qpm population, one of whom was discontinued for dyspnea and the other for tachycardia (Tables 19A and 19B, Vol. 2.116, pp. 450-478; Table 20A, Vol. 2.116, pp. 479-502). In the combined trials, 4 additional patients were discontinued for vital sign abnormalities, all for episodes of dyspnea. Two of these patients were in the osteoarthritis [redacted] 30mg qam population and two were in the chronic pain [redacted] 100% population (Sponsor's 11-01-00 submission, Attachment 2, Table 20, pp. 16-21).

7.3.6.2.5 Summary of Vital Sign Analysis

Analysis of vital sign changes in both healthy volunteer and clinical trials revealed no noteworthy trends toward abnormality that could be attributed to the use of [redacted] Examination of the data appeared to demonstrate that these changes occurred more commonly in the osteoarthritis group and with [redacted] exposure as opposed to MS Contin. However, the number of patients experiencing these adverse events was a very small percentage of the population. Although opioid-naïve patients may be more sensitive to the effects of vasodilation triggered by exposure to narcotics, the small numbers elicited from this analysis do not support a signal for treatment-related vital sign abnormalities.

8 USE IN SPECIAL POPULATIONS

8.1 Adequacy of By-Gender Investigation and Analyses

The sponsor conducted no specific by-gender analysis other than to compare the demographic characteristics between treatment groups. However, in both double-blind and open-label trials, the treatment groups were similar with respect to gender distribution. Likewise, no specific racial analysis was conducted. Demographically, in all studies, 80-90% of the population was Caucasian, 10-20% was African American, and other races were rarely represented.

8.2 Elderly Population

The mean age of the osteoarthritis population (Trial 004-04) was approximately 62 years whereas the mean age in the chronic pain population was approximately 50 years. This disparity is explained by the inclusion criteria for the individual trials - ≥40 years for the osteoarthritis patients and ≥21 years for the chronic pain population.

8.3 Pediatric Program Evaluation

At the pre-NDA meeting of January 18, 2000, the agency requested that the sponsor develop a plan to address pediatric use of [redacted] The following summary of a trial to address the pharmacokinetics, efficacy, and safety in the pediatric population was submitted.

- Objectives – to evaluate efficacy, safety, and pharmacokinetics (using sparse sampling techniques) of [redacted]qd in a pediatric oncology population
- Population – 24 children (12 > age 12 yrs, 12 < age 12 yrs but > 3 yrs); oral dose of extended-release morphine at least 30 mg per 24 hours for 7 days prior and oral rescue medication exceeding 25% of total daily dose of morphine; adequate renal and hepatic function; expected survival > 3 mos.
- Plan – 7 day stabilization period with diary to record all medication taken; open-label [redacted] dosing approximating baseline dose and administered approximately one-hour before normal hour of sleep; duration for 10 days or until rescue requirement stable for 3 days (will be dropped after 10 days); rescue medication consisting of oxycodone solution 10% of daily [redacted]dose (1 mg [redacted]= 0.3 mg oxycodone)
- Daily diary – dose and timing of administration including rescue medication; self-reporting scales based on drawings, VAS (recorded upon arising, at noon, and prior to evening dose); daily global evaluation
- Assessments – efficacy (difference in pain scores, difference in rescue medication requirement, daily global evaluation); safety - no specific testing, spontaneous reports of adverse events); PK – collected on patients with both stable and unstable rescue doses

Evaluation of Proposed Pediatric Plan:

- As with the adult trials, one of the major concerns with this proposed trial is that of inappropriate timing of data collection. The sponsor has not established a specific time for evaluation of pain with respect to timing of [redacted] or rescue medication

dosing. The submitted data collection plan may lead to an inability to compare change in pain score with change in amount of rescue medication required.

- Limiting the number of participants to 24 with an equal number above and below the age of 12 years may not provide an adequate amount of data, especially when the requirement for withdrawal if there is inadequate pain control after 10 days is taken into consideration.
- This trial as submitted is an open-label study of efficacy safety, and pharmacokinetics in pediatric patients. Although the study design may be adequate to obtain safety and pharmacokinetic data, no reliable efficacy data can be obtained without the inclusion of an active control arm.

8.4 Abuse Liability

Morphine sulfate, the active component of ———— has a well-established profile of causing psychological and physiological dependence. It has been identified and labeled as a Schedule II substance. In their submission, the sponsor has provided a brief description of the symptoms and treatment of overdosage. They have also included a cautionary statement about precipitation of an acute abstinence syndrome with an abrupt or complete reversal of opioid effects.

8.5 120-Day Safety Update

All additional information contained in the safety update has been incorporated into the relevant parts of this review.

9 REVIEW OF PACKAGE INSERT

The review of the package insert is in progress. This review will be submitted to the NDA as an addendum to this review.

Patricia Hartwell, MD MBA
Medical Officer

Bob Rappaport, MD
Deputy Division Director

Sharon Hertz, MD
Medical Officer

cc: Division File
Original NDA
HFD-170: McCormick, Rappaport, Hartwell, Hoberman, Kim, Haberny, Matura, Compton, Hertz

10 Appendices

10.1 Appendix A – Healthy Volunteer Studies in the ——— Development Program

Protocol #	Study Design	Treatment/Doses	# Entered in Each Treatment
Bio 0596008	Single dose	——— 60mg Oral morphine 10mg q4hr	24
Bio 0596009	Single dose cross-over	——— 30, 60, 90, 120mg	30
Bio 0698002	Single dose cross-over	——— 60mg Capsule vs. Sprinkle formulations	30
Bio 097006	Steady state comparative study	——— 60mg qd x 5d (2 different formulations) Oral morphine 10mg q4hr x 5d	30
Two PK Studies Conducted on 6 Different Early Formulations			
0197006	Single dose cross-over	———60mg (2 different formulations)	12
1096003	Single dose cross-over	———60mg (4 different formulations	15

