631-720)	Month 27 (Days 721-810)	Month 30 (Days 811-900)	> Month 30 (Days >900)
Etodolac ER 800 mg QD	334	271	179	78	30	21	14	9
Etodolac ER 1200 mg QD	400	313	212	90	29	21	18	9
Total	734	584	391	168	59	42	32	18

TABLE 3.3 NON-CUMULATIVE DURATION OF EXPOSURE FOR THE POOLED ETODOLAC ER PATIENT POPULATION

Treatment	Week 1 (Days 0-7)	Month 1 (Days 8-30)	Month 2 (Days 31-60)	Month 3 (Days 61-90)	Month 4 (Days 90-120)	Month 5 (Days 121-150)	Week 24 (Days 151-168)	Month 6 (Days 169-180)	Month 9 (Days 181-270)
Etodolac ER 800 mg QD	28	173	68	35	30	32	19	21	38
Etodolac ER 1200 mg QD	18	176	64	29	30	30	18	34	75
Total	46	349	132	64	60	62	37	55	113

	Month 12 (Days 271-360)	Month 15 (Days 361-450)	Month 18 (Days 451-540)	Month 21 (Days 541-630)	Year 2 (Days 631-720)	Month 27 (Days 721-810)	Month 30 (Days 811-900)	> Month 30 (Days >900)	TOTAL
Etodolac ER 800 mg QD	63	92	101	48	9	7	5	9	778
Etodolac ER 1200 mg QD	87	101	122	61	8	3	9	9	874
Total	150	193	223	109	17	10	14	18	1652[A]

TABLE 3.4. PATIENTS WHO RECEIVED[a] 1200MG ETODOLAC FOR ≥ 185 DAYS

	Days on Drug	N	(%)
6 months	185	424	(100)
	211	399	(94)
	241	378	(89)
	271	333	(79)
	301	309	(73)
	331	289	(68)
	361	245	(58)
1 year	366	237	(56)
	451	117	(28)
	541	41	(10)
	631	20	(5)
	721	2	(<1)

a: cumulative extent of exposure to an actual continuous dose of 1200 mg QD

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TABLE 4.1. ETODOLAC ER EXPOSURE POPULATION: DEMOGRAPHIC CHARACTERISTICS

Demographic Characteristic	Predominant Dose of Etodolac ER		
	800 mg QD	1200 mg QD	Total
Total Enrolled	779	875	1654
Age (yrs)			
Mean	64	62.3	63.1
Range	33-91	31-86	31-91
S.D.	10.3	10.1	10.3
< 65	368	493	861
≥ 65	411	382	793
Sex			
Female, N	536	607	1143
%	*(69)*	*(69)*	*(69)*
Male, N	243	268	511
(%)	*(31)*	*(31)*	*(31)*
Weight (kg)			
N	779	874	1653
Mean	87.5	92	89.9
Range	49-172	46-190	46-190
S.D.	18.9	20.8	20.1
Height (cm)			
N	776	875	1651
Mean	166.9	167.1	167
Range	137-203	142-198	137-203
S.D.	10	9.8	9.9
Race			
Black, N	59	84	143
(%)	*(8)*	*(10)*	*(9)*
Other, N	26	21	47
(%)	*(3)*	*(2)*	*(3)*
White, N	694	770	1464
(%)	*(89)*	*(88)*	*(89)*

TABLE 4.6. ETODOLAC ER EXPOSURE POPULATION:
DEMOGRAPHIC CHARACTERISTICS FOR ELDERLY AND NON-ELDERLY PATIENTS

Demographic Characteristic		—— Predominant Dose of Etodolac ER —— 800 mg QD <55 years	1200 mg QD <65 years	Total <65 years	800 mg QD ≥65 years	1200 mg QD ≥65 years	Total ≥65 years
Age (yrs)	N	368	493	861	411	382	793
	Mean	55.2	55.2	55.2	71.8	71.5	71.7
	Minimum	33	31	31	65	65	65
	Maximum	64	64	64	91	86	91
	S.D.	7.1	6.9	7.0	5.2	4.8	5.0
Women	N	255	348	603	281	259	540
	%	*69*	*71*	*70*	*68*	*68*	*68*
Men	N	113	145	258	130	123	253
	%	*31*	*29*	*30*	*32*	*32*	*32*
Weight (kg)	N	368	493	861	411	381	792
	Mean	93.4	96.7	95.3	82.2	86.0	84.0
	Minimum	54.4	45.6	45.6	49.4	48.5	48.5
	Maximum	172.4	190.5	190.5	137.9	137.4	137.9
	S.D.	20.1	22.3	21.4	16.1	17.0	16.6
Height (cm)	N	365	493	858	411	382	793
	Mean	168.4	167.9	168.1	165.6	166.1	165.9
	Minimum	146.1	146.1	146.1	137.2	142.2	137.2
	Maximum	203.2	198.1	203.2	195.6	198.1	198.1
	S.D.	9.8	9.6	9.7	10.0	9.9	10.0
Black	N	36	44	80	23	40	63
	%	*10*	*9*	*9*	*6*	*10*	*8*
Other	N	15	13	28	11	8	19
	%	*4*	*3*	*3*	*3*	*2*	*2*
White	N	317	436	753	377	334	711
	%	*86*	*88*	*87*	*92*	*87*	*90*

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TABLE 5.7 TESE REPORTED FOR ≥3% PATIENTS WHO RECEIVED ETODOLAC ER 1200 MG QD FOR ≥6 MONTHS

Body System Preferred term	N (%) of 424
Any event	*373 (88)*
Body As A Whole	**156 (37)**
Accidental injury	61 (14)
Chest pain	17 (4)
Flu syndrome	29 (7)
Infection	34 (8)
Pain	36 (8)
Cardiovascular	**51 (12)**
Hypertension	15 (4)
Digestive	**147 (35)**
>>> Abdominal pain	28 (7)
Diarrhea	32 (8)
Dyspepsia	39 (9)
Nausea	15 (4)
Hemic And Lymphatic	**15 (4)**
Metabolic And Nutritional	**59 (14)**
Peripheral edema	21 (5)
Musculoskeletal	**143 (34)**
>>> Back pain	38 (9)
>>> Neck pain	13 (3)

