CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-584/S003

STATISTICAL REVIEW(S)

550 Keener

AUG 18 1998

Statistical Review and Evaluation

NDA: 20-584 / S003

Drug Class: Nonsteroidal Anti-inflammatory Agent

Name of Drug: Lodine XL (Etodolac Extended Release) 400, 500 and 600 mg

Indications: Treatment of Signs/Symptoms of OA; Pain Relief

Applicant: Wyeth Ayerst

Submission Date: November 11, 1997

Controlled Clinical Studies: 654-D-323-US; 654-D-357-US; 654-D-358-US; 654-D-370-US; 654-D-371-US + Open Label Extensions on All

Volumes Reviewed: 1; 71; 73; 74; 76-78 + electronic data

Review Date: June 30, 1998
User Fee Date: November 12, 1998
Statistical Reviewer: Lillian Patrician, MS, MBA

1. Background

This statistical report is based on a review of data on the use of Lodine XL (etodolac extended release) formulation taken at a 1200 mg QD dose. The protocols, study reports, and case report forms also refer to Lodine XL as Etodolac ER (extended release) in Studies 357, 358, 370, and 371, and Etodolac SR (sustained release) in Study 323. The sponsor was asked to provide data from at least 300 patients treated for at least 6 months with 1200 mg/day continuous dosing, to support subsequent approval of a maximum daily dose of 1200 mg/day. The sponsor is seeking a labeling change from 1000 mg qd to 1200 mg qd.

Etodolac is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic, and antipyretic activity. The mechanism of action is not known, but it is believed to be associated with the inhibition of prostaglandin biosynthesis. Etodolac (Lodine) was approved by the FDA in January, 1991 under NDA 18-922 for acute and long-term use in the management of the signs and symptoms of osteoarthritis (OA) and for the management of pain. Etodolac Extended Release (ER) was developed under [redacted] to provide a once-daily dosage form. The sponsor reports that Lodine and etodolac ER both contain etodolac, and that they differ only in their release characteristics. "Etodolac is released from Lodine tablets or capsules in the stomach and small intestine, whereas Etodolac ER slowly releases etodolac from the tablet throughout the gastrointestinal tract as a result of the hydration and erosion characteristics of the tablet matrix." ***[Vol 1.1, page 81]***

The sponsor is not seeking a claim for treatment of patients with rheumatoid arthritis because "in controlled clinical trials, Lodine was generally not as effective as treatment with other marketed NSAIDs". Etodolac ER is also not being recommended for treatment of acute pain because "it would be expected to have a delayed analgesic response due to its extended-release characteristics". ***[Vol 1.1, pages 94-96]***

Prior to approval of Lodine XL formulation, the FDA statistical review of Study 654-D-022-US (gastrointestinal micro bleeding study in healthy volunteers); and Studies 654-D-321 and 654-D-323-US (clinical efficacy studies in patients with osteoarthritis of the knee) was completed January, 1996. The Statistical Reviewer concluded that both etodolac ER 800mg qd and etodolac ER 1200mg qd were generally comparable with etodolac 400mg tid in relieving the signs and symptoms of osteoarthritis in patients with OA of the knee for about 8 to 12 weeks. For treatment beyond 12 weeks, etodolac 400mg tid appeared to be slightly more efficacious that the 2 doses of etodolac ER. It was suggested that beyond 12 weeks some patients taking ER 800mg qd may also need to increase the dosage to ER 1200mg qd. The reviewer determined that both studies suggested adverse events in the digestive system may be slightly lower in the ER than in the immediate release formulation.

II. Studies 654-D-323-US; 654-D-357-US; 654-D-358-US; 654-D-370-US; 654-D-371-US

1. Study Designs ***[Attachment # 1 - Page 8]***

These were 5 double-blind, randomized, parallel group studies in outpatients with knee OA. Those with initial double blind segments were placebo-controlled and compared 2 doses of etodolac ER (800 mg and 1200 mg QD) with either Naproxen or Nabumetone. Some had a subsequent single blind segment. All 5 studies had an open-label extension with etodolac ER for up to 2 years.

The sponsor submitted data for those patients who took a predominant etodolac ER dose of either 800 or 1200 mg QD. After comparing the number of days a patient had taken each dose of etodolac ER (800 or 1200), the sponsor determined the predominant dose as that taken for the higher number of days. These patients received a dose of 800 or 1200 mg QD for at least 185 days (6 months) and continued until the patient discontinued or changed dose.

2. Sponsor's Results

With regard to adverse reactions, the sponsor reports, "In comparative trials in 567 patients with osteoarthritis who received etodolac ER or Lodine (600 to 1200 mg/day), there were generally no differences in the occurrence of study events. The overall occurrence of Digestive System events was lower in patients treated with etodolac ER than with those treated with Lodine. Overall, the incidence of dyspepsia was approximately 46% lower in patients treated with etodolac ER than those treated with Lodine". The extended-release formulation is being marketed since 1994 in 11 countries outside the U.S.A., and has not been withdrawn from any market for regulatory, safety, or marketing reasons. ***[Vol 1.1, page 109]***

3. Data Examined *[Attachment # 2 - Page 9]*

The data examined in this review are a pool from 5 separate studies of patients who received for at least 6 months a predominant daily dose of either 800 mg or 1200 mg of etodolac ER. These patients received varying levels of study drug during the full course of study (double-blind, single-blind, and then-open-label), but much of the determination for predominant dose was indicated during the open label extension period.

Because of the pooling across studies, the mix of treatment periods and blinding, and the lack of comparator arms (both placebo and active drug comparators such as Naproxen and Nabutemone), formal statistical analyses of between-treatment group comparisons of event rates and discontinuation rates were not performed. However, this reviewer developed descriptive statistics in examining occurrence rates for study events and discontinuations of these patients according to their predominant dose group. The sponsor termed "study event" as "any negative medical event that a patient experienced during the study, e.g. adverse drug reaction, adverse experience, treatment-emergent signs and symptoms, new intercurrent illness." ***[Vol 106, protocol 358]***

4. Enrollment and Evaluable for Safety: *[Attachment # 2 - Page 9]*

Of the 1,654 patients enrolled in Studies 654-D-323, -357, -358, -370, and -371, 779 (47%) received a predominant dose of 800 mg Etodolac ER and 875 (53%) received 1200 mg. As would be expected in populations of osteoarthritis patients, there were more women (1,143 or 69%) than men (511 or 31%). Slightly more females and males received the predominant dose of 1200 mg etodolac ER; 607 females (37%) and 268 males (16%) received 1200 mg, whereas 536 females (32%) and 243 males (15%) received 800 mg. The patient enrollment was predominantly Caucasian (1,464 or 89%), although 143 were of black (9%) and 47 were of other (3%) ethnic origin. Fifteen percent of the patients receiving 800 mg dose were 40 to 60 years of age and 31% were greater than 60 years old, whereas 20% of the 1200 mg dose group were 40 to 60 years of age and 32% were greater than 60 years old.

5. Discontinuation from Study: *[Attachments # 3 & 4 - Pages 10 - 11]*

The comparisons of reported reasons for discontinuation are between the 800 mg and 1200 mg doses of etodolac ER, and do not include any comparative data for patients receiving placebo or active comparator agents.