10.2 Appendix B – Clinical Studies in the [redacted] Development Program

Protocol #/ Principal Investigators	Completion Status (Start/Stop dates	Location	Full Report Volumes	Study Design	Treatment/ Doses	# Entered in Each Treatment	Age Range (Mean)	% M/F B/C/O	Duration of Treatment
Clinical Pharmacology Studies in Patients									
TRG004-01	Complete (11/5/98-8/8/99)	USA	Sec 8: 52-54 Sec 10 144-146	Open-label, non-randomized, two-period	100% MS Contin 100% [redacted]	10 9	28-65 (44.5)	20/80 2/7/1	10 days
TRG004-05	Terminated (3/25/99-6/24/99)	GER UK	Sec 8: 45-51 Sec 10 137-143	Double-blind, randomized, 2 period, crossover	MST Continus BID [redacted] 50% 100%	1 3 3	42-80 (65.0)	33/67 0/3/0	7 days each period
TRG004-06	Completed (8/23/99-10/23/99)	USA	Sec 8: 45-51 Sec 10: 137-143	Double-blind, randomized, 2 period, crossover	MS Contin BID [redacted] 50% 100%	16 17 33	28-75 (49.3)	60/40 1/32/1	7 days each period
Controlled Clinical Studies									
TRG004-02	Complete (10/29/98-10/27/99)	U.S.A	Sec 8: 55-71 Sec 10: 147-163	Multicenter, DB, randomized, parallel group with positive control	50% 100% 133% 100% MS Contin	70 69 69 71	29-81 (51.3) 29-81 (49.7) 28-79 (49.8) 26-78 (49.6)	45.7/54.3 5.7/8.5.7/8.6 40.6/59.4 1.4/92.8/5.8 47.8/52.2 7.2/82.6/10.1 45.6/53.5 2.8/90.1/7.0	7 days
TRG004-04 Double-Blind	Complete (12/4/98-10/20/99)	U.S.A	Sec 8: 72-90 Sec 10: 164-182	Multicenter, DB, randomized, PBO and positive controlled parallel group	Placebo MS Contin 15mg Q12 [redacted] 30mg QAM [redacted] 30mg	73 76 73 73	41-83 (61.9) 42-87 (61.9) 39-82 (62.6) 39-84 (63.1)	30.1/69.9 19.2/79.5/1.4 36.8/63.2 10.5/89.5/0.0 41.1/58.9 9.6/86.3/4.1 42.5/57.5 15.1/82.2/2.7	4 weeks
Uncontrolled Studies									
TRG004-03	Interim analysis (12/15/98-11/12/99)	U.S.A	Sec 8: 91-97 Sec 10: 183-189	Non-randomized, Open-extension	60 – 1000mg	118	26-79 (50.7)	45/55 5.9/89.8/4.2	1 year
TRG004-04 Open Label	Interim analysis (1/13/99-10/19/99)	U.S.A.	Sec 8: 98-105 Sec 10: 190-197	Non-randomized, Open-extension	[redacted] 30mg QAM Morphelan 30mg QPM	95 86	39-82 42-87	36.8/63.2 15.8/82.1/2.1 39.5/60.5 14.0/83.7/2.3	27 weeks

From Sponsor's in-text Table 1.1, Vol. 2.1, pg. 226.

10.3 Appendix C – CRF's Examined During ——— NDA Review

Study	Deaths	Serious Adverse Events	Withdrawals
0698002			13/FH
TRG004-06		01-S06/01113 04-S01/04124	03-S04/03114
TRG004-05		01-S02/01103	
TRG004-02 ———	103-009/20006 123-004/13004 138-001/12001	167-014/45013 171-009/50009 103-001/20001 106-005/11004 115-013/08011 123-001/13001 161-001/42001	115-001/08001 115-006/08006 115-008/08007 115-015/08010 126-004/05004 133-018/25011 160-006/38006 169-005/52004 169-006/52005 172-009/51008
TRG004-04 ———		16-S03/02007 21-S02/03010 21-S09/12001 23-S20/10006 24-S13/07015 36-S15/20013	10-S04/05005 10-S06/05006 10-S02/01005 12-S13/09002 12-S16/09006 12-S19/12005 12-S23/12006 12-S24/12007 14-S02/01014 14-S03/01015 16-S04/02008 16-S14/08009 16-S20/11012 16-S30/14005 16-S36/16010 16-S37/16011 18-S02/02016 18-S08/10016 19-S05/03004 19-S06/05009 19-S07/05010 19-S10/06016 20-S07/17013 21-S13/19009 22-S01/03013 22-S02/03014 22-S05/06009 22-S07/06010 22-S09/06011 22-S15/10009 22-S18/10011 22-S19/10012 22-S24/11003 23-S04/04012 36-S05/19001 36-S07/19003 37-S04/16016 36-S05/19001 36-S07/19003 37-S04/16016 37-S09/02011 38-S04/17011 38-S10/19015 30-S09/15016 30-S14/04015 30-S03/15011 32-S06/14014

APPEARS THIS WAY
ON ORIGINAL

Appendix C, continued
CRF's Examined During [redacted] NDA Review

Study	Deaths	Serious Adverse Events	Withdrawals
TRG004-04 [redacted]			32-S11/15002 33-S01/15005 33-S03/15006 36-S04/17003 23-S14/10001 23-S16/10002 23-S27/11007 24-S18/08015 27-S02/09009 28-S06/17005 28-S08/17007
TRG004-04 [redacted]		16-S17/08012 23-S15/08004 31-S03/13014	10-S07/05007 12-S01/01007 12-S05/01008 12-S15/09005 12-S18/09008 14-S01/01013 15-S02/02001 16-S09/06004 16-S13/08008 18-S07/10015 19-S02/03003 23-S02/04010 23-S11/08001 23-S19/10005 23-S25/11005 23-S26/11006 27-S03/09010 30-S07/15015 30-S10/18001 31-S08/13016 31-S09/14001 32-S02/14010 34-S03/18007 34-S06/07006 37-S03/16015 38-S11/19016 39-S02/20005
TRG004-03	03-S01/00104 103-002/20002 103-004/20007 103-011/20008 104-001/14001 106-005/11002 106-006/11023 110-003/21002 110-001/22025 123-001/13001	103-001/20001 103-006/20005 106-002/11001 109-001/19001 111-001/22001 115-001/08002 115-003/08004 117-008/03008 120-002/09002 122-001/02001 122-003/02003 122-007/02006 122-008/02007 123-002/13002 123-003/13003 129-001/12901 131-005/28004 123-003/13003 129-001/12901 131-005/28004 132-002/24001 133-007/25006	103-010/20003 103-013/20009 114-003/06002 115-002/08003 120-008/09006 129-004/00005 133-006/25003 143-012/10012

APPEARS THIS WAY
ON ORIGINAL

10.4 Appendix D – Pain Descriptor Scale (PDS)

Moderate	Just Noticeable	Strong
Mild		Excruciating
Severe	No Pain	Weak

To be recorded four times daily (include time of evaluation)

- Morning – before first dose of medication
- Lunch-time – around 12:00 noon
- Afternoon – around 4:00 pm
- Evening – before last dose of the day

From Sponsor's sample CRF, Vol. 2.55, pg. 32.

10.5 Appendix E – Quality of Sleep Scale

TO BE COMPLETED PRIOR TO FIRST DOSE OF THE DAY

0	1	2	3	4	5	6	7	8	9	10
Does Not Interfere										Completely Interferes

Circle one number that describes how, during the past 24 hours, pain has interfered with your sleep (record time of evaluation)

From Sponsor's sample CRF, Vol. 2.55, pg. 288.

10.6 Appendix F – Karnofsky Performance Status Scale

100	Normal, no complaints; no evidence of disease
90	Able to carry on normal activity; minor sins or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Cares for self but unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of personal needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization is indicated although death not imminent
20	Very ill; hospitalization and active supportive care necessary
10	Moribund
0	Dead

10.7 Appendix G – WOMAC Index

Pain Subscale Scale (100mm VAS Scale)
The following question concerns the amount of PAIN you have experienced due to arthritis in your study joint. For each situation, please enter the amount of pain experienced since your last visit. (At the Screening Visit, enter the amount of pain experienced over the past week.)

1. Walking on a flat surface
2. Going up or down stairs
3. At night while in bed
4. Sitting or lying
5. Standing upright

A visual analog scale (VAS) will be used.