TABLE 5.7 TESE REPORTED FOR ≥3% PATIENTS WHO RECEIVED ETODOLAC ER 1200 MG QD FOR ≥6 MONTHS

Body System Preferred term	N (%) of 424
Arthralgia	71 (17)
Arthrosis	13 (3)
Bursitis	14 (3)
Joint disorder	11 (3)
Tenosynovitis	12 (3)
Nervous	**117 (28)**
>>> Headache	58 (14)
Dizziness	18 (4)
Respiratory System	**139 (33)**
Bronchitis	32 (8)
Cough increased	11 (3)
Pharyngitis	53 (13)
Rhinitis	20 (5)
Sinusitis	39 (9)
Skin And Appendages	**65 (15)**
Rash	14 (3)
Special Senses	**31 (7)**
Urogenital	**54 (13)**
Urinary tract infection	13 (3)

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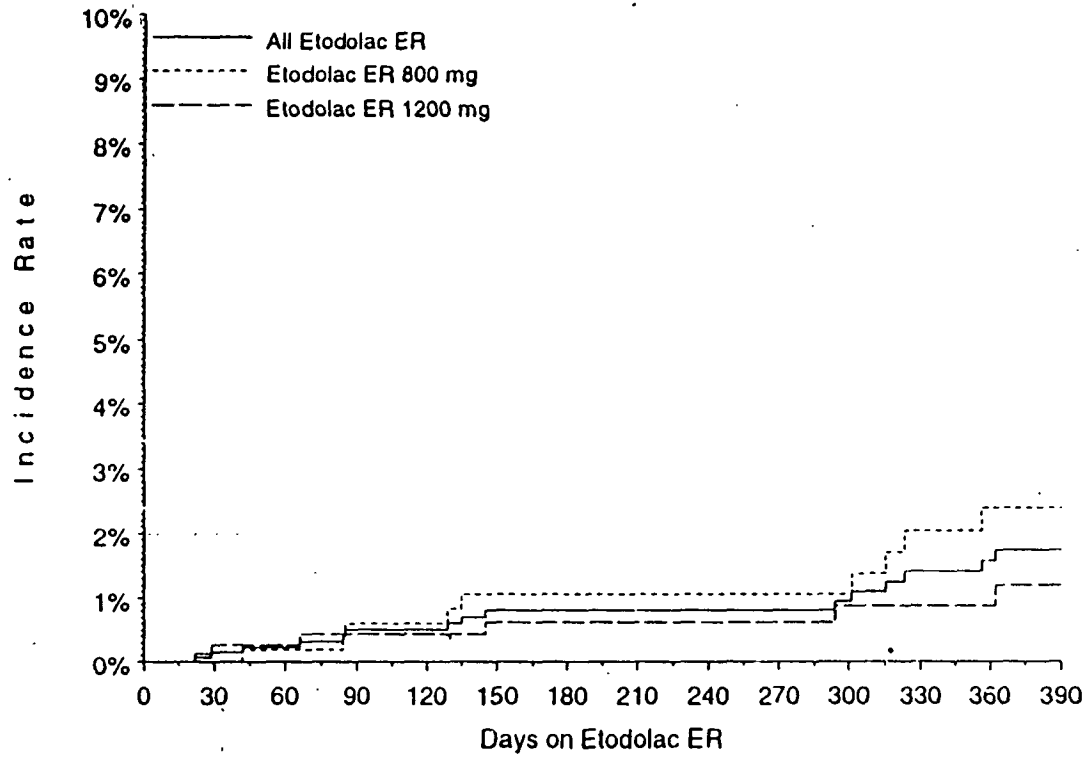
TABLE 5.8. TESE REPORTED FOR ≥3% OF PATIENTS WHO RECEIVED ETODOLAC ER 1200 MG QD FOR ≥ 1 YEAR

Body System Event	N (%) of 237
Any event	*217 (92)*
Body as a whole	**96 (41)**
Accidental injury	35 (15)
Chest pain	12 (5)
Cyst	6 (3)
Flu syndrome	18 (8)
Infection	25 (11)
Pain	16 (7)
Cardiovascular	**33 (14)**
Hypertension	10 (4)
Digestive	**83 (35)**
>>> Abdominal pain	14 (6)
Constipation	8 (3)
Diarrhea	21 (9)
Dyspepsia	22 (9)
Nausea	11 (5)
Endocrine	**6 (3)**
Hemic & lymphatic	**8 (3)**
Peripheral edema	10 (4)
Musculoskeletal	**93 (39)**
>>> Back pain	25 (11)
>>> Neck pain	7 (3)
Arthralgia	46 (19)
Arthrosis	8 (3)
Bursitis	10 (4)
Joint disorder	6 (3)
Tenosynovitis	7 (3)
Nervous	**82 (35)**
>>> Headache	44 (19)
Depression	7 (3)
Dizziness	12 (5)
Respiratory	**94 (40)**
Bronchitis	23 (10)
Dyspnea	7 (3)
Pharyngitis	33 (14)
Rhinitis	16 (7)
Sinusitis	28 (12)
Skin & appendages	**40 (17)**
Rash	9 (4)
Special senses	**17 (7)**
Study event assoc. W. Misc. Factors	**6 (3)**
Urogenital	**33 (14)**
Urinary tract infection	9 (4)

FIGURE 5.1 LIFE TABLE ANALYSIS OF UPPER GASTROINTESTINAL ULCERS AND BLEEDING EVENTS REPORTED FOR PATIENTS TREATED WITH ETODOLAC ER



Entering	1654	1257	1124	1060	1000	939	847	802	768	734	684	629	584	527
No. Censored	395	132	61	60	58	92	45	34	34	49	52	44	56	526
No. Evts	2	1	3	0	3	0	0	0	0	1	3	1	1	1

Footnotes to graph: Entering = number of patients entering the time interval. Censored = number of patients who discontinued or completed the study in that time interval without having the event. Evts = number of patients who had an event.