Patients from the 2 dose groups discontinued from study at approximately the same rate, with the highest percentage of dropouts (24%) for both groups realized in the first six months. The primary reason for discontinuation was unsatisfactory efficacy response with a significantly higher rate of discontinuation seen in the 1200 mg dose group; during the first 6 months of study 11% of the 1200 mg patient group and 6% of the 800 mg dose group discontinued due to unsatisfactory response with regard to efficacy. An additional 9% of the patients in both groups discontinued due to adverse experiences, most of which occurred during the first 6 months of study. There were also comparably high discontinuations for administrative requests (7%) and patient requests (3%). The remaining discontinuations from study were reported as other

medical/nonmedical events (5% for each group), protocol violations (2% for each group), and failure to return (1% for each group).

Deaths: One death occurred in the 800 mg dose group and 4 in the 1200 mg dose group. All patients were over 60 years of age; diagnosed with degenerative joint disease of the knee; under study for more than 6 months; and determined to have died from causes unrelated to study drug. The 800 mg etodolac ER patient, #35704-0026, was a 72 year old white male who was on study for 423 days and died of meningitis. Of the 4 patients receiving 1200 mg etodolac ER, #35811-0019 was a 69 year old white male on study for 214 days with cause of death, acute cardiac dysrhythmia. The second patient, #37007-0026, was an 81 year old white male on study for 261 days who died of congestive heart failure and pneumonia. The third, #37013-0018, was a 77 year old white male on study for 469 days whose cause of death was gastrointestinal carcinoma (liver cancer). The fourth 1200 mg patient, #37115-0004, was a 64 year old female of other ethnic background who was on study for 212 days and died of a myocardial infarct during her sleep.

6. Adverse Experiences: *[Attachments # 5 - 7 - Pages 12 - 24]*

A total of 5,135 adverse experiences (one incident per patient although multiple incidences at times occurred) were reported for the 1,654 patients in both dose groups.

800 mg Dose Group: Of the 779 patients receiving 800 mg etodolac ER, 638 or 80% reported 2,393 adverse experiences (47% of all experiences reported), 871 or 36% of which occurred during the first 6 months of study and 1,522 or 64% after 6 months on study. Of these 779 patients who were evaluable for safety, 411 or 53% reported treatment-related adverse experiences and 154 or 20% discontinued for reasons associated with the adverse experiences.

One death occurred after 6 months on study. Of the 2,393 experiences reported by this 800 mg patient group, 2,259 or 94% were deemed as treatment-emergent side effects. Two hundred nine (209) or 9% were severe, 1047 or 44% were moderate, and 1137 or 47% were mild. Eight hundred eleven (811) of the adverse experiences were deemed drug-related (10 definitely and 801 possibly/probably) with 437 or 54% occurring during the first 6 months and 374 or 46% occurring after 6 months on study.

Of the 2,393 adverse experiences reported, 1,083 or 45% persisted; 1,056 or 44% required that specific therapy be given to the patient; 338 or 14% required other action such as hospitalization; 232 or 10% required discontinuation from scheduled study plan; 125 or 5% required temporary stoppage of study drug; and 19 or less than 1% required reduction in dose of study drug.

The highest incidence of adverse experiences was 634 or 26% seen in the digestive system for which 7 reports were deemed definitely drug-related and 443 probably/possibly related. Forty-seven or 2% were classified as severe, 244 or 10% moderate, and 343 or 14% mild in severity. Six hundred eleven (611) or 26% were considered treatment emergent side effects. Three hundred ninety-three (393) disappeared, whereas 241 persisted.

The second most prevalent incidence was 311 or 13% reported under the nervous system. One was definitely related and 97 were probably/possibly related. Twenty-five (25) were severe; 123

or 5% were moderate; and 163 or 7% were mild in severity.

Of the 2,393 adverse experiences, 10 or less than 1% were deemed definitely related to etodolac ER (7 definitely-related incidences occurred in the digestive system). However, 801 or 33% were considered probably/possibly related to study drug. Of these, 443 occurred in the digestive system, 97 in the nervous system, and 62 in the metabolic and nutritional systems.

1200 mg Dose Group Of the 875 patients receiving 1200 mg etodolac ER, 738 or 84% reported 2,742 adverse experiences (53% of all reported), 845 or 31% of which occurred during the first 6 months on study and 1,897 or 69% after 6 months on study. Of these 875 patients who were evaluable for safety, 445 or 51% reported treatment-related adverse experiences and 128 or 15% discontinued due to the adverse experiences.

Four deaths occurred after 6 months on study. Of the 2,742 experiences reported by the 1200 mg patient group, 2,594 or 95% were deemed as treatment-emergent side effects. Two hundred seventy-six (276) or 10% were severe; 1253 or 46% were moderate; and 1213 or 44% were mild. Eight hundred twenty-one (821) of the adverse experiences were deemed drug-related (13 definitely and 808 possibly/probably) with 396 or 48% occurring during the first 6 months and 425 or 52% occurring after 6 months on study.

Of the 2,742 adverse experiences reported, 1,233 or 45% persisted; 1,253 or 46% required that specific therapy be given to the patient; 404 or 15% required other action such as hospitalization; 193 or 7% required discontinuation from scheduled study plan; 113 or 4% required temporary stoppage of study drug; and 11 or less than 1% required reduction in dose of study drug.

Again, the highest incidence of adverse experiences was 649 or 24% seen in the digestive system for which 10 reports were deemed definitely drug-related and 426 probably/possibly related. Sixty or 2% were classified as severe, 257 or 9% moderate, and 332 or 12% mild in severity. Six hundred twenty-six (626) or 23% were considered treatment emergent side effects. Three hundred eighty-five (385) disappeared, whereas 262 persisted.

Of the 335 or 12% of adverse experiences reported under the nervous system, none were definitely related and 91 were probably/possibly related. Twenty-eight (28) were severe; 143 or 5% were moderate; and 164 or 6% were mild in severity.

Of the 2,742 adverse experiences, 13 or less than 1% were deemed definitely related to etodolac ER (10 definitely-related incidences occurred in the digestive system). However, 808 or 29% were considered probably/possibly related to study drug. Of these, 426 occurred in the digestive system, 91 in the nervous system, and 86 in the metabolic and nutritional systems.

7. Adverse Experiences - Digestive System: *[Attachments # 8 & 9 - Pages 25 - 31]*

Of the 1,283 adverse experiences classified under the Digestive System, 634 occurred in patients receiving 800 mg etodolac ER and 649 in those in the 1200 mg dose group. Most cases were moderate to mild in severity, with comparable incidence between dose groups: 587 cases in the 800 mg group and 589 in the 1200 mg group.

Abdominal pain exhibited the highest incidence in both dose groups: a total of 189 cases distributed as 25 severe cases reported by 11 patients receiving 800 mg and 14 receiving 1200 mg; 98 moderate cases reported by 56 patients receiving 800 mg and 42 patients receiving 1200 mg; and 66 mild cases reported by 29 patients receiving 800 mg and 37 patients receiving 1200 mg.

Other digestive system events of noteworthy yet still comparable incidence between the 2 dosage groups were:

diarrhea	(227 cases:	108 or 14% in 800 mg group and 117 or 14% in 1200 mg group);
dyspepsia	(215 cases:	107 or 14% in 800 mg group and 92 or 11% in 1200 mg group);
nausea	(121 cases:	60 in 800 mg group and 61 in 1200 mg group);
constipation	(81 cases:	42 in 800 mg group and 39 in 1200 mg group);
flatulence	(70 cases:	35 in 800 mg group and 35 in 1200 mg group);
abnormal liver function tests	(46 cases:	16 in 800 mg group and 30 in 1200 mg group).