No Pain |_____| Extreme Pain

The line will be 100 mm in length. The patient will be instructed to make a single vertical mark on each line to indicate the pain intensity in the index joint

Stiffness Subscale Scale (100mm VAS Scale)

The following question concerns the amount of joint stiffness you have experienced due to arthritis in your study joint since your last visit. (At the Screening Visit, enter the amount of stiffness experienced over the past week.) Stiffness is a sensation of restriction or slowness in the ease with which you move your joints.

1. How severe is your stiffness after first awakening in the morning?
2. How severe is your stiffness after sitting, lying, or resting later in the day?

A visual analog scale (VAS) will be used.

No Stiffness |_____| Extreme Stiffness

The line will be 100 mm in length. The patient will be instructed to make a single vertical mark on each line to indicate the stiffness in the index joint

Appendix G – WOMAC Index continued:

Physical Function Subscale Scale (100mm VAS Scale)

The following question concerns your physical function. By this we mean you ability to move around and to look after yourself. . For each of the following activities, please indicate the degree of difficulty experienced since your last visit due to arthritis in you study joint. (At the Screening Visit, enter the degree of difficulty experienced over the past week.)

What degree of difficulty did you have with:

1. Descending stairs
2. Ascending stairs
3. Rising from sitting.
4. Standing
5. Bending to floor
6. Walking on a flat surface
7. Getting in/out of car.
8. Going shopping
9. Putting on socks/stockings
10. Rising from bed.
11. Taking off socks/stockings
12. Lying in bed
13. Getting in/out of bath
14. Sitting
15. Getting on/off toilet
16. Heavy domestic duties
17. Light domestic duties

A visual analog scale (VAS) will be used.

No Difficulty |_____| Extreme Difficulty

The line will be 100 mm in length. The patient will be instructed to make a single vertical mark on each line to indicate the degree of difficulty with the physical function.

From Sponsor's protocol, Vol. 2.72, pg. 135.

APPEARS THIS WAY
ON ORIGINAL

10.8 Appendix H – Overall Arthritis Pain Intensity (100mm VAS Scale)

Patient will be asked to assess the overall level of osteoarthritis pain in the index joint at Screening, Baseline, and each subsequent visit (except Week 31). At Baseline, the pain intensity on this scale must be ≥40mm for patient to be admitted to the study.

Pain will be assessed by answering the question:

> **"Overall, how much pain have you experienced in your study joint since your last visit?"**

No Pain |_____| Extreme Pain

Make a single vertical mark on this line to indicate the pain intensity in the index joint

From Sponsor's protocol, Vol. 2.72, pg. 136.

APPEARS THIS WAY
ON ORIGINAL

10.9 Appendix I - Patient and Physician Global Assessment of Arthritis

The patient will be asked, "Considering all the ways your arthritis condition affects you, i.e. pain, stiffness and limitation of activity, how are you doing today?"

The physician will be answer the question, "How is the patient doing today?"

Each will perform the evaluation independently. A visual analog scale (VAS) will be used.

Very good Very poor

The line will be 100 mm in length. The patient and physician will be instructed to make a single vertical mark on each line to indicate the their assessments.

From Sponsor's protocol, Vol. 2.72, pg. 141.

10.10 Appendix J - Patients Assessment of Sleep

The patients will be asked to respond to questions concerning the impact of pain on sleep.

1. Since your last visit, how often have you had trouble falling asleep because of pain?
2. Since your last visit, how often have you needed sleeping medication to help you fall asleep?
3. Since your last visit, how often have you been awakened by pain during the night?
4. Since your last visit, how often have you been awakened by pain in the morning?

A visual analog scale (VAS) will be used.

never always

The line will be 100 mm in length. The patient will be instructed to make a vertical mark on the line to indicate their response to the questions.

The patient will also be asked to score the quality of sleep with a100 mm VAS (anchors : very poor to excellent). Patients will be asked, "Since your last visit, how would you rate the overall quality of your sleep?"

From Sponsor's protocol, Vol. 2.72, pg. 142

10.11 Appendix K– Deaths (Double Blind Trials)

Study # Patient #	Sex	Age	Treatment	Last Dose to Time of Death	Cause of Death	Days on Study Drug	Relationship to Study Drug (Reviewers Assessment)
TRG004-02 103-009	F	78	MS Contin	16 days after completing treatment	Progression of endometrial cancer	14 days stabilization (MS Contin) plus 7 days double-blind treatment	Questionable
TRG004-02 123-004	F	67	[redacted] 100%	5 days after completing treatment	Progression of metastatic bladder cancer	7 days stabilization (MS Contin) plus 7 days double-blind treatment	Unrelated
TRG004-02 138-001	M	66	[redacted] 100%	28 days after completing treatment	Sepsis and progression of non-small cell lung cancer	7 days stabilization (MS Contin) plus 7 days double-blind treatment	Unrelated

From Sponsor's Table 5-13, Vol. 2.109, pg. 341

APPEARS THIS WAY
ON ORIGINAL

Appendix K, continued – Deaths (Open Label Trials)

Study # Patient #	Sex	Age	Treatment	Last Dose to Time of Death	Cause of Death	Days on Study Drug	Relationship to Study Drug (Reviewer's Assessment)
TRG004-03 O3-S01	F	42	240mg	38 days after discontinuation for gynecologic bleeding	Worsening of general condition, likely due to metastatic cervical cancer	49	Unrelated
TRG004-03 103-002	M	62	240mg	21 days after discontinuation for fever, restlessness, and confusion	Progression of lung cancer	2	Unrelated
TRG004-03 103-004	F	78	120mg	6 days after discontinuation for pneumonia	Progression of metastatic colon cancer	60	Questionable
TRG004-03 104-001	M	59	90mg	22 days after discontinuation	Progression of metastatic prostate cancer	96	Unrelated
TRG004-03 110-103	M	61	180mg	24 days after discontinuation	Progression of metastatic lung cancer	110	Unrelated
TRG004-03 123-001	M	62	60mg	2 days after discontinuation for acidosis and hypercarbia	End-stage lung cancer	19	Questionable
TRG004-03 103-006	M	61	120mg	12 days after discontinuation	Lung carcinoma	341	Unrelated
TRG004-03 103-011	M	78	240mg	1 day after discontinuation	Sepsis and pancreatic cancer	280	Unrelated
TRG004-03 106-005	M	44	180mg	On trial drug at time of death	Metastatic prostate cancer	177	Unrelated
TRG004-03 106-006	F	67	150mg	3 days after discontinuation	Metastatic breast cancer	292	Questionable
TRG004-03 109-001	M	72	300mg	On trial drug at time of death	Lung carcinoma	231	Questionable
TRG004-03 111-001	F	68	180mg	On trial drug at time of death	Lymphoma	306	Unrelated
TRG004-03 153-002	M	55	90mg	16 days after discontinuation	Ruptured aneurysm	203	Questionable

From Sponsor's Table 5-13, Vol. 2.109, pg.341; Table 13.1-1, Vol. 1.68 (120d Safety Update), pg. 21.