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TABLE 5.9C LIFE TABLE ANALYSIS OF UPPER GASTROINTESTINAL ULCERS AND BLEEDING EVENTS REPORTED FOR PATIENTS TREATED WITH ETODOLAC ER

Days on Etodolac ER	Incidence (PUB) Rate			95% Confidence Interval		
	800 mg ER	1200 mg ER	Total	800 mg ER	1200 mg ER	Total
0-14	0.0%	0.0%	0.0%	(0.0% - 0.0%)	(0.0% - 0.0%)	(0.0% - 0.0%)
15-30	0.0%	0.0%	0.0%	(0.0% - 0.0%)	(0.0% - 0.0%)	(0.0% - 0.0%)
31-60	0.0%	0.3%	0.1%	(0.0% - 0.0%)	(0.0% - 0.6%)	(0.0% - 0.3%)
61-90	0.2%	0.3%	0.2%	(0.0% - 0.5%)	(0.0% - 0.6%)	(0.0% - 0.5%)
91-120	0.6%	0.4%	0.5%	(0.0% - 1.3%)	(0.0% - 0.9%)	(0.1% - 0.9%)
121-150	0.6%	0.4%	0.5%	(0.0% - 1.3%)	(0.0% - 0.9%)	(0.1% - 0.9%)
151-180	1.1%	0.6%	0.8%	(0.1% - 2.0%)	(0.0% - 1.2%)	(0.3% - 1.3%)
181-210	1.1%	0.6%	0.8%	(0.1% - 2.0%)	(0.0% - 1.2%)	(0.3% - 1.3%)
211-240	1.1%	0.6%	0.8%	(0.1% - 2.0%)	(0.0% - 1.2%)	(0.3% - 1.3%)
241-270	1.1%	0.6%	0.8%	(0.1% - 2.0%)	(0.0% - 1.2%)	(0.3% - 1.3%)
271-300	1.1%	0.6%	0.8%	(0.1% - 2.0%)	(0.0% - 1.2%)	(0.3% - 1.3%)
301-330	1.1%	0.9%	0.9%	(0.1% - 2.0%)	(0.1% - 1.7%)	(0.4% - 1.5%)
331-360	2.0%	0.9%	1.5%	(0.6% - 3.5%)	(0.1% - 1.7%)	(0.7% - 2.4%)
≥361	2.4%	0.9%	1.5%	(0.8% - 4.0%)	(0.1% - 1.7%)	(0.7% - 2.4%)

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TABLE 5.3. DOUBLE-BLIND PLACEBO-CONTROLLED OA STUDIES: TESE REPORTED WITH STATISTICALLY SIGNIFICANT P-VALUES INCLUDING PREMATURE DISCONTINUATION RATE FOR EACH TESE [N (%)]

	-- Etodolac ER --		Naproxen	Nabumetone	Placebo	-- Statistical Test --	
TESE	800 mg QD	1200 mg QD	500 mg BID	1500 mg QD		Chi squared	Pairwise
Discontinuation	(N= 460)	(N= 464)	(N= 219)	(N= 244)	(N= 458)	P-Value	Comparisons
Digestive, any	130 (28)	143 (31)	65 (30)	59 (24)	88 (19)	0.001	dgl
Discontinued for event	*23 (5)*	*24 (5)*	*11 (5)*	*7 (3)*	*19 (4)*		
abdominal pain	27 (6)	35 (8)	8 (4)	6 (2)	14 (3)	0.004	fg
Discontinued for event	*10 (2)*	*8 (2)*	*1 (<1)*	*2 (<1)*	*6 (1)*		
constipation	12 (3)	17 (4)	17 (8)	6 (2)	14 (3)	0.009	behl
Discontinued for event	*0*	*0*	*0*	*0*	*6 (1)*		
diarrhea	35 (8)	45 (10)	10 (5)	13 (5)	16 (3)	0.001	defg
Discontinued for event	*8 (2)*	*7 (2)*	*1 (<1)*	*2 (<1)*	*5 (1)*		
flatulence	11 (2)	19 (4)	6 (3)	6 (2)	3 (<1)	0.021	g
Discontinued for event	*1 (<1)*	*1 (<1)*	*0*	*1 (<1)*	*1 (<1)*		
liver function tests abnormal	6 (1)	8 (2)	0	1 (<1)	1 (<1)	0.045	g
Discontinued for event	*1 (<1)*	*0*	*0*	*1 (<1)*	*0*		
hyperglycemia	1 (<1)	1 (<1)	0	5 (2)	3 (<1)	0.009	ef
Discontinued for event	*0*	*0*	*0*	*1 (<1)*	*0*		
insomnia	4 (<1)	3 (<1)	2 (<1)	4 (2)	13 (3)	0.038	dg
Discontinued for event	*0*	*1 (<1)*	*0*	*0*	*0*		
pharyngitis	16 (3)	7 (2)	11 (5)	12 (5)	12 (3)	0.045	cf
Discontinued for event	*0*	*0*	*0*	*0*	*0*		
sinusitis	6 (1)	2 (<1)	0	1 (<1)	9 (2)	0.049	gl
Discontinued for event	*0*	*0*	*0*	*0*	0		

a: E800 vs 1200
b: E800 vs Naproxen
c: E800 vs Nabumetone
d: E800 vs Placebo
e: E1200 vs Naproxen
f: E1200 vs Nabumetone
g: E1200 vs Placebo
h: Naproxen vs Nabumetone
i: Naproxen vs placebo
j: Nabumetone vs placebo