There were also reports of anorexia; colitis; dry mouth; eructation; esophagitis; gastritis; gastroenteritis; gatrointestinal disorder; mouth ulceration; vomiting; abnormal stool; and rectal hemorrhage.

8. Patients Receiving Etodolac ER for at least 6 months

Of the 834 patients remaining on study for at least 6 months, 369 or 44% were receiving a predominant continuous daily dose of 800 mg etodolac ER, and 465 or 56% were receiving 1200 mg etodolac ER. Both dose groups show a comparable rate of discontinuation, i.e. 67% patients remaining 6 months into study for each group discontinued. However, there was again a greater percentage of those receiving a predominant dose of 1200 mg who discontinued for reasons of unsatisfactory response in efficacy. Twenty percent of the 1200 mg patient group versus 14% of the 800 mg group discontinued for lack of efficacy. More patients receiving 800 mg etodolac ER reported adverse experiences during this time period; 20% of the 800 mg group discontinued due to adverse experiences versus 14% of the 1200 mg group.

III. Reviewer's Overall Comments

This Reviewer's comparisons of safety data with regard to reasons for discontinuation and adverse experiences are between the daily 800 mg and 1200 mg doses of etodolac ER for the entire time period in which study drug was taken; i.e. this review is an examination of safety data for drug taken during the first 6 months and after 6 months. A greater percentage of patients

receiving a predominant dose of 1200 mg ER discontinued for reasons of unsatisfactory response in efficacy (198 or 23% of the 1200 mg group versus 127 or 16% of the 800 mg group). However, more patients receiving 800 mg etodolac ER discontinued due to adverse experiences (154 or 20% of the 800 mg group versus 128 or 15% of the 1200 mg group).

This examination of safety data does not include any comparative data for patients receiving placebo or active comparator agents. Therefore, the comparability between dosage groups with regard to incidence rates of adverse experiences and discontinuation rates does not imply an acceptable safety profile.

This Statistical Reviewer's examination of this submission is in agreement with the sponsor's conclusion in that 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 experiences. However, the overall safety and efficacy profiles for both dosages reveals areas of concern. The number of patients discontinuing for reasons of unsatisfactory response in efficacy, and the number of adverse experiences and discontinuations due to adverse experiences, patient requests, and failure to return generates reasonably serious concern regarding a decision on approval.

/S/

Lillian Patrician, MS, MBA
Mathematical Statistician

/S/ 8/18/98

Concur: Stan Lin, Ph.D.
Statistical Team Leader

Archival: Orig. NDA 20-584 and NDA 18-922

cc: Related [redacted]
HFD-550/File
HFD-550/DeLap
HFD-550/Hyde
HFD-550/Witter
HFD-550/Koerner
HFD-725/File
HFD-725/Patrician
Chron.

This report has a total of thirty-one [31] pages including nine [9] attachments.

NDA 20-584 / S003 Attachment # 1
Lodine XL (Etodolac ER)

Summary Data for U.S. Efficacy and Safety Studies using 1200 mg/day

Study	Design	Title of Protocol	Regimen: Enrollment
654-D-323	Double-blind, double-dummy, randomized, multicenter, parallel group in outpatients with knee OA	Comparison of Safety and Efficacy of Two Doses of Etodolac Sustained Release (Etodolac SR) Tablets versus Conventional Etodolac Capsules in Patients with OA of the Knee	etodolac SR 800mg qd; etodolac SR 1200mg qd etodolac 400 mg tid
654-D-357	Double-blind, double-dummy, multicenter, randomized, parallel group, placebo-controlled in outpatients with knee OA	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of Two Doses of Etodolac Extended Release (Etodolac ER) Tablets with Naproxen followed by Open Label Extension with Etodolac ER for up to Two Years in Patients with OA of the Knee	etodolac ER 800mg qd etodolac ER 1200mg qd naproxen 500mg bid Placebo
654-D-358	Double-blind, double-dummy, multicenter, randomized, parallel group, placebo-controlled in outpatients with knee OA	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of Two Doses of Etodolac Extended Release (Etodolac ER) Tablets with Nabumetone followed by Open Label Extension with Etodolac ER in Patients with OA of the Knee	etodolac ER 800mg qd etodolac ER 1200mg qd nabumetone 1500 mg bid Placebo
654-D-370	Double-blind, double-dummy, multicenter, randomized, parallel group, placebo-controlled in outpatients with knee OA	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of Two Doses of Etodolac Extended Release (Etodolac ER) Tablets with Naproxen followed by Open Label Extension with Etodolac ER in Patients with OA of the Knee	etodolac ER 800mg qd etodolac ER 1200mg qd naproxen 500mg bid Placebo
654-D-371	Double-blind, double-dummy, multicenter, randomized, parallel group, placebo-controlled in outpatients with knee OA	Double-blind, Placebo-controlled Comparison of Safety and Efficacy of Two Doses of Etodolac Extended Release (Etodolac ER) Tablets with Nabutemone followed by Open Label Extension of Etodolac ER in Patients with OA of the Knee	etodolac ER 800mg qd etodolac ER 1200mg qd nabumetone 1500 mg bid Placebo

NDA 20-584 / S003 Attachment # 2

Lodine XL (Etodolac ER)

Summary of Patient Disposition for Open Label Extensions of 5 Studies

Reviewer's Results	Studies 654-D-323 / -357 / -358 / -370 / -371								
Number of Patients	800 mg/day			1200 mg/day			Total		
	<6 mo	>6 mo	Total (%)	<6 mo	>6 mo	Total (%)	<6mo	>6mo	Total (%)
# Enrolled	410	369	779 (47)	410	465	875 (53)	820	834	1654 (100)
Protocol - 323	86	47	133 (08)	80	32	112 (07)	166	79	245
Protocol - 357	102	26	128 (08)	89	29	118 (07)	191	55	246
Protocol - 358	70	116	186 (11)	86	148	234 (14)	156	264	420
Protocol - 370	73	111	184 (11)	75	123	198 (12)	148	234	382
Protocol - 371	79	69	148 (09)	80	133	213 (13)	159	202	361
# Evaluable for Safety	410	369	779 (47)	410	465	875 (53)	820	834	1654
# Completed	001	258	259 (16)	001	286	287 (17)	002	544	546
completers	409	111	520 (31)	409	179	588 (36)	818	290	1108
# deaths	0	1	1	0	4	4	0	5	5
# Patients with Any AE	309	329	638 (39)	302	436	738 (45)	611	765	1376
w Trt-related AE	226	185	411 (25)	206	239	445 (27)	432	424	856
w AE Discontin	123	31	154 (09)	99	29	128 (08)	222	60	282
# Males	122	121	243 (15)	122	146	268 (16)	244	267	511
# Females	288	248	536 (32)	288	319	607 (37)	576	567	1143
# Age < 40 years	5	7	12 (<1)	4	9	13 (<1)	9	16	25
# Age 40 - 60 years	135	118	253 (15)	138	193	331 (20)	273	311	584
# Age > 60 years	270	244	514 (31)	268	263	531 (32)	538	507	1045
# Caucasian	367	327	694 (42)	358	412	770 (47)	725	739	1464
# Black	28	31	59 (04)	41	43	84 (05)	69	74	143
# Other	15	11	26 (02)	11	10	21 (01)	26	21	47

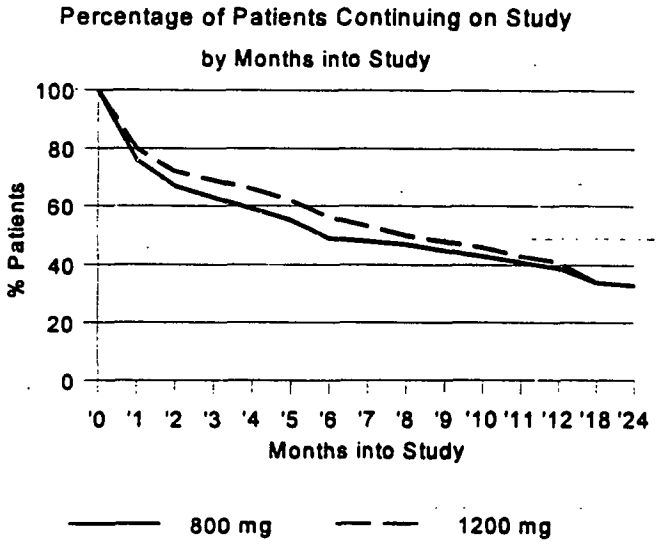
*** Percentages are in terms of all patients in both 800 mg and 1200 mg dose groups.