10.12 Appendix L – Serious Adverse Events (Combined Populations)

Event	Treatment Groups							
	n 133% N = 69	*100% N = 384*	*50% N = 86*	*30mgAM N = 164*	*30mgPM N = 163*	*All N = 866*	*MS Contin All N = 164*	*Placebo N = 73*
Any Adverse Event	2 (2.9%)	54 (14.1%)	0	6 (3.7%)	12 (7.4%)	74 (8.5%)	3 (1.8%)	1 (1.4%)
Abdominal Pain					1 (0.6%)	1 (0.1%)		1 (1.4%)
Accidental Injury		1 (0.3%)				1 (0.1%)		
Asthenia								
Back Pain				1 (0.6%)		1 (0.1%)		
Cellulitis		2 (0.5%)			1 (0.6%)	3 (0.3%)		
Chest Pain	1 (1.4%)	2 (0.5%)				3 (0.3%)		
Chills		1 (0.3%)			1 (0.6%)	2 (0.2%)		
Fever		2 (0.5%)			2 (1.2%)	4 (0.5%)		
Headache		1 (0.3%)				1 (0.1%)		
Hernia					1 (0.6%)	1 (0.1%)		
Infection		2 (0.5%)				2 (0.2%)		
Mucous Memb Dsr		1 (0.3%)				1 (0.1%)		
Neck Pain		1 (0.3%)				1 (0.1%)		
Pain		1 (0.3%)				1 (0.1%)	1 (1.1%)	
Reaction ?		1 (0.3%)				1 (0.1%)		
Sepsis		2 (0.5%)			1 (0.6%)	3 (0.3%)		
Viral Infection		1 (0.3%)			1 (0.6%)	2 (0.2%)		
Angina		1 (0.3%)				1 (0.1%)		
Atrial Fib		1 (0.3%)				1 (0.1%)		
Bradycardia		1 (0.3%)		1 (0.6%)		2 (0.2%)		
Cardiac Arrest		1 (0.3%)				1 (0.1%)		
Cardiomyopathy		1 (0.3%)				1 (0.1%)		
Cong Ht. Failure				1 (0.6%)		1 (0.1%)		
Hemorrhage		1 (0.3%)				1 (0.1%)		
Hypotension		1 (0.3%)				1 (0.1%)		
Myocardial Infarct		1 (0.3%)				1 (0.1%)		
Palpitation		1 (0.3%)				1 (0.1%)		
Tachycardia				1 (0.6%)		1 (0.1%)		
Thrombphlb. Deep		2 (0.5%)				2 (0.2%)		
Thrombophlebitis				1 (0.6%)	1 (0.6%)	2 (0.2%)		
Cholecystitis		1 (0.3%)			1 (0.6%)	2 (0.2%)		
Cholelithiasis					1 (0.6%)	1 (0.1%)		
Colitis		1 (0.3%)				1 (0.1%)		
Constipation		1 (0.3%)			2 (1.2%)	3 (0.3%)		
Diarrhea		2 (0.5%)		1 (0.6%)		3 (0.3%)		
Duodenal Hemorr.		1 (0.3%)		1 (0.6%)		2 (0.2%)		
Enteritis				1 (0.6%)		1 (0.1%)		
Gastritis		2 (0.5%)		1 (0.6%)		3 (0.3%)		
Hepatic Failure	1 (1.4%)					1 (0.1%)		
Abnormal LFT's							1 (0.6%)	
Ileus		1 (0.3%)				1 (0.1%)		
Int. Obstruction							1 (0.6%)	
Nausea		3 (0.8%)		1 (0.6%)	1 (0.6%)	5 (0.6%)		
Vomiting		2 (0.5%)		1 (0.6%)	3 (1.8%)	6 (0.7%)		

Appendix L, continued – Serious Adverse Events (Combined Populations)

Event	Treatment Groups							
	n 133% N = 69	*100% N = 384*	*50% N = 86*	*30mgAM N = 164*	*30mgPM N = 163*	*All N = 866*	*MS Contin All N = 164*	*Placebo N = 73*
Leukopenia		2 (0.5%)				2 (0.2%)		
Acidosis		1 (0.3%)				1 (0.1%)		
Dehydration		3 (0.8%)		1 (0.6%)	1 (0.6%)	5 (0.6%)		
Electrolyte Abn.	1 (1.4%)			1 (0.6%)		2 (0.2%)		
Obesity		1 (0.3%)				1 (0.1%)		
Edema				1 (0.6%)		1 (0.1%)		
Resp. Acidosis		1 (0.3%)				1 (0.1%)		
Bone Disorder		3 (0.8%)				3 (0.3%)		
Anxiety		1 (0.3%)				1 (0.1%)		
Aphasia		1 (0.3%)				1 (0.1%)		
Confusion		2 (0.5%)				2 (0.2%)		
Depression		3 (0.8%)				3 (0.3%)		
Drug Dependence		2 (0.5%)				2 (0.2%)		
MS		1 (0.3%)				1 (0.1%)		
Nervousness		1 (0.3%)				1 (0.1%)		
Neuralgia		1 (0.3%)				1 (0.1%)		
Neuropathy		2 (0.5%)				2 (0.2%)		
Psychotic Deprsn		1 (0.3%)				1 (0.1%)		
Thinking Abn		1 (0.3%)				1 (0.1%)		
Tremor		1 (0.3%)				1 (0.1%)		
Withdrawal Synd.		1 (0.3%)				1 (0.1%)		
Dyspnea		5 (1.3%)			1 (0.6%)	6 (0.7%)		
Pneumonia		4 (1.0%)			1 (0.6%)	5 (0.6%)		
Pulm. Embolus		1 (0.3%)		1 (0.6%)		2 (0.2%)		
Sweating		1 (0.3%)			1 (0.6%)	2 (0.2%)		
Kidney Stone					1 (0.6%)	1 (0.1%)		
Kidney Fxn Abn		1 (0.3%)				1 (0.1%)		
Metorrhagia		1 (0.3%)				1 (0.1%)		
Prostate Cancer		1 (0.3%)				1 (0.1%)		
Pyelonephritis		1 (0.3%)				1 (0.1%)		
UTI		1 (0.3%)				1 (0.1%)		
GU Disorder		1 (0.3%)				1 (0.1%)		

From Sponsor's Table 21, Correspondence 10-30-00, pp. 21-25.