(table continues)

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TABLE 5.3. DOUBLE-BLIND PLACEBO-CONTROLLED OA STUDIES: TESE REPORTED WITH STATISTICALLY SIGNIFICANT P-VALUES INCLUDING PREMATURE DISCONTINUATION RATE FOR EACH TESE [N (%)]

	-- Etodolac ER --		Naproxen	Nabumetone	Placebo	-- Statistical Test --	
TESE	800 mg QD	1200 mg QD	500 mg BID	1500 mg QD		Chi squared	Pairwise
Discontinuation	(N= 460)	(N= 464)	(N= 219)	(N= 244)	(N= 458)	P-Value	Comparisons
Skin & Appendages, any	33 (7)	45 (10)	7 (3)	6 (2)	24 (5)	0	cefg
Discontinued for event	*2 (<1)*	*4 (<1)*	*1 (<1)*	*3 (1)*	*3 (<1)*		
pruritus	7 (2)	16 (3)	2 (<1)	2 (<1)	6 (1)	0.035	fg
Discontinued for event	*1 (<1)*	*0*	*0*	*1 (<1)*	*1 (<1)*		

a: E800 vs 1200
b: E800 vs Naproxen
c: E800 vs Nabumetone
d: E800 vs Placebo
e: E1200 vs Naproxen
f: E1200 vs Nabumetone
g: E1200 vs Placebo
h: Naproxen vs Nabumetone
i: Naproxen vs placebo
j: Nabumetone vs placebo

TABLE 5.5. ETODOLAC ER EXPOSURE POPULATION: SIGNIFICANT DIFFERENCES[a] IN TESE BETWEEN ELDERLY AND NON-ELDERLY PATIENTS, BY DOSE OF ETODOLAC ER [N (%)]

	Etodolac ER 800 mg QD			Etodolac ER 1200 mg QD		
Event	Elderly n=411	Non-Elderly n=368	p-value	Elderly n=382	Non-Elderly n=493	p-value
Accidental injury	28 (7)	44 (12)	0.018 *	38 (10)	58 (12)	0.446
Anxiety	5 (1)	4 (1)	1.000	2 (<1)	11 (2)	0.048 *
Arrhythmia	2 (<1)	2 (<1)	1.000	6 (2)	1 (<1)	0.048 *
Asthenia	16 (4)	17 (5)	0.722	18 (5)	8 (2)	0.009 *
Back pain	26 (6)	19 (5)	0.540	18 (5)	45 (9)	0.012 *
Body as a whole , any event	86 (21)	118 (32)	0.000 *	105 (27)	147 (30)	0.498
Dizziness	22 (5)	8 (2)	0.025 *	27 (7)	19 (4)	0.046 *
Ear pain	4 (<1)	3 (<1)	1.000	0	8 (2)	0.011 *
Endocrine system , any event	2 (<1)	9 (2)	0.030 *	1 (<1)	10 (2)	0.028 *
Flu syndrome	7 (2)	27 (7)	0.000 *	17 (4)	32 (6)	0.236
Headache	41 (10)	64 (17)	0.003 *	44 (12)	89 (18)	0.008 *
Hypotension	0	0	1.000	4 (1)	0	0.036 *
Melena	3 (<1)	1 (<1)	0.626	4 (1)	0	0.036 *
Migraine	1 (<1)	7 (2)	0.030 *	1 (<1)	5 (1)	0.240
Palpitation	6 (1)	4 (1)	0.756	2 (<1)	11 (2)	0.048 *
Respiratory system, any event	101 (25)	94 (26)	0.804	85 (22)	144 (29)	0.024 *
Rhinitis	17 (4)	18 (5)	0.730	9 (2)	27 (5)	0.025 *
Sinusitis	17 (4)	22 (6)	0.253	14 (4)	44 (9)	0.002 *
Vasodilatation	6 (1)	0	0.032 *	1 (<1)	1 (<1)	1.000

a: This table includes all TESE (in alphabetical order) for which there was a significant difference between elderly and non-elderly patients for either the 800 or 1200 mg dose of etodolac ER.

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TABLE 5.6. ETODOLAC ER EXPOSURE POPULATION: SIGNIFICANT DIFFERENCES[a] IN TESE BETWEEN MEN AND WOMEN PATIENTS, BY DOSE OF ETODOLAC ER [N (%)]

	Etodolac ER 800 mg QD			Etodolac ER 1200 mg QD		
Body System	Men	Women		Men	Women	
Event	n=243	n=536	p-value	n=268	n=607	p-value
Any event	*178 (73)*	*447 (83)*	*0.001* *	*213 (79)*	*513 (85)*	*0.079*
Arrhythmia	2 (<1)	2 (<1)	0.593	5 (2)	2 (<1)	0.031 *
Bursitis	3 (1)	22 (4)	0.046 *	4 (1)	16 (3)	0.461
Diarrhea	26 (11)	79 (15)	0.141	26 (10)	92 (15)	0.032 *
Digestive system , any event	90 (37)	252 (47)	0.010 *	104 (39)	282 (46)	0.039 *
Dyspepsia	32 (13)	68 (13)	0.908	14 (5)	86 (14)	0.000 *
Endocrine system	2 (<1)	9 (2)	0.517	0	11 (2)	0.022 *
Eye hemorrhage	3 (1)	0	0.030 *	2 (<1)	2 (<1)	0.590
Flu syndrome	5 (2)	29 (5)	0.037 *	10 (4)	39 (6)	0.150
Fungal dermatitis	3 (1)	0	0.030 *	2 (<1)	5 (<1)	1.000
Headache	20 (8)	85 (16)	0.003 *	26 (10)	107 (18)	0.002 *
Hematuria	5 (2)	1 (<1)	0.013 *	2 (<1)	2 (<1)	0.590
Hernia	4 (2)	1 (<1)	0.035 *	3 (1)	2 (<1)	0.171
Local reaction to procedure	0	1 (<1)	1.000	3 (1)	0	0.029 *
Musculoskeletal system , any event	43 (18)	136 (25)	0.021 *	65 (24)	178 (29)	0.140
Nervous system , any event	51 (21)	158 (29)	0.014 *	60 (22)	190 (31)	0.007 *
Peripheral edema	5 (2)	31 (6)	0.026 *	8 (3)	44 (7)	0.013 *
Prostatic disorder	3 (1)	0	0.030 *	3 (1)	0	0.029 *
Pruritus	4 (2)	11 (2)	1.000	3 (1)	24 (4)	0.032 *
Respiratory system , any event	52 (21)	143 (27)	0.129	57 (21)	172 (28)	0.030 *
Sinusitis	9 (4)	30 (6)	0.293	10 (4)	48 (8)	0.026 *
Skin and appendages , any event	24 (10)	75 (14)	0.131	31 (12)	111 (18)	0.013 *
Sweating	0	4 (<1)	0.316	5 (2)	2 (<1)	0.031 *
Tenosynovitis	1 (<1)	22 (4)	0.003 *	3 (1)	13 (2)	0.415
Weight loss	4 (2)	1 (<1)	0.035 *	2 (<1)	4 (<1)	1.000