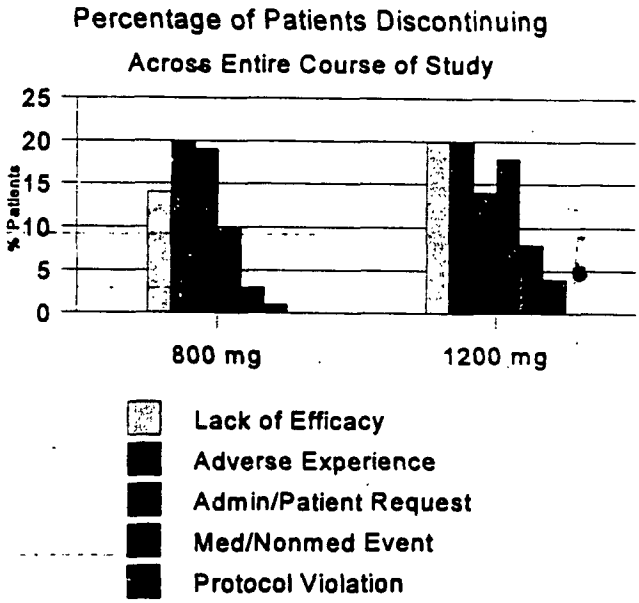
NDA 20-584 / S003 Attachment # 3
Lodine XL (Etodolac ER)
Summary of Patient Discontinuations for Open Label Extensions of 5 Studies

Reviewer's Results	Studies 654-D-323 / -357 / -358 / -370 / -371								
Number of Patients	800 mg/day			1200 mg/day			Total		
	<6 mo (%)	>6 mo (%)	Total (%)	<6 mo (%)	>6 mo (%)	Total (%)	<6mo	>6mo	Total
# Enrolled	410 (53)	369 (47)	779 (100)	410 (47)	465 (53)	875 (100)	820	834	1654
# Completed	1 (<1)	258 (33)	259 (33)	1 (<1)	286 (33)	287 (33)	2	544	546
# Noncompleters	409 (53)	111 (14)	520 (67)	409 (47)	179 (20)	588 (67)	818	290	1108
# Deaths	0	1	1	0	4	4	0	5	5
Reasons for Discontin									
- Unsat Efficacy Resp	93 (12)	34 (04)	127 (16)	116 (13)	82 (09)	198 (23)	209	116	325
- Adverse Reaction	123 (16)	31 (04)	154 (20)	99 (11)	29 (03)	128 (15)	222	60	282
- Admin Request	93 (12)	2 (<1)	95 (12)	115 (13)	3 (<1)	118 (13)	208	5	213
- Other Med Event	38 (05)	24 (03)	62 (08)	27 (03)	33 (04)	60 (07)	65	57	122
atient Request	45 (06)	14 (02)	59 (08)	32 (04)	17 (02)	49 (06)	77	31	108
- Protocol Violation	25 (03)	12 (02)	37 (05)	24 (03)	23 (03)	47 (05)	49	35	84
- Failed to Return	8 (01)	7 (<1)	15 (02)	14 (02)	10 (01)	24 (03)	22	17	39
- Non-Med Event	15 (02)	5 (<1)	20 (03)	10 (01)	5 (<1)	15 (02)	25	10	35
# Patients Discond By Month_to_Disc									
< 1 Month	184 (24)	0	184(24)	178 (20)	1 (<1)	179(20%)	362	1	363
1- 3 Months	99 (13)	0	99(13)	96 (11)	0	96(11%)	195	0	195
3- 6 Months	115 (15)	0	115(15)	120 (14)	0	120(14%)	235	0	235
> 6 Months	11 (01)	111 (14)	122(16)	15 (02)	178 (20)	193(22%)	26	289	315
6- 12 Months	11 (01)	66 (08)	77(10)	15 (02)	110 (13)	125(14%)	26	176	202
> 12 Months	0	45 (06)	45(06)	0	68 (08)	68(08%)	0	113	113

*** Percentages are in terms of each etodolac ER dose group.

Summary of Discontinuations for Double-Blind and Open Label Extensions





** The 6th and right-most group reflected in the above bar chart is "Failed to Return"

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NDA 20-584 / S003 Attachment # 5

Lodine XL (Etodolac ER)

Summary of Adverse Experiences - Double-Blind + Open Label Extensions

Reviewer's Results	Studies 654-D-323 / -357 / -358 / -370 / -371								
Number of Patients	800 mg/day			1200 mg/day			Total		
	<6 mo (%)	>6 mo (%)	Total (%)	<6 mo (%)	>6 mo (%)	Total (%)	<6mo	>6mo	Total
# Enrolled	410 (53)	369 (47)	779 (100)	410 (47)	465 (53)	875 (100)	820	834	1654
# Completed Study	1	258	259 (33)	1	286	287 (33)	2	544	546
# Noncompleters	409 (53)	111 (14)	520 (67)	409 (47)	179 (20)	588 (67)	818	290	1108
# Patients with AE	309 (40)	329 (42)	638 (82)	302 (35)	436 (50)	738 (84)	611	765	1376
# w Trt-related AE	226 (29)	185 (24)	411 (53)	206 (24)	239 (27)	445 (51)	432	424	856
# Discontd due to AE	123 (16)	31 (04)	154 (20)	99 (11)	29 (03)	128 (15)	222	60	282
# Adverse Experiences	871	1522	2393 (100)	845	1897	2742(100)	1716	3419	5135
- Severe	92	117	209 (09)	103	173	276 (10)	195	290	485
- Moderate	385	662	1047 (44)	377	876	1253 (46)	762	1538	2300
- Mild	394	743	1137 (48)	365	848	1213 (44)	759	1591	2350
# Treat-emergent AEs	814	1445	2259 (94)	790	1804	2594 (95)	1604	3249	4853
'g-related AEs	437	374	811 (34)	396	425	821 (30)	833	799	1632
Definitely related	5	5	10	8	5	13	13	10	23
- Possibly related	320	332	652	301	375	676	621	707	1328
- Probably related	112	37	149	87	45	132	199	82	281
- Not related	434	1148	1582	449	1472	1921	883	2620	3503
# Deaths	0	1	1 (<1)	0	4	4 (<1)	0	5	5
# Outcomes Persisted	368	715	1083 (45)	388	845	1233 (45)	756	1560	2316
# Outcomes Disappeared	503	805	1308 (55)	457	1046	1503 (55)	960	1851	2811
# AEs requiring Action									
- Study Plan Discont	188	44	232 (10)	137	56	193 (07)	325	100	425
- Drug Stopped Temp	39	76	125 (05)	52	61	113 (04)	91	137	238
- Drug Dose Reduced	4	15	19 (<1)	2	9	11 (<1)	6	24	30
- Specific Therapy Req	317	739	1056 (44)	303	950	1253 (46)	620	1689	2309
- Other Action Required	106	232	338 (14)	99	305	404 (15)	205	537	742
- No Action Required	322	538	860 (36)	353	673	1026 (37)	675	1211	1886