10.13 Appendix M – Treatment Emergent Adverse Events Causing Discontinuation (Double Blind Trials)

Event	Treatment Groups									
	133% N = 69	*100% N = 104*	*50% N = 86*	*30mgAM N = 73*	*30mgPM N = 73*	*All N = 405*	*MS Contin 100% N = 88*	*MS Contin 15mgBID N = 76*	*MS Contin All N =164*	*Placebo N = 73*
Any Adverse Event	5 (7.2%)	1 (1.0%)	2 (2.3%)	17 (23.3%)	19 (26.0%)	44 (10.9%)	3 (3.4%)	18 (23.7%)	21 (12.8%)	4 (5.5%)
Abdominal Pain				1 (1.4%)	1 (1.4%)	2 (0.5%)				2 (2.7%)
Asthenia	1 (1.4%)				2 (2.7%)	3 (0.7%)				
Back Pain				1 (1.4%)		1 (0.2%)				
Chest Pain	1 (1.4%)				1 (1.4%)	2 (0.5%)				
Headache					1 (1.4%)	1 (0.2%)		1 (1.3%)	1 (0.6%)	
Neck Pain								1 (1.3%)	1 (0.6%)	
Pain							1 (1.1%)	1 (1.3%)	2 (1.2%)	1 (1.4%)
Tachycardia					1 (1.4%)	1 (0.2%)				
Thrombophlebitis					1 (1.4%)	1 (0.2%)				
Anorexia				1 (1.4%)		1 (0.2%)				
Constipation				7 (9.6%)	5 (6.8%)	12 (3.0%)	1 (1.1%)	5 (6.6%)	6 (3.7%)	
Diarrhea										1 (1.4%)
Dysphagia				1 (1.4%)		1 (0.2%)				
Gastritis		1 (1.0%)				1 (0.2%)				
Abnormal LFT's								1 (1.3%)	1 (0.6%)	
Melena				1 (1.4%)		1 (0.2%)				
Nausea	2 (2.9%)		1 (1.2%)	5 (6.8%)	10 (13.7%)	18 (4.4%)		6 (7.9%)	6 (3.7%)	
Stomatitis				1 (1.4%)		1 (0.2%)				
Vomiting	1 (1.4%)		1 (1.2%)[9]	1 (1.4%)	5 (6.8%)	8 (2.0%)		4 (5.3%)	4 (2.4%)	
Edema								1 (1.3%)	1 (0.6%)	
Arthritis								1 (1.3%)	1 (0.6%)	
Rheum. Arthritis								1 (1.3%)	1 (0.6%)	
Abn. Dreams			1 (1.2%)			1 (0.2%)				
Abn. Gait					1 (1.2%)	1 (0.2%)				
Confusion	1 (1.4%)			1 (1.4%)		2 (0.5%)				
Depression				1 (1.4%)		1 (0.2%)				
Dizziness				2 (2.7%)	2 (2.7%)	4 (1.0%)		4 (5.3%)	4 (2.4%)	1 (1.4%)
Dry Mouth				1 (1.4%)	1 (1.4%)	2 (0.5%)				
Hallucinations			1 (1.2%)		1 (1.4%)	2 (0.5%)				
Insomnia										1 (1.4%)
Nervousness										1 (1.4%)
Somnolence	1 (1.4%)			3 (4.1%)	3 (4.1%)	7 (1.7%)		4 (5.3%)	4 (2.4%)	
Tremor							1 (1.1%)	1 (1.3%)	2 (1.2%)	
Vertigo				2 (2.7%)		2 (0.5%)				
Dyspnea					1 (1.4%)	1 (0.2%)				
Pneumonia					1 (1.4%)	1 (0.2%)				
Pruritus				1 (1.4%)	2 (2.7%)	3 (0.7%)		1 (1.3%)	1 (0.6%)	
Rash				1 (1.4%)		1 (0.2%)		1 (1.3%)	1 (0.6%)	
Sweating				1 (1.4%)		1 (0.2%)		1 (1.3%)	1 (0.6%)	1 (1.4%)
Urticaria				1 (1.4%)		1 (0.2%)				
Diplopia					1 (1.4%)	1 (0.2%)				
Eye Pain					1 (1.4%)	1 (0.2%)				
Taste Alteration					1 (1.4%)	1 (0.2%)				
Dysuria				2 (2.7%)		2 (0.5%)				

From Sponsor's Table 20A, Vol. 2.116, pp. 484-502.

Appendix M, continued – Treatment Emergent Adverse Events Causing Discontinuation (Combined Populations)

Event	Treatment Groups									
	133% N = 69	*100% N = 384*	*50% N = 86*	*30mgAM N = 164*	*30mgPM N = 163*	*All N = 866*	*MS Contin 100% N = 88*	*MS Contin 15mgBID N = 76*	*MS Contin All N =164*	*Placebo N = 73*
Any Adverse Event	5 (7.2%)	41 (10.7%)	2 (2.3%)	49 (29.9%)	43 (26.4%)	140 (16.2%)	3 (3.4%)	18 (23.7%)	21 (12.7%)	4 (5.5%)
Abdominal Pain		1 (0.3%)		2 (1.2%)	3 (1.8%)	6 (0.7%)				2 (2.7%)
Accidental Injury				1 (0.6%)		1 (0.1%)				
Asthenia	1 (1.4%)	1 (0.3%)		2 (1.2%)	3 (1.8%)	7 (0.8%)				
Back Pain				2 (1.2%)	1 (0.6%)	3 (0.3%)				
Chest Pain	1 (1.4%)				1 (0.6%)	2 (0.2%)				
Chills					1 (0.6%)	1 (0.1%)				
Edema		1 (0.3%)				1 (0.1%)				
Fever		1 (0.3%)			2 (1.2%)	3 (0.3%)				
Halitosis		1 (0.3%)				1 (0.1%)				
Headache		2 (0.5%)		2 (1.2%)	1 (0.6%)	5 (0.6%)		1 (1.3%)	1 (0.6%)	
Hernia				1 (0.6%)	1 (0.6%)	2 (0.2%)				
Neck Pain								1 (1.3%)	1 (0.6%)	
Pain		1 (0.3%)		1 (0.6%)		2 (0.2%)	1 (1.1%)	1 (1.3%)	2 (1.2%)	1 (1.4%)
Sepsis					1 (0.6%)	1 (0.1%)				
Viral Infection					1 (0.6%)	1 (0.1%)				
CHF				1 (0.6%)		1 (0.1%)				
Syncope					1 (0.6%)	1 (0.1%)				
Tachycardia					1 (0.6%)	1 (0.1%)				
Thrombophlebitis					1 (0.6%)	1 (0.1%)				
Vasodilation		1 (0.3%)		1 (0.6%)	1 (0.6%)	3 (0.3%)				
Anorexia		1 (0.3%)		1 (0.6%)	1 (0.6%)	3 (0.3%)				
Colitis				1 (0.6%)		1 (0.1%)				
Constipation		4 (1.0%)		20 (12.2%)	10 (6.1%)	34 (3.9%)	1 (1.1%)	5 (6.6%)	6 (3.6%)	
Diarrhea				4 (2.4%)	1 (0.6%)	5 (0.6%)				1 (1.4%)
Dyspepsia		1 (0.3%)		1 (0.6%)	1 (0.6%)	3 (0.3%)				
Dysphagia		1 (0.3%)		1 (0.6%)		2 (0.2%)				
Enteritis		2 (0.5%)		2 (1.2%)		4 (0.5%)				
GI Hemorrhage				1 (0.6%)		1 (0.1%)				
Ileus		1 (0.3%)				1 (0.1%)				
Abnormal LFT's		1 (0.3%)		1 (0.6%)		2 (0.2%)		1 (1.3%)	1 (0.6%)	
Melena				1 (0.6%)		1 (0.1%)				
Nausea	2 (2.9%)	2 (0.5%)	1 (1.2%)	9 (5.5%)	17 (10.4%)	31 (3.6%)		6 (7.9%)	6 (3.6%)	
Stomatitis				1 (0.6%)		1 (0.1%)				
Vomiting	1 (1.4%)		1 (1.2%)	2 (1.2%)	9 (5.5%)	13 (1.5%)		4 (5.3%)	4 (2.4%)	
Anemia		1 (0.3%)				1 (0.1%)				
Coag Disorders					1 (0.6%)	1 (0.1%)				
Leukopenia		1 (0.3%)				1 (0.1%)				
Acidosis		1 (0.3%)				1 (0.1%)				
Dehydration				1 (0.6%)	1 (0.6%)	2 (0.2%)				
Edema		2 (0.6%)		3 (1.8%)	1 (0.6%)	5 (0.6%)		1 (1.3%)	1 (0.6%)	
Hyponatremia				1 (0.6%)		1 (0.1%)				
Resp. Acidosis		1 (0.3%)				1 (0.1%)				
Weight Gain					1 (0.6%)	1 (0.1%)				
Weight Loss				2 (1.2%)		2 (0.2%)				