a: This table includes all TESE (in alphabetical order) for which there was a significant difference between men and women patients for either the 800 or 1200 mg dose of etodolac ER.

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TABLE 6.1. NUMBER (%) OF ETODOLAC ER PATIENTS PREMATURELY DISCONTINUED, BY PATIENT POPULATION

	Pooled Etodolac ER Etodolac ER[A]			Double-Blind Placebo-Controlled OA Studies: Etodolac ER[B]		Open-Label OA Studies: Etodolac ER[A]		
Category	800 mg QD (n= 779)	1200 mg QD (n= 875)	Total (n= 1654)	800 mg QD (n= 460)	1200 mg QD (n= 464)	800 mg QD (n=520)	1200 mg QD (n=599)	Total (n=1119)
Total Discontinued[D]	520 (67)	588 (67)	1108 (67)	64 (14)	60 (13)	264 (51)	310 (52)	574 (51)
< 65 years [C]	232 (45)	302 (51)	534 (48)	30 (47)	24 (40)	115 (44)	172 (56)	287 (50)
≥ 65 years [C]	288 (55)	286 (49)	574 (52)	34 (53)	36 (60)	149 (56)	138 (44)	287 (50)
Men [C]	162 (31)	175 (30)	337 (30)	21 (33)	14 (23)	81 (31)	102 (33)	183 (32)
Women [C]	358 (69)	413 (70)	771 (70)	43 (67)	46 (77)	183 (69)	208 (67)	391 (68)
Reasons For Discontinuation								
Adverse Reaction								
Primary	154 (20)	125 (14)	279 (17)	27 (6)	29 (6)	115 (22)	57 (10)	172 (15)
[All]	[154 (20)]	[128 (15)]	[282 (17)]	[27 (6)]	[29 (6)]	[115 (22)]	[57 (10)]	[172 (15)]
Failed to Return								
Primary	11 (1)	19 (2)	30 (2)	2 (<1)	2 (<1)	11 (2)	13 (2)	24 (2)
[All]	[15 (2)]	[24 (3)]	[39 (2)]	[2 (<1)]	[2 (<1)]	[15 (3)]	[17 (3)]	[32 (3)]
Patient Request								
Primary	53 (7)	45 (5)	98 (6)	0	20 (4)	22 (4)	18 (3)	40 (4)
[All]	[59 (8)]	[49 (6)]	[108 (7)]	[2 (<1)]	[22 (5)]	[25 (5)]	[23 (4)]	[38 (4)]
Unsatisfactory Response (efficacy)								
Primary	106 (14)	176 (20)	282 (17)	25 (5)	20 (4)	49 (9)	140 (23)	189 (17)
[All]	[127 (16)]	[198 (23)]	[325 (20)]	[27 (6)]	[22 (5)]	66 (13)	157 (26)	223 (20)

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TABLE 6.1. NUMBER (%) OF ETODOLAC ER PATIENTS PREMATURELY DISCONTINUED, BY PATIENT POPULATION

	Pooled Etodolac ER Etodolac ER[A]			Double-Blind Placebo-Controlled OA Studies: Etodolac ER[B]		Open-Label OA Studies: Etodolac ER[A]		
Category	800 mg QD (n= 779)	1200 mg QD (n= 875)	Total (n= 1654)	800 mg QD (n= 460)	1200 mg QD (n= 464)	800 mg QD (n=520)	1200 mg QD (n=599)	Total (n=1119)
Total Discontinued[D]	520 (67)	588 (67)	1108 (67)	64 (14)	60 (13)	264 (51)	310 (52)	574 (51)
Protocol Violation								
Primary	25 (3)	36 (4)	61 (4)	5 (1)	3 (<1)	15 (3)	28 (5)	43 (4)
[All]	[37 (5)]	[47 (5)]	[84 (5)]	[7 (2)]	[3 (<1)]	[24 (5)]	[40 (7)]	[64 (6)]
Patient Uncooperative								
Primary	0	0	0	0	0	0	0	0
[All]	[1 (<1)]	[0]	[1 (<1)]	[0]	[0]	[1 (<1)]	[0]	[1 (<1)]
Other Medical Event								
Primary	59 (8)	59 (7)	118 (7)	3 (<1)	3 (<1)	49 (9)	48 (8)	97 (9)
[All]	[62 (8)]	[60 (7)]	[122 (7)]	[3 (<1)]	[3 (<1)]	[50 (10)]	[50 (8)]	[100 (9)]
Other non-Medical Event								
Primary	17 (2)	11 (1)	28 (2)	2 (<1)	1 (<1)	3 (<1)	6 (1)	9 (<1)
[All]	[20 (3)]	[15 (2)]	[35 (2)]	[2 (<1)]	[1 (<1)]	[3 (<1)]	[9 (2)]	[12 (1)]
Administrative Reason								
Primary	95 (12)[E]	117 (13)[E]	212 (13)[E]	0	0	0	0	0
[All]	[95 (12)]	[118 (13)]	[213 (13)]	[0]	[1 (<1)]	[0]	[0]	[0]

A: Shown by predominant daily dose of etodolac ER.