*** Percentages are in terms of each etodolac ER dose group.

Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
TOTAL ADVERSE EXPERIENCES		871	36	1522	64	2393	100
SEVERE	TOTAL	92	4	117	5	209	9
	DIGESTIVE SYSTEM	28	1	19	1	47	2
	MUSCULOSKELETAL	20	1	27	1	47	2
MODERATE	TOTAL	385	16	662	28	1047	44
	DIGESTIVE SYSTEM	122	5	122	5	244	10
	BODY AS A WHOLE	50	2	95	4	145	6
	MUSCULOSKELETAL	40	2	98	4	138	6
	NERVOUS SYSTEM	51	2	72	3	123	5
	RESPIRATORY SYSTEM	28	1	99	4	127	5
	METABOLIC AND NUTRITIONAL	17	1	30	1	47	2
MILD	DIGESTIVE SYSTEM	147	6	196	8	343	14
	NERVOUS SYSTEM	66	3	97	4	163	7
	RESPIRATORY SYSTEM	27	1	103	4	130	5
	BODY AS A WHOLE	24	1	70	3	94	4
	MUSCULOSKELETAL	16	1	67	3	83	3
	SKIN AND APPENDAGES	27	1	50	2	77	3
	METABOLIC AND NUTRITIONAL	23	1	35	1	58	2
	SPECIAL SENSES	16	1	35	1	51	2
	UROGENITAL SYSTEM	21	1	37	2	58	2

Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
DRUG RELATED	TOTAL	5	0	5	0	10	0
DEFINITELY	DIGESTIVE SYSTEM	4	0	3	0	7	0
	METABOLIC AND NUTRITIONAL	0	0	2	0	2	0
	NERVOUS SYSTEM	1	0	0	0	1	0
PROBABLY/POSSIBLY	TOTAL	432	18	369	15	801	33
	DIGESTIVE SYSTEM	236	10	207	9	443	19
	METABOLIC AND NUTRITIONAL	34	1	28	1	62	3
	NERVOUS SYSTEM	55	2	42	2	97	4
TREATMENT EMERGENT	TOTAL	814	34	1445	60	2259	94
	DIGESTIVE SYSTEM	288	12	323	13	611	26
	NERVOUS SYSTEM	122	5	175	7	297	12
	BODY AS A WHOLE	78	3	175	7	253	11
	RESPIRATORY SYSTEM	55	2	207	9	262	11
	MUSCULOSKELETAL	70	3	181	8	251	10
	CARDIOVASCULAR	38	2	76	3	114	5
	SKIN AND APPENDAGES	48	2	70	3	118	5
	SPECIAL SENSES	27	1	61	3	88	4
	UROGENITAL SYSTEM	31	1	68	3	99	4
	METABOLIC AND NUTRITIONAL	38	2	58	2	96	4
	HEMIC AND LYMPHATIC	12	1	25	1	37	2

Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
DEATH	TOTAL	0	0	1	0	1	0
	NERVOUS SYSTEM	0	0	1	0	1	0
DISAPPEARED	TOTAL	503	21	805	34	1308	55
	DIGESTIVE SYSTEM	199	8	194	8	393	16
PERSISTED	TOTAL	368	15	715	30	1083	45
	DIGESTIVE SYSTEM	98	4	143	6	241	10
	MUSCULOSKELETAL	44	2	108	5	152	6
	NERVOUS SYSTEM	55	2	90	4	145	6
	RESPIRATORY SYSTEM	32	1	92	4	124	5
	BODY AS A WHOLE	21	1	57	2	78	3
	CARDIOVASCULAR	21	1	43	2	64	3
	METABOLIC AND NUTRITIONAL	26	1	47	2	73	3
	SKIN AND APPENDAGES	28	1	38	2	66	3
	SPECIAL SENSES	10	0	29	1	39	2
	UROGENITAL SYSTEM	19	1	34	1	53	2

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Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
BODY AS A WHOLE	TOTAL	84	4	182	8	266	11
	MILD	24	1	70	3	94	4
	MODERATE	50	2	95	4	145	6
	SEVERE	10	0	17	1	27	1
	DEFINITELY	0	0	0	0	0	0
	NOT	75	3	170	7	245	10
	PROBABLY/POSSIBLY	9	0	12	1	21	1
	TREATMENT EMERGENT						
	NO	6	0	7	0	13	1
	YES	78	3	175	7	253	11
	OUTCOME						
	DISAPPEARED	63	3	125	5	188	8
	PERSISTED	21	1	57	2	78	3
DIGESTIVE SYSTEM	TOTAL	297	12	337	14	634	26
	SEVERITY CODE						
	MILD	147	6	196	8	343	14
	MODERATE	122	5	122	5	244	10
	SEVERE	28	1	19	1	47	2
	DEFINITELY	4	0	3	0	7	0
	NOT	57	2	127	5	184	8
	PROBABLY/POSSIBLY	236	10	207	9	443	19
	TREATMENT EMERGENT						
	NO	9	0	14	1	23	1
	YES	288	12	323	13	611	26
	OUTCOME						
	DISAPPEARED	199	8	194	8	393	16
	PERSISTED	98	4	143	6	241	10

Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
HEMIC AND LYMPHATIC SYSTEM	TOTAL	14	1	25	1	39	2
	MILD	10	0	8	0	18	1
	MODERATE	4	0	16	1	20	1
	SEVERE	0	0	1	0	1	0
	DEFINITELY	0	0	0	0	0	0
	NOT	11	0	11	0	22	1
	PROBABLY/POSSIBLY	3	0	14	1	17	1
	TREATMENT EMERGENT						
	NO	2	0	0	0	2	0
	YES	12	1	25	1	37	2
	OUTCOME						
	DISAPPEARED	3	0	8	0	11	0
	PERSISTED	11	0	17	1	28	1
METABOLIC AND NUTRITIONAL	TOTAL	43	2	67	3	110	5
	MILD	23	1	35	1	58	2
	MODERATE	17	1	30	1	47	2
	SEVERE	3	0	2	0	5	0
	DEFINITELY	0	0	2	0	2	0
	NOT	9	0	37	2	46	2
	PROBABLY/POSSIBLY	34	1	28	1	62	3
	TREATMENT EMERGENT						
	NO	5	0	9	0	14	1
	YES	38	2	58	2	96	4
	OUTCOME						
	DISAPPEARED	17	1	20	1	37	2
	PERSISTED	26	1	47	2	73	3