Appendix M, continued – Treatment Emergent Adverse Events Causing Discontinuation (Combined Populations)

Event	Treatment Groups									
	133% N = 69	*100% N = 384*	*50% N = 86*	*30mgAM N = 164*	*30mgPM N = 163*	*All N = 866*	*MS Contin 100% N = 88*	*MS Contin 15mgBID N = 76*	*MS Contin All N = 164*	*Placebo N = 73*
Arthritis		1 (0.3%)				1 (0.1%)		1 (1.3%)	1 (0.6%)	
Rheum. Arthritis								1 (1.3%)	1 (0.6%)	
Abn. Dreams			1 (1.2%)			1 (0.1%)				
Abn. Gait					1 (0.6%)	1 (0.1%)				
Confusion	1 (1.4%)	6 (1.6%)		1 (0.6%)		8 (0.9%)				
Depression		1 (0.3%)		3 (1.8%)		4 (0.5%)				
Dizziness				4 (2.4%)	5 (3.1%)	9 (1.0%)		4 (5.3%)	4 (2.4%)	1 (1.4%)
Drug Dependence		2 (0.5%)				2 (0.2%)				
Dry Mouth				2 (1.2%)	2 (1.2%)	4 (0.5%)				
Hallucinations		1 (0.3%)	1 (1.2%)		1 (0.6%)	3 (0.3%)				
Hypertonia		1 (0.3%)				1 (0.1%)				
Insomnia		1 (0.3%)				1 (0.1%)				1 (1.4%)
Nervousness		1 (0.3%)		1 (0.6%)	1 (0.6%)	3 (0.3%)				1 (1.4%)
Paresthesia		1 (0.3%)				1 (0.1%)				
Somnolence	1 (1.4%)	5 (1.3%)		4 (2.4%)	7 (4.3%)	17 (2.0%)		4 (5.3%)	4 (2.4%)	
Thinking Abn		1 (0.3%)		1 (0.6%)	2 (1.2%)	4 (0.5%)				
Tremor		1 (0.3%)			1 (0.6%)	2 (0.2%)	1 (1.1%)	1 (1.3%)	2 (1.2%)	
Vertigo				3 (1.8%)		3 (0.3%)				
Dyspnea		2 (0.5%)		2 (1.2%)	1 (0.6%)	5 (0.6%)				
Lung Disorder					1 (0.6%)	1 (0.1%)				
Pneumonia					1 (0.6%)	1 (0.1%)				
Pruritus				1 (0.6%)	2 (1.2%)	3 (0.3%)		1 (1.3%)	1 (0.6%)	
Rash		1 (0.3%)		1 (0.6%)		2 (0.2%)		1 (1.3%)	1 (0.6%)	
Sweating		1 (0.3%)		2 (1.2%)	1 (0.6%)	4 (0.5%)		1 (1.3%)	1 (0.6%)	1 (1.4%)
Uricaria				1 (0.6%)		1 (0.1%)				
Deafness				2 (1.2%)		2 (0.2%)				
Diplopia					1 (0.6%)	1 (0.1%)				
Dry Eyes					1 (0.6%)	1 (0.1%)				
Eye Pain					1 (0.6%)	1 (0.1%)				
Taste Alteration					1 (0.6%)	1 (0.1%)				
Vis Field Alter.				1 (0.6%)		1 (0.1%)				
Dysuria				2 (1.2%)		2 (0.2%)				
Renal Calculus					1 (0.6%)	1 (0.1%)				
Renal Fxn Abn		1 (0.3%)				1 (0.1%)				
Metorrhagia		1 (0.3%)				1 (0.1%)				
Pyelonephritis		1 (0.3%)				1 (0.1%)				
Sexual Fxn Abn		1 (0.3%)				1 (0.1%)				
Urinary Incont				1 (0.6%)		1 (0.1%)				

From Sponsor's Additional Correspondence (11-01-00) Table 21, pp. 484-502.

APPEARS THIS WAY
ON ORIGINAL

10.14 Appendix N – Adverse Events in ≥5% of Patients (Combined Populations)

Event	Treatment Groups									
	133% N = 69	*100% N = 384*	*50% N = 86*	*30mgAM N = 164*	*30mgPM N = 163*	*All N = 866*	*MS Contin 100% N = 88*	*MS Contin 15mgBID N = 76*	*MS Contin All N = 164*	*Placebo N = 73*
Any Event	38 (55.1%)	282 (73.4%)	43 (50.0%)	134 (81.7%)	129 (79.1%)	626 (72.3%)	34 (37.8%)	50 (65.8%)	84 (50.6%)	28 (38.4%)
Constipation	3 (4.3%)	53 (13.8%)	5 (5.8%)	70 (42.7%)	58 (35.6%)	189 (21.8%)	4 (4.4%)	22 (28.9%)	26 (15.7%)	2 (2.7%)
Nausea	7 (10.1%)	58 (15.1%)	5 (5.8%)	26 (15.9%)	41 (25.2%)	137 (15.8%)	5 (5.6%)	20 (26.3%)	25 (15.1%)	7 (9.6%)
Somnolence	3 (4.3%)	32 (8.3%)	4 (4.7%)	26 (15.9%)	17 (10.4%)	82 (9.5%)	2 (2.2%)	9 (11.8%)	11 (6.6%)	
Pain	1 (1.4%)	38 (9.9%)	1 (1.2%)	7 (4.3%)	13 (8.0%)	60 (6.9%)	2 (2.2%)	4 (5.3%)	6 (3.6%)	1 (1.4%)
Asthenia	4 (5.8%)	33 (8.6%)	4 (4.7%)	5 (3.0%)	6 (3.7%)	52 (6.0%)	1 (1.1%)	7 (9.2%)	8 (4.8%)	
Periph Edema	2 (2.9%)	34 (8.9%)		5 (3.0%)	9 (5.5%)	50 (5.8%)		1 (1.3%)	1 (0.6%)	
Dizziness	5 (7.2%)	22 (5.7%)	2 (2.3%)	12 (7.3%)	18 (11.0%)	59 (6.8%)	4 (4.4%)	9 (11.8%)	13 (7.8%)	1 (1.4%)
Headache	7 (10.1%)	35 (9.1%)	2 (2.3%)	13 (7.9%)	8 (4.9%)	65 (7.5%)	6 (6.7%)	5 (6.6%)	11 (6.6%)	4 (5.5%)
UTI	2 (2.9%)	28 (7.3%)		3 (1.8%)	6 (3.7%)	39 (4.5%)				
Vomiting	6 (8.7%)	36 (9.4%)	4 (4.7%)	8 (4.9%)	19 (11.7%)	73 (8.4%)	5 (5.6%)	6 (7.9%)	11 (6.6%)	1 (1.4%)
Sweating	1 (1.4%)	19 (4.9%)	7 (8.1%)	5 (3.0%)	2 (1.2%)	34 (3.9%)	1 (1.1%)	2 (2.6%)	3 (1.8%)	1 (1.4%)
Diarrhea		20 (5.2%)	3 (3.5%)	14 (8.5%)	13 (8.0%)	50 (5.8%)	1 (1.1%)	1 (1.3%)	2 (1.2%)	4 (5.4%)
Anorexia		16 (4.2%)	3 (3.5%)	5 (3.0%)	3 (1.8%)	27 (3.1%)				1 (1.4%)
Confusion	1 (1.4%)	11 (2.9%)		3 (1.8%)		15 (1.7%)				
Depression		19 (4.9%)		5 (3.0%)	2 (1.2%)	26 (3.0%)				
Paresthesia		26 (6.8%)	2 (2.3%)	1 (0.6%)	1 (0.6%)	30 (3.5%)	2 (2.2%)		2 (1.2%)	
Rash	1 (1.4%)	25 (6.5%)	1 (1.2%)	5 (3.0%)	3 (0.3%)	36 (4.2%)		2 (2.6%)	2 (1.2%)	1 (1.4%)
Dyspnea	1 (1.4%)	14 (3.6%)	2 (2.3%)	2 (1.2%)	4 (2.5%)	23 (2.7%)	1 (1.1%)	1 (1.3%)	2 (1.2%)	
Fever	1 (1.4%)	24 (6.3%)	1 (1.2%)	2 (1.2%)	4 (2.5%)	32 (3.7%)	1 (1.1%)	1 (1.3%)	2 (1.2%)	