B: Does not include those patients who did not enter the open-label segment because of Adverse Reaction, Other Medical Event, or Unsatisfactory Response (efficacy) in the washout.

C: Percentages based on total number of patients discontinued for that treatment group.

D: Percentages based on total number of patients in treatment group.

E: 212 of the 213 patients who completed the double-blind segment but did not continue into the open-label segment were ineligible because the open-label protocol amendment had not yet been approved.

TABLE 6.4: ETODOLAC ER EXPOSURE POPULATION: STUDY EVENTS CAUSING DISCONTINUATION[a] (AND SPECIFIC EVENTS REPORTED FOR ≥3% IN ANY GROUP) BY BODY SYSTEM [N(%) PATIENTS]

	Predominant Dose of Etodolac ER		
Body System	800 mg QD	1200 mg QD	TOTAL
Event	(n=779)	(n=875)	(n=1654)
Any Adverse Experience	*214 (27)*	*187 (21)*	*401(24)*
Body As A Whole	17 (2)	20 (2)	37 (2)
Cardiovascular System	26 (3)	16 (2)	42 (3)
Digestive System	104 (13)	96 (11)	200 (12)
>>> Abdominal pain	36 (5)	26 (3)	62 (4)
Diarrhea	30 (4)	30 (3)	60 (4)
Dyspepsia	15 (2)	23 (3)	38 (2)
Endocrine System	1 (<1)	0	1 (<1)
Hemic And Lymphatic System	4 (<1)	6 (<1)	10 (1)
Metabolic And Nutritional	20 (3)	8 (<1)	28 (2)
Musculoskeletal System	21 (3)	21 (2)	42 (3)
Nervous System	28 (4)	21 (2)	49 (3)
Skin And Appendages	18 (2)	18 (2)	36 (2)
Special Senses	8 (1)	2 (<1)	10 (1)
Urogenital System	5 (<1)	9 (1)	14 (1)

a: Events causing any discontinuation for Adverse Event or Other Medical Event

TABLE 6.5A ETODOLAC ER EXPOSURE POPULATION STUDIES
N (%) OF PATIENTS WHO PREMATURELY DISCONTINUED FROM THE DOUBLE-BLIND SEGMENTS

Reason for Discontinuation	Etodolac ER 800 mg QD (n=460)	Etodolac ER 1200 mg QD (n=464)	Nabumetone 1500 mg QD (n=244)	Naproxen 500 mg BID (n=219)	Placebo – (n=458)	p-value
Total Discontinued	*64 (14)*	*60 (13)*	*35 (14)*	*35 (16)*	*139 (30)*	*<0.001*
Adverse Reaction						
Primary	27 (6)	29 (6)	11 (5)	14 (6)	19 (4)	0.550
[All]	[27 (6)]	[29 (6)]	[11 (5)]	[14 (6)]	[19 (4)]	0.550
Failed to Return						
Primary	2 (<1)	2 (<1)	0	1 (<1)	0	0.544
[All]	[2 (<1)]	[3 (<1)]	[0]	[2 (<1)]	[1 (<1)]	0.524
Patient Request						
Primary	0	2 (<1)	3 (1)	1 (<1)	6 (1)	0.098
[All]	[2 (<1)]	[2 (<1)]	[3 (1)]	[1 (<1)]	[6 (1)]	0.388
Unsatisfactory Response (efficacy)						
Primary	25 (5)	20 (4)	19 (8)	16 (7)	99 (22)	<0.001
[All]	[27 (6)]	[22 (5)]	[23 (9)]	[17 (8)]	[106 (23)]	<0.001
Patient Uncooperative						
Primary	0	0	0	0	0	
[All]	[0]	[0]	[0]	[0]	[1 (<1)]	0.553
Protocol Violation						
Primary	5 (1)	3 (<1)	2 (<1)	0	7 (2)	0.350
[All]	[7 (2)]	[3 (<1)]	[3 (1)]	[0]	[8 (2)]	0.227
Other Medical Event						
Primary	3 (<1)	3 (<1)	0	3 (1)	7 (2)	0.230
[All]	[3 (<1)]	[3 (<1)]	[0]	[3 (1)]	[7 (2)]	0.230
Other non-Medical Event						
Primary	2 (<1)	1 (<1)	0	0	1 (<1)	0.733
[All]	[2 (<1)]	[1 (<1)]	[0]	[0]	[1 (<1)]	0.733
Administrative Reason						
Primary	0	0	0	0	0	
[All]	[0]	[1 (<1)]	[0]	[0]	[0]	0.562

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TABLE 6.6 ETODOLAC ER EXPOSURE POPULATION STUDIES
STUDY EVENTS CAUSING PREMATURE DISCONTINUATION[a,b] [N (%) PATIENTS]