Lodine XL (Etodolac ER) 800 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 800		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
MUSCULOSKELETAL SYSTEM	TOTAL	76	3	192	8	268	11
	MILD	16	1	67	3	83	3
	MODERATE	40	2	98	4	138	6
	SEVERE	20	1	27	1	47	2
	DEFINITELY	0	0	0	0	0	0
	NOT	71	3	179	7	250	10
	PROBABLY/POSSIBLY	5	0	13	1	18	1
	TREATMENT EMERGENT						
	NO	6	0	11	0	17	1
	YES	70	3	181	8	251	10
	OUTCOME						
	DISAPPEARED	32	1	84	4	116	5
	PERSISTED	44	2	108	5	152	6
NERVOUS SYSTEM	TOTAL	127	5	184	8	311	13
	MILD	66	3	97	4	163	7
	MODERATE	51	2	72	3	123	5
	SEVERE	10	0	15	1	25	1
	DEFINITELY	1	0	0	0	1	0
	NOT	71	3	142	6	213	9
	PROBABLY/POSSIBLY	55	2	42	2	97	4
	TREATMENT EMERGENT						
	NO	5	0	9	0	14	1
	YES	122	5	175	7	297	12
	OUTCOME						
	DEATH	0	0	1	0	1	0
	DISAPPEARED	72	3	93	4	165	7
	PERSISTED	55	2	90	4	145	6

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
TOTAL		845	31	1897	69	2742	100
MILD	TOTAL	365	13	848	31	1213	44
	DIGESTIVE SYSTEM	131	5	201	7	332	12
	NERVOUS SYSTEM	49	2	115	4	164	6
	RESPIRATORY SYSTEM	41	1	107	4	148	5
	SKIN AND APPENDAGES	33	1	66	2	99	4
	BODY AS A WHOLE	27	1	98	4	125	5
	METABOLIC AND NUTRITIONAL	18	1	71	3	89	3
	MUSCULOSKELETAL	19	1	68	2	87	3
MODERATE	TOTAL	377	14	876	32	1253	46
	DIGESTIVE SYSTEM	126	5	131	5	257	9
	BODY AS A WHOLE	31	1	152	6	183	7
	MUSCULOSKELETAL	45	2	156	6	201	7
	RESPIRATORY SYSTEM	40	1	130	5	170	6
	NERVOUS SYSTEM	43	2	100	4	143	5
	SKIN AND APPENDAGES	23	1	52	2	75	3
	METABOLIC AND NUTRITIONAL	24	1	38	1	62	2
	UROGENITAL SYSTEM	17	1	39	1	56	2
SEVERE	TOTAL	103	4	173	6	276	10
	DIGESTIVE SYSTEM	38	1	22	1	60	2
	BODY AS A WHOLE	10	0	39	1	49	2
	MUSCULOSKELETAL	13	0	45	2	58	2
	NERVOUS SYSTEM	8	0	20	1	28	1
	RESPIRATORY SYSTEM	8	0	14	1	22	1

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
DEFINITELY	TOTAL	8	0	5	0	13	0
	DIGESTIVE SYSTEM	6	0	4	0	10	0
	BODY AS A WHOLE	1	0	1	0	2	0
	MUSCULOSKELETAL	1	0	0	0	1	0
PROBABLY/POSSIBLY	TOTAL	388	14	420	15	808	29
	DIGESTIVE SYSTEM	214	8	212	8	426	16
	METABOLIC AND NUTRITIONAL	30	1	56	2	86	3
	NERVOUS SYSTEM	42	2	49	2	91	3
	SKIN AND APPENDAGES	44	2	31	1	75	3
TREATMENT EMERGENT	TOTAL	790	29	1804	66	2594	95
	DIGESTIVE SYSTEM	287	10	339	12	626	23
	BODY AS A WHOLE	58	2	275	10	333	12
	MUSCULOSKELETAL	71	3	251	9	322	12
	NERVOUS SYSTEM	94	3	224	8	318	12
	RESPIRATORY SYSTEM	80	3	239	9	319	12
	SKIN AND APPENDAGES	57	2	121	4	178	6
	METABOLIC AND NUTRITIONAL	39	1	104	4	143	5
	CARDIOVASCULAR	30	1	74	3	104	4
	UROGENITAL SYSTEM	28	1	72	3	100	4
	SPECIAL SENSES	19	1	55	2	74	3
	HEMIC AND LYMPHATIC	19	1	27	1	46	2

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
DEATHS	TOTAL	0	0	4	0	4	0
	CARDIOVASCULAR	0	0	3	0	3	0
	DIGESTIVE SYSTEM	0	0	1	0	1	0
	RESPIRATORY SYSTEM	0	0	1	0	1	0
PERSISTED	TOTAL	389	14	845	31	1234	45
	DIGESTIVE SYSTEM	111	4	151	6	262	10
	MUSCULOSKELETAL	42	2	158	6	200	7
	NERVOUS SYSTEM	48	2	86	3	134	5
	RESPIRATORY SYSTEM	53	2	93	3	146	5
	BODY AS A WHOLE	26	1	91	3	117	4
	METABOLIC AND NUTRITIONAL	33	1	71	3	104	4
	SKIN AND APPENDAGES	32	1	57	2	89	3
	UROGENITAL SYSTEM	12	0	41	1	53	2
BODY AS A WHOLE	TOTAL	68	2	289	11	357	13
	MILD	27	1	98	4	125	5
	MODERATE	31	1	152	6	183	7
	SEVERE	10	0	39	1	49	2
	DRUG RELATED						
	DEFINITELY	1	0	1	0	2	0
	NOT	60	2	275	10	335	12
	PROBABLY/POSSIBLY	7	0	13	0	20	1
	TREATMENT EMERGENT						
	NO	10	0	14	1	24	1
	YES	58	2	275	10	333	12
	OUTCOME						
	DISAPPEARED	42	2	198	7	240	9
	PERSISTED	26	1	91	3	117	4

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
DIGESTIVE SYSTEM	TOTAL	295	11	354	13	649	24
	MILD	131	5	201	7	332	12
	MODERATE	126	5	131	5	257	9
	SEVERE	38	1	22	1	60	2
	DEFINITELY	6	0	4	0	10	0
	NOT	75	3	138	5	213	8
	PROBABLY/POSSIBLY	214	8	212	8	426	16
	TREATMENT EMERGENT						
	YES	287	10	339	12	626	23
	OUTCOME						
	DEATH	0	0	1	0	1	0
	DISAPPEARED	184	7	201	7	385	14
	PERSISTED	111	4	151	6	262	10
HEMIC AND LYMPHATIC SYSTEM	TOTAL	21	1	29	1	50	2
	MILD	13	0	20	1	33	1
	MODERATE	6	0	9	0	15	1
	SEVERE	2	0	0	0	2	0
	DEFINITELY	0	0	0	0	0	0
	NOT	8	0	17	1	25	1
	PROBABLY/POSSIBLY	13	0	12	0	25	1
	TREATMENT EMERGENT						
	NO	2	0	2	0	4	0
	YES	19	1	27	1	46	2
	OUTCOME						
	DISAPPEARED	11	0	8	0	19	1
	PERSISTED	10	0	21	1	31	1

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
METABOLIC AND NUTRITIONAL	TOTAL	45	2	111	4	156	6
	MILD	18	1	71	3	89	3
	MODERATE	24	1	38	1	62	2
	SEVERE	3	0	2	0	5	0
	DEFINITELY	0	0	0	0	0	0
	NOT	15	1	55	2	70	3
	PROBABLY/POSSIBLY	30	1	56	2	86	3
	TREATMENT EMERGENT						
	NO	6	0	7	0	13	0
	YES	39	1	104	4	143	5
	OUTCOME						
	DISAPPEARED	12	0	40	1	52	2
	PERSISTED	33	1	71	3	104	4
MUSCULOSKELETAL SYSTEM	TOTAL	77	3	269	10	346	13
	MILD	19	1	68	2	87	3
	MODERATE	45	2	156	6	201	7
	SEVERE	13	0	45	2	58	2
	DEFINITELY	1	0	0	0	1	0
	NOT	69	3	255	9	324	12
	PROBABLY/POSSIBLY	7	0	14	1	21	1
	TREATMENT EMERGENT						
	NO	6	0	18	1	24	1
	YES	71	3	251	9	322	12
	OUTCOME						
	DISAPPEARED	35	1	111	4	146	5
	PERSISTED	42	2	158	6	200	7