From Sponsor's in-text Table 6-4, Vol. 2.109, pg. 47 and Table 14, Sponsor's correspondence (11-01-00), Attachment 2, pp. 1-15
Shaded areas represent most common adverse events noted in double-blind patient trials.

10.15 Appendix O – Laboratory Tests Recorded as Adverse Events

Patient	*Study*	*Treatment Group*	*Abnormality*	*Medical History*	*Discontinued*
36-S15	TRG004-04	MS Contin bid	↑ LFTs; normalized after discontinuation	Osteoarthritis	X
171-009	TRG004-02	133%	↑ LFTs, electrolyte imbalance	Lymphoma	X
23-S02	TRG004-04 and OL	30mg PM	↑ LFTs at end of double blind; continued elevation through week 5	Osteoarthritis	X
12-S03	TRG004-04 and OL	Placebo, 30mg PM	Coagulation disorder (no data available)	Osteoarthritis	X
103-004	TRG004-03 OL		↑ AP, creatinine, BUN	Chronic pain	
126-001	TRG004-02, 03 OL		↑ Hct, transient proteinuria during double blind; ↑ LFTs during open label	SLE, fibromyalgia	
115-003	TRG004-03 OL		↓ Hct, renal insufficiency	Diabetic neuropathy	
115-008	TRG004-03 OL		↑ creatinine	Chronic pain	
002-104	TRG004-03 OL		↑ LFTs	Chronic pain	
126-020	TRG004-03 OL		↑ LFTs (also at baseline)	Chronic pain	
120-010	TRG004-02, 03 OL		↑ AP (156)	Chronic pain	
105-005	TRG004-03 OL		↓ WBC (800) assoc. with sepsis; ↑ (3300) with antibiotics	Metastatic prostate CA	
103-002	TRG004-03 OL		↓ WBC assoc. with fever; ↑ with antibiotics	Metastatic lung CA	
171-001	TRG004-02	50%	↓ WBC (1.41) on entry; ↑ (1.48) at end of study	Metastatic breast CA	
110-003	TRG004-02	50%	↓ WBC (1.52) after chemotherapy	Prostate, lung CA	
151-001	TRG004-02	100%	↓ WBC (2.23) on entry; ↑ (6.03) at end of study	Nodular lymphoma	
03-S01	TRG004-02	MS Contin.	WBC 4.27 on entry; ↓ (2.53) at end of study	Thyroid CA	
153-001	TRG004-02, 03 OL	MS Contin	WBC 3.77 on entry to OL, ↓ to 3.51 then 1.56, then ↑ to 4.37 at end of study	Metastatic breast CA	

Vol. 2.109, pp. 39, 57.

10.16 Appendix P – Blood Pressure Changes (at least 10mm HG) by Summary Population Double-Blind Trials

Population Number (%)	Treatment Groups									
	133%	*100%*	*50%*	*30mg am*	*30mg pm*	*All*	*MS Contin 100%*	*MS Contin 15mg bid*	*MS Contin All*	*Placebo*
Overall										
Systolic	17 (24.6)	14 (21.6)	19 (27.5)	27 (37)	28 (38.4)	105 (29.8)	10 (14)	37 (48.7)	47 (32.4)	25 (34.2)
Diastolic	17 (24.6)	12 (17.6)	9 (13)	11 (15.1)	17 (23.6)	66 (18.8)	11 (15.9)	23 (30.3)	34 (23.4)	15 (20.5)
Prior Use										
Systolic	17 (24.6)	14 (21.6)	19 (27.5)	16 (47.1)	10 (30.3)	76 (27.8)	10 (14)	15 (55.6)	25 (26)	6 (20)
Diastolic	17 (24.6)	12 (17.6)	9 (13)	9 (26.5)	6 (18.2)	53 (19.4)	11 (15.9)	9 (33.3)	20 (20.8)	3 (10)
Chronic Use										
Systolic	17 (24.6)	14 (21.6)	19 (27.5)			50 (24.3)	10 (14)		10 (14.5)	
Diastolic	17 (24.6)	12 (17.6)	9 (13)			38 (18.4)	11 (15.9)		11 (15.9)	
Intermittent Use										
Systolic				16 (47.1)	10 (30.3)	26 (38.8)		15 (55.6)	15 (55.6)	6 (20)
Diastolic				9 (26.5)	6 (18.2)	15 (22.4)		9 (33.3)	9 (33.3)	3 (10)
Opioid Naive										
Systolic				11 (28.2)	18 (45)	29 (36.7)		22 (44.9)	22 (44.9)	19 (44.2)
Diastolic				2 (5.1)	11 (27.5)	13 (16.5)		14 (28.6)	14 (28.6)	12 (27.9)
Osteoarthritis										
Systolic				27 (37)	28 (38.4)	55 (37.7)		37 (48.7)	37 (48.7)	25 (34.2)
Diastolic				11 (15.1)	17 (23.6)	28 (19.5)		23 (30.3)	23 (30.3)	15 (20.5)

From Sponsor's Appendix 5, Table 23A(2), Vol. 2.118, pp. 97-98.

/s/

Sharon Hertz
3/21/01 05:28:18 PM
MEDICAL OFFICER

OK by BR

Bob Rappaport
3/21/01 05:38:22 PM
MEDICAL OFFICER
I concur with Dr. Hertz's conclusions and agree that this product has demonstrated adequate effectiveness and a relatively balanced degree o f safety for approval.

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-03
Center for Drug Evaluation and Research

Proprietary Name Review

DATE OF REVIEW: **February 7, 2001**

NDA: **21-260**

NAME OF DRUG: **Avinza (Morphine Sulfate extended-release) Capsules 30 mg, 60 mg, 90 mg and 120 mg**

NDA HOLDER: **Elan Pharmaceuticals**

I. INTRODUCTION

This consult is in response to a February 5, 2001, request from the Division of Anesthetic, Critical Care and Addiction Drug Products (HFD-170), to evaluate the revised container labels and labeling for the proposed tradename Avinza.

OPDRA was originally consulted on October 2, 2000 for assessment of the tradename Avinza, regarding potential name confusion with other proprietary/generic drug names. OPDRA did not recommend the use of the proprietary name at that time and also made recommendations for labeling revisions to minimize potential errors with the use of this product. (See OPDRA Consult 00-0264).

PRODUCT INFORMATION

Avinza is the proposed proprietary name for morphine sulfate, USP. Avinza is formulated as a once-a-day extended-release capsule that contains both immediate release and extended release beads of morphine sulfate for oral administration. Each Avinza capsule contains 30 mg, 60 mg, 90 mg, or 120 mg of morphine sulfate, USP. Avinza is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. Avinza will be available in both blister pack cartons and bottles of 30, 100, 250, 500 counts.

APPEARS THIS WAY
ON ORIGINAL

2. The established name should include the dosage form as follows:

---

3. In order to accomplish these recommendations, we recommend that only the Manufacturer or the Distributor be listed on the unit-dose label.

IV. RECOMMENDATIONS

OPDRA recommends the above labeling revisions, which might lead, to safer use of the product.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-3244.

Alina Mahmud, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

/s/

Alina Mahmud
2/9/01 11:01:22 AM
PHARMACIST

Jerry Phillips
2/9/01 03:22:42 PM
DIRECTOR

Martin Himmel
2/14/01 08:41:59 AM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):	FROM:
OPDRA, HFD-400, (15B-33) Mary Dempsey, Project Manager.	HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Kim Compton, Project Manager

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
[redacted]2001		21-260	New NDA	January 30, 2001

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Avinza (morphine sulfate)	High	3S	03/01/2001

NAME OF FIRM: Elan Pharmaceuticals (co-marketed by Ligand Pharmaceuticals Inc.-which will handle the correspondence with the Agency)

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ■ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the enclosed color mock-ups of the carton and container labels for acceptability in terms of safety and appearance. Although OPDRA has recommended against the use of the tradename "Avinza", the sponsor is considering appealing that recommendation and so has included the name in it's labeling.

If you have any questions, please contact Kim Compton, Regulatory Project Manager, at 301-827-7432. Thank you for your assistance.

Cc: Aleta Crane 7-7410 (Please cc Aleta Crane in DFS when you return your review.)

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
Kim Compton, Project Manager, HFD-170 (initialed by Schumaker 2-5-01)	☐ MAIL ■ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

/s/

Kimberly Compton
2/5/01 02:29:58 PM

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-260

Elan Pharmaceuticals
1300 Gould Drive
Gainesville,.GA 30504

Attention: Sharon Hamm, Pharm.D.
Senior Vice President, R&D Technical Operations

Dear Dr. Hamm:

Please refer to your pending new drug application NDA) dated April 14, 2000, received April 17, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for morphine sulfate rapid onset extended-release capsules.

We also refer to your submissions dated February 21, April 26, and June 29, 2001.

We have completed our review of the suggested tradename AVINZA and we find it acceptable at this time, however, we have the following comments.

1. We have reservations about potential confusion of AVINZA with Albenza, in handwritten prescriptions. If, rather than choosing an alternate name, you plan to educate and counsel health-care providers with regard to this potential confusion, please submit a formal outline along with your planned launch promotional materials.

2. There will be a very low tolerance for reports of dispensing errors involving AVINZA and Albenza, since such errors could have serious clinical consequences. FDA may require a name change in the future if such errors are reported.

3. Any post-marketing medication error reports or reports of potential errors should be submitted as expedited (15-day) reports for the first 6 months of product distribution, regardless of patient outcome.

We remind you that the final approval of the tradename is pending approval of this application. We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, call Kimberly Compton, Regulatory Project Manager, at (301) 827-7432.

Sincerely,

{See appended electronic signature page}

Cynthia McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:
Ligand Pharmaceuticals
10275 Science Center Drive
San Diego, CA 92121-1117

Attention: Howard T. Holden, Ph.D.
Vice President, Regulatory Affairs and Compliance

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Cynthia McCormick
3/5/02 06:39:32 PM

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)

DATE RECEIVED: 11/8/01	DUE DATE: 01/07/02	ODS CONSULT: 01-0195-1

TO:
Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Kim Compton
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

PRODUCT NAME:	**NDA SPONSOR:**
—————— (Morphine Sulfate Extended-Release Capsules) 30 mg, 60 mg, 90 mg, and 120 mg **NDA #:** 21-260	Ligand Pharmaceuticals for Elan Pharmaceuticals

SAFETY EVALUATOR: Nora Roselle, PharmD

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name ——————" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS does not recommend the use of the proprietary name ——————DMETS has provided a re-review of the previously reviewed tradenames and is recommending the use of the proprietary name "Avinza".

Carol Holquist, RPh
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: 301-827-3242 Fax: 301-443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 7, 2002

NDA NUMBER: 21-260

NAME OF DRUG: ———————
(Morphine Sulfate Extended-Release Capsules)
30 mg, 60 mg, 90 mg, and 120 mg

NDA HOLDER: Ligand Pharmaceuticals for Elan Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), for assessment of the tradename "———————", regarding potential name confusion with other proprietary/generic drug names.

———————is the new proprietary tradename submitted by the sponsor. Prior proprietary tradename submissions by the sponsor for this product included "Avinza" (DMETS Consult 00-0264), ——— (DMETS Consult 01-0049), ——————— (DMETS Consult 01-0105), and ——— DMETS Consult 01-0195); all names were found unacceptable by DMETS. Labeling comments for this product was provided by DMETS in Consult 01-0029.

PRODUCT INFORMATION

"———————" is the proposed name for morphine sulfate extended-release. It is formulated as a once-a-day capsule, which contains both immediate-release and extended-release beads of morphine sulfate for oral administration. "——————" is indicated for the relief of moderate to severe pain and is intended for use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. "———————" will be supplied as 30 mg, 60 mg, 90 mg, and 120 mg.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound alike or look alike to "————" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's trademark electronic search system[4] (TESS) was conducted. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name "————". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. The expert panel is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion (EPD) that were thought to have potential for confusion with ————These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have concerns about the name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
————	Morphine Sulfate Extended-Release Capsule 30 mg, 60 mg, 90 mg, 120 mg	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Melphalan (generic name for Alkeran)	Melphalan Tablet: 2 mg Powder for solution: 50 mg	Multiple myeloma: Oral: 6 mg/day adjusted to patient response and weekly blood counts, repeat at 4 to 6 wk intervals IV: 16 mg/m^2 at 2 wk intervals x 4 doses, then monthly	S/A, L/A
Marplan	Isocarboxazid ~~Tablet: 10 mg~~	20 mg/day in divided doses ~~Maximum Dose: 40 mg/day~~	S/A
Naprelan	Naproxen, controlled release tablet 375 mg, 500 mg	Rheumatoid Arthritis: Two-375 mg tablets once a day or Two-500 mg tablets once