Body system	Etodolac ER 800 QD	Etodolac ER 1200	Nabumetone 1500 QD	Naproxen 500 BID	Placebo –
Event	n=460	n=464	n=244	n=219	n=458
Total Discontinued for Study Event	*35 (8)*	*39 (8)*	*16 (7)*	*19 (9)*	*31 (7)*
Body as a whole	2 (<1)	2 (<1)	1 (<1)	3 (1)	5 (1)
Accidental injury	1 (<1)	0	1 (<1)	0	1 (<1)
Chest pain	0	0	0	2 (<1)	1 (<1)
Chills	0	1 (<1)	0	0	1 (<1)
Fever	0	1 (<1)	0	0	1 (<1)
Flu syndrome	0	0	0	0	1 (<1)
Hernia	0	0	0	1 (<1)	0
Infection	1 (<1)	0	0	0	0
Pain	0	1 (<1)	0	1 (<1)	1 (<1)
Sepsis	0	0	0	0	1 (<1)
Cardiovascular system	4 (<1)	3 (<1)	0	3 (1)	3 (<1)
Atrial fibrillation	1 (<1)	0	0	0	0
Cerebral ischemia	0	0	0	0	1 (<1)
Hypertension	1 (<1)	0	0	1 (<1)	1 (<1)
Hypotension	0	0	0	0	1 (<1)
Migraine	0	0	0	1 (<1)	0
Myocardial infarct	1 (<1)	0	0	0	0
Palpitation	1 (<1)	3 (<1)	0	1 (<1)	0
Tachycardia	0	0	0	0	1 (<1)
Vasodilatation	0	0	0	0	1 (<1)
Digestive system	23 (5)	24 (5)	7 (3)	11 (5)	19 (4)
>>> Abdominal pain	10 (2)	8 (2)	2 (<1)	1 (<1)	6 (1)
Anorexia	0	0	0	0	1 (<1)
Cholecystitis	0	1 (<1)	0	0	0
Cholelithiasis	0	0	0	1 (<1)	0
Constipation	0	0	0	0	2 (<1)
Diarrhea	8 (2)	7 (2)	2 (<1)	1 (<1)	5 (1)
Duodenitis	0	0	0	1 (<1)	0
Dyspepsia	2 (<1)	8 (2)	4 (2)	4 (2)	3 (<1)
Eructation	1 (<1)	0	0	0	0
Esophagitis	0	0	0	0	1 (<1)
Fecal incontinence	0	1 (<1)	0	0	0
Flatulence	1 (<1)	1 (<1)	1 (<1)	0	1 (<1)
Gastritis	0	0	0	1 (<1)	0
Gastrointestinal disorder	1 (<1)	0	0	0	0
Gastrointestinal hemorrhage	0	1 (<1)	0	0	0
Hepatitis	0	1 (<1)	0	0	0
Liver function tests abnormal	1 (<1)	0	1 (<1)	0	0
Melena	0	1 (<1)	0	0	0
Nausea	6 (1)	2 (<1)	1 (<1)	4 (2)	5 (1)
Rectal disorder	0	0	0	1 (<1)	0
Stomatitis	1 (<1)	0	0	0	0
Stools abnormal	1 (<1)	0	0	0	0
Vomiting	0	2 (<1)	0	0	2 (<1)

(table continues)

TABLE 6.6 ETODOLAC ER EXPOSURE POPULATION STUDIES
STUDY EVENTS CAUSING PREMATURE DISCONTINUATION[a,b] [N (%) PATIENTS]

Body system Event	Etodolac ER 800 QD n=460	Etodolac ER 1200 n=464	Nabumetone 1500 QD n=244	Naproxen 500 BID n=219	Placebo n=458
Metabolic and nutritional	1 (<1)	2 (<1)	2 (<1)	2 (<1)	0
BUN increased	0	1 (<1)	0	1 (<1)	0
Creatinine increased	0	1 (<1)	0	0	0
Generalized edema	0	0	1 (<1)	1 (<1)	0
Hyperglycemia	0	0	1 (<1)	0	0
Peripheral edema	1 (<1)	1 (<1)	0	0	0
Musculoskeletal system	1 (<1)	1 (<1)	0	0	5 (1)
>>> Back pain	0	1 (<1)	0	0	2 (<1)
>>> Neck pain	0	0	0	0	1 (<1)
Arthritis	0	0	0	0	1 (<1)
Joint disorder	0	0	0	0	1 (<1)
Leg cramps	0	0	0	0	1 (<1)
Myalgia	1 (<1)	0	0	0	0
Nervous system	9 (2)	9 (2)	3 (1)	4 (2)	5 (1)
>>> Asthenia	1 (<1)	1 (<1)	0	0	0
>>> Headache	2 (<1)	2 (<1)	0	2 (<1)	2 (<1)
>>> Malaise	0	0	0	0	1 (<1)
Circumoral paresthesia	1 (<1)	0	0	0	0
Dizziness	4 (<1)	2 (<1)	3 (1)	3 (1)	1 (<1)
Facial paralysis	0	1 (<1)	0	0	0
Insomnia	0	1 (<1)	0	0	0
Nervousness	1 (<1)		0	0	0
Somnolence	1 (<1)	1 (<1)	0	0	1 (<1)
Tremor	0	1 (<1)	0	0	0
Respiratory system	2 (<1)	1 (<1)	0	0	0
Dyspnea	1 (<1)	1 (<1)	0	0	0
Epistaxis	1 (<1)	0	0	0	0
Lung edema	1 (<1)	0	0	0	0
Skin and appendages	2 (<1)	4 (<1)	3 (1)	1 (<1)	3 (<1)
>>> Allergic reaction	1 (<1)	0	0	0	1 (<1)
Maculopapular rash	0	1 (<1)	1 (<1)	0	1 (<1)
Pruritus	1 (<1)	0	1 (<1)	0	1 (<1)
Rash	0	2 (<1)	1 (<1)	1 (<1)	0
Urticaria	0	1 (<1)	0	0	0
Special senses	3 (<1)	0	0	1 (<1)	1 (<1)
>>> Vertigo	2 (<1)	0	0	0	0
Abnormality of accommodation	0	0	0	0	1 (<1)
Tinnitus	1 (<1)	0	0	1 (<1)	0
Urogenital system	0	2 (<1)	0	0	0
Oliguria	0	1 (<1)	0	0	0
Urinary frequency	0	1 (<1)	0	0	0

a: Includes patients who did not enroll in the open-label segments because of Adverse Reaction and Other Medical Event.
b: Reasons for discontinuation include Adverse Reaction and Other Medical Event

TABLE 6.9: ETODOLAC ER EXPOSURE POPULATION: N(%) OF ELDERLY AND NON-ELDERLY PATIENTS WHO PREMATURELY DISCONTINUED TREATMENT, BY PREDOMINANT DOSE OF ETODOLAC ER

Reason for Discontinuation	Etodolac ER 800 mg QD			Etodolac ER 1200 mg QD		
	Elderly (n=411)	Non-elderly (n=368)	p-value	Elderly (n=382)	Non-elderly (n=493)	p-value
Total Discontinued	***230 (56)***	***195 (53)***	***0.428***	***225 (59)***	***246 (50)***	***0.009***
Adverse Reaction						
Primary	88 (21)	66 (18)	0.242	68 (18)	57 (12)	0.011
All	88 (21)	66 (18)	0.242	70 (18)	58 (12)	0.007
Failed to Return						
Primary	3 (<1)	8 (2)	0.127	5 (1)	14 (3)	0.161
All	5 (1)	10 (3)	0.190	7 (2)	17 (3)	0.210
Patient Request						
Primary	26 (6)	27 (7)	0.669	20 (5)	25 (5)	1.000
All	29 (7)	30 (8)	0.589	22 (6)	27 (5)	0.883
Unsatisfactory Response - Efficacy						
Primary	50 (12)	56 (15)	0.250	78 (20)	98 (20)	0.865
All	65 (16)	62 (17)	0.699	91 (24)	107 (22)	0.465
Protocol Violation						
Primary	18 (4)	7 (2)	0.066	16 (4)	20 (4)	1.000
All	26 (6)	11 (3)	0.042	19 (5)	28 (6)	0.763
Patient Uncooperative						
Primary	0	0	1.000	0	0	1.000
All	1 (<1)	0	1.000	0	0	1.000
Other Medical Event						
Primary	40 (10)	19 (5)	0.021	32 (8)	27 (5)	0.103
All	43 (10)	19 (5)	0.008	33 (9)	27 (5)	0.079
Other Non-Medical Event						
Primary	5 (1)	12 (3)	0.083	6 (2)	5 (1)	0.547
All	6 (1)	14 (4)	0.043	6 (2)	9 (2)	1.000
Administrative Reason						
Primary	58 (14)	37 (10)	0.100	61 (16)	56 (11)	0.057
All	58 (14)	37 (10)	0.100	62 (16)	56 (11)	0.046

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TABLE 7.4A. NUMBER OF PATIENTS IN THE ETODOLAC ER EXPOSURE STUDIES : DOUBLE-BLIND[a] SEGMENTS
PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT HEPATIC LABORATORY TEST RESULTS[b]

Laboratory Test	Level of Potential Clinical Importance	-------Etodolac ER------- 800 mg QD	1200 mg QD	Etodolac 400 mg TID	Naproxen 500 mg BID	Nabumetone 1500 mg QD	Placebo --
		(n = 566)	(n = 576)	(n = 113)	(n = 219)	(n = 244)	(n = 458)
SGOT	≥ 3.0 times UNL[c]	1 [37012-0022][d,e]	2 [37102-0015][d] [37115-0016][d]	0	0	1 [35821-0025][d]	1 [37003-0010]
SGPT	≥ 3.0 times UNL	2 [37012-0022][e] [37021-0022]	3 [35701-0007] [37102-0015] [37115-0016]	0	0	1 [35821-0025]	0
Alkaline phosphatase	≥ 3.0 times UNL	0	2 [37102-0015] [37115-0016]	0	0	0	0
Total bilirubin	≥ 1.8 mg/dL	5 [32313-0012] [32318-0009] [35801-0024] [37004-0007] [37119-0023]	8 [32317-0002] [32323-0006] [35803-0002] [35805-0030] [35812-0002] [35813-0032] [37004-0025] [37102-0015]	1 [32313-0001]	1 [35715-0022]	0	2 [37007-0014] [37016-0005]

a: This table includes patients from Double-blind studies 0654D-323-US, -357-US, -358-US, -370-US, -371-US.
b: Patient identification numbers given in brackets.
c: UNL = upper limit of the normal range.
d: Patients had elevations in multiple lab tests.
e: elevations observed at Baseline.

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TABLE 7.8A. NUMBER OF PATIENTS IN THE ETODOLAC ER EXPOSURE STUDIES : DOUBLE-BLIND[a] SEGMENTS
PATIENTS WITH POTENTIALLY CLINICALLY IMPORTANT RENAL LABORATORY TEST RESULTS[b]

	Level of Potential	-------Etodolac ER-------		Etodolac	Naproxen	Nabumetone	Placebo
Laboratory Test	Clinical Importance	800 mg QD	1200 mg QD	400 mg TID	500 mg BID	1500 mg QD	--
		(n = 566)	(n = 576)	(n = 113)	(n = 219)	(n = 244)	(n = 458)
BUN	≥ 40 mg/dL	2 [32301-0003] [32309-0001][c]	5 [32320-0011] [35811-0012] [37003-0001] [37013-0013][c] [37015-0005]	0	1 [35714-0017]	2 [35805-0013] [37116-0011]	2 [35716-0016] [35718-0030][c]
Creatinine	≥ 2.0 mg/dL	2 [32309-0001] [37110-0017]	3 [32323-0006] [37013-0013] [37014-0015]	1 [32303-0015]	1 [37003-0007]	0	2 [35711-0014] [35718-0030]

a: This table includes patients from Double-blind studies 0654D-323-US, -357-US, -358-US, -370-US, -371-US
b: Patient identification numbers given in brackets.
c: Patient had elevations in multiple lab tests.