Lodine XL (Etodolac ER) 1200 mg Dose Group

Summary of Highest Incidence Adverse Experiences for Each Predominant Dose Group

ETODOLAC ER 1200		< 6 MONTHS		> 6 MONTHS		TOTAL	
			%		%		%
NERVOUS SYSTEM	TOTAL	100	4	235	9	335	12
	MILD	49	2	115	4	164	6
	MODERATE	43	2	100	4	143	5
	SEVERE	8	0	20	1	28	1
	DEFINITELY	0	0	0	0	0	0
	NOT	58	2	186	7	244	9
	PROBABLY/POSSIBLY	42	2	49	2	91	3
	TREATMENT EMERGENT						
	NO	6	0	11	0	17	1
	YES	94	3	224	8	318	12
	OUTCOME						
	DISAPPEARED	52	2	149	5	201	7
	PERSISTED	48	2	86	3	134	5

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Lodine XL (Etodolac ER)

Digestive System Adverse Experiences by Severity

			ETOD ER 800			ETOD ER 1200			TOTAL		
			<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	SEVERE	>>> ABDOMINAL PAIN	7	4	11	9	5	14	16	9	25
		CHOLECYSTITIS	0	0	0	2	0	2	2	0	2
		CONSTIPATION	2	0	2	0	2	2	2	2	4
		DIARRHEA	9	2	11	10	4	14	19	6	25
		DYSPEPSIA	2	0	2	3	2	5	5	2	7
		ERUCTATION	0	0	0	1	1	2	1	1	2
		ESOPHAGITIS	0	1	1	1	0	1	1	1	2
		FLATULENCE	1	1	2	2	0	2	3	1	4
		GASTRITIS	0	1	1	0	1	1	0	2	2
		GASTROENTERITIS	0	1	1	1	0	1	1	1	2
		GI CARCINOMA	0	2	2	0	1	1	0	3	3
		GI DISORDER	2	2	4	0	0	0	2	2	4
		GI HEMORRHAGE	0	1	1	1	0	1	1	1	2
		GLOSSITIS	0	1	1	0	0	0	0	1	1
		HEMORRHAGIC GASTRITIS	1	0	1	0	0	0	1	0	1
		INCREASED APPETITE	1	0	1	0	0	0	1	0	1
		INTESTINAL PERFORATION	0	0	0	1	0	1	1	0	1
		LIVER FUNCTION TESTS ABNORMAL	1	0	1	1	2	3	2	2	4
		MELENA	0	1	1	1	0	1	1	1	2
		MOUTH ULCERATION	0	1	1	0	0	0	0	1	1
		NAUSEA	0	0	0	2	1	3	2	1	3
		PERIODONTAL ABSCESS	1	0	1	0	1	1	1	1	2
		RECTAL HEMORRHAGE	1	0	1	0	0	0	1	0	1
		STOMACH ULCER	0	0	0	0	1	1	0	1	1
		THIRST	0	0	0	0	1	1	0	1	1
		TOOTH DISORDER	0	0	0	1	0	1	1	0	1
		VOMITING	0	1	1	2	0	2	2	1	3

Digestive System Adverse Experiences by Severity

			ETOD ER 800			ETOD ER 1200			TOTAL		
			<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	MODERATE	>>> ABDOMINAL PAIN	31	25	56	24	18	42	55	43	98
		ANOREXIA	2	2	4	1	0	1	3	2	5
		BLOODY DIARRHEA	2	0	2	0	0	0	2	0	2
		CARDIOSPASM	0	0	0	1	0	1	1	0	1
		CHOLECYSTITIS	0	1	1	0	1	1	0	2	2
		CHOLELITHIASIS	0	0	0	1	2	3	1	2	3
		CHOLESTATIC JAUNDICE	1	0	1	0	0	0	1	0	1
		COLITIS	2	1	3	0	3	3	2	4	6
		CONSTIPATION	4	8	12	7	7	14	11	15	26
		DIARRHEA	24	18	42	22	22	44	46	40	86
		DRY MOUTH	0	2	2	1	1	2	1	3	4
		DUODENAL ULCER	1	1	2	0	1	1	1	2	3
		DUODENITIS	1	0	1	0	1	1	1	1	2
		DYSPEPSIA	12	18	30	20	17	37	32	35	67
		DYSPHAGIA	1	1	2	0	0	0	1	1	2
		ERUCTATION	2	2	4	2	2	4	4	4	8
		ESOPHAGEAL STENOSIS	0	0	0	0	1	1	0	1	1
		ESOPHAGEAL ULCER	2	0	2	0	0	0	2	0	2
		ESOPHAGITIS	0	1	1	1	3	4	1	4	5
		FECAL INCONTINENCE	0	0	0	1	0	1	1	0	1
		FLATULENCE	6	6	12	6	4	10	12	10	22
		GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	0	1	0	1	1	0	1
		GASTRITIS	2	2	4	0	3	3	2	5	7
		GASTROENTERITIS	0	3	3	1	4	5	1	7	8
		GASTROINTESTINAL DISORDER	2	2	4	0	5	5	2	7	9

Lodine XL (Etodolac ER)
Digestive System Adverse Experiences by Severity

			ETOD ER 800			ETOD ER 1200			TOTAL		
			<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	MODERATE	GASTROINTESTINAL HEMORRHAGE	3	0	3	1	0	1	4	0	4
		GLOSSITIS	0	1	1	0	0	0	0	1	1
		HEPATITIS	0	0	0	1	0	1	1	0	1
		INCREASED APPETITE	1	1	2	0	0	0	1	1	2
		INTESTINAL OBSTRUCTION	0	0	0	1	0	1	1	0	1
		LIVER FUNCTION TESTS ABNORMAL	3	3	6	6	6	12	9	9	18
		MELENA	0	0	0	1	0	1	1	0	1
		MOUTH ULCERATION	0	2	2	1	0	1	1	2	3
		NAUSEA	13	7	20	17	9	26	30	16	46
		PERIODONTAL ABSCESS	2	6	8	0	3	3	2	9	11
		PERIODONTITIS	0	1	1	0	0	0	0	1	1
		RECTAL DISORDER	1	0	1	0	3	3	1	3	4
		RECTAL HEMORRHAGE	1	1	2	1	2	3	2	3	5
		STENOSIS OF COLON	0	0	0	0	1	1	0	1	1
		STOMACH ULCER	1	1	2	2	0	2	3	1	4
		STOMATITIS	1	0	1	1	0	1	2	0	2
		STOOLS ABNORMAL	0	1	1	2	0	2	2	1	3
		TOOTH CARIES	0	0	0	0	2	2	0	2	2
		TOOTH DISORDER	0	0	0	1	1	2	1	1	2
		ULCERATIVE PROCTITIS	0	1	1	0	0	0	0	1	1
		ULCERATIVE STOMATITIS	0	0	0	0	2	2	0	2	2
		VOMITING	1	4	5	2	7	9	3	11	14

Lodine XL (Etodolac ER)

Digestive System Adverse Experiences by Severity

			ETOD ER 800			ETOD ER 1200			TOTAL		
			<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	MILD	>>> ABDOMINAL PAIN	15	14	29	20	17	37	35	31	66
		ANOREXIA	1	2	3	1	1	2	2	3	5
		BLOODY DIARRHEA	0	1	1	0	0	0	0	1	1
		CHEILITIS	0	1	1	0	3	3	0	4	4
		CHOLELITHIASIS	1	0	1	0	0	0	1	0	1
		COLITIS	0	2	2	0	2	2	0	4	4
		CONSTIPATION	12	16	28	7	16	23	19	32	51
		DIARRHEA	21	34	55	31	30	61	52	64	116
		DRY MOUTH	3	1	4	3	1	4	6	2	8
		DYSPEPSIA	32	43	75	23	43	66	55	86	141
		DYSPHAGIA	0	0	0	0	4	4	0	4	4
		ERUCTATION	4	6	10	1	7	8	5	13	18
		ESOPHAGITIS	1	1	2	0	1	1	1	2	3
		FECAL INCONTINENCE	0	1	1	0	0	0	0	1	1
		FLATULENCE	9	12	21	11	12	23	20	24	44
		GASTRITIS	0	1	1	1	2	3	1	3	4
		GASTROENTERITIS	0	4	4	0	3	3	0	7	7
		GASTROINTESTINAL DISORDER	0	5	5	1	3	4	1	8	9
		GINGIVITIS	0	1	1	0	2	2	0	3	3
		GLOSSITIS	0	0	0	0	2	2	0	2	2
		INCREASED APPETITE	1	1	2	0	0	0	1	1	2
		INTESTINAL ULCER	0	1	1	0	1	1	0	2	2
		LIVER FUNCTION TESTS ABNORMAL	3	6	9	7	8	15	10	14	24
		MELENA	2	1	3	0	2	2	2	3	5
		MOUTH ULCERATION	3	1	4	1	5	6	4	6	10

NDA 20-584 / S003 Attachment # 8

Lodine XL (Etodolac ER)

Digestive System Adverse Experiences by Severity

			ETOD ER 800			ETOD ER 1200			TOTAL		
			<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	MILD	PERIODONTAL ABSCESS	0	0	0	0	1	1	0	1	1
		NAUSEA	22	18	40	13	19	32	35	37	72
		RECTAL DISORDER	3	5	8	0	1	1	3	6	9
		RECTAL HEMORRHAGE	4	6	10	3	6	9	7	12	19
		STOMATITIS	1	1	2	0	1	1	1	2	3
		STOOLS ABNORMAL	1	5	6	3	3	6	4	8	12
		THIRST	1	1	2	0	0	0	1	1	2
		TOOTH CARIES	0	0	0	0	1	1	0	1	1
		TOOTH DISORDER	1	0	1	0	0	0	1	0	1
		ULCERATIVE STOMATITIS	1	0	1	0	0	0	1	0	1
		VOMITING	5	5	10	5	4	9	10	9	19

APPEARS THIS WAY
ON ORIGINAL

Lodine XL (Etodolac ER)
Digestive System Adverse Experiences

		ETOD ER 800			ETOD ER 1200			TOTAL		
		<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL	<6mo	>6mo	TOTAL
DIGESTIVE SYSTEM	>>> ABDOMINAL PAIN	53	43	96	53	40	93	106	83	189
	ANOREXIA	3	4	7	2	1	3	5	5	10
	BLOODY DIARRHEA	2	1	3	0	0	0	2	1	3
	CARDIOSPASM	0	0	0	1	0	1	1	0	1
	CHEILITIS	0	1	1	0	3	3	0	4	4
	CHOLECYSTITIS	0	1	1	2	1	3	2	2	4
	CHOLELITHIASIS	1	0	1	1	2	3	2	2	4
	CHOLESTATIC JAUNDICE	1	0	1	0	0	0	1	0	1
	COLITIS	2	3	5	0	5	5	2	8	10
	CONSTIPATION	18	24	42	14	25	39	32	49	81
	DIARRHEA	54	54	108	63	56	119	117	110	227
	DRY MOUTH	3	3	6	4	2	6	7	5	12
	DUODENAL ULCER	1	1	2	0	1	1	1	2	3
	DUODENITIS	1	0	1	0	1	1	1	1	2
	DYSPEPSIA	46	61	107	46	62	108	92	123	215
	DYSPHAGIA	1	1	2	0	4	4	1	5	6
	ERUCTATION	6	8	14	4	10	14	10	18	28
	ESOPHAGEAL STENOSIS	0	0	0	0	1	1	0	1	1
	ESOPEAGEAL ULCER	2	0	2	0	0	0	2	0	2
	ESOPHAGITIS	1	3	4	2	4	6	3	7	10
	FECAL INCONTINENCE	0	1	1	1	0	1	1	1	2
	FLATULENCE	16	19	35	19	16	35	35	35	70
	GAMMA GLUTAMYL TRANSPEPTIDASE INCREASED	0	0	0	1	0	1	1	0	1
	GASTRITIS	2	4	6	1	6	7	3	10	13
	GASTROENTERITIS	0	8	8	2	7	9	2	15	17
	GASTROINTESTINAL CARCINOMA	0	2	2	0	1	1	0	3	3

Lodine XL (Etodolac ER)

Digestive System Adverse Experiences by Severity

DIGESTIVE SYSTEM	GASTROINTESTINAL DISORDER	4	9	13	1	8	9	5	17	22
	GASTROINTESTINAL HEMORRHAGE	3	1	4	2	0	2	5	1	6
	GINGIVITIS	0	1	1	0	2	2	0	3	3
	GLOSSITIS	0	2	2	0	2	2	0	4	4
	HEMORRHAGIC GASTRITIS	1	0	1	0	0	0	1	0	1
	HEPATITIS	0	0	0	1	0	1	1	0	1
	INCREASED APPETITE	3	2	5	0	0	0	3	2	5
	INTESTINAL OBSTRUCTION	0	0	0	1	0	1	1	0	1
	INTESTINAL PERFORATION	0	0	0	1	0	1	1	0	1
	INTESTINAL ULCER	0	1	1	0	1	1	0	2	2
	LIVER FUNCTION TESTS ABNORMAL	7	9	16	14	16	30	21	25	46
	MELENA	2	2	4	2	2	4	4	4	8
	MOUTH ULCERATION	3	4	7	2	5	7	5	9	14
	NAUSEA	35	25	60	32	29	61	67	54	121
	PERIODONTAL ABSCESS	3	6	9	0	5	5	3	11	14
	PERIODONTITIS	0	1	1	0	0	0	0	1	1
	RECTAL DISORDER	4	5	9	0	4	4	4	9	13
	RECTAL HEMORRHAGE	6	7	13	4	8	12	10	15	25
	STENOSIS OF COLON	0	0	0	0	1	1	0	1	1
	STOMACH ULCER	1	1	2	2	1	3	3	2	5
	STOMATITIS	2	1	3	1	1	2	3	2	5
	STOOLS ABNORMAL	1	6	7	5	3	8	6	9	15
	THIRST	1	1	2	0	1	1	1	2	3
	TOOTH CARIES	0	0	0	0	3	3	0	3	3
	TOOTH DISORDER	1	0	1	2	1	3	3	1	4
	ULCERATIVE PROCTITIS	0	1	1	0	0	0	0	1	1
	ULCERATIVE STOMATITIS	1	0	1	0	2	2	1	2	3
	VOMITING	6	10	16	9	11	20	15	21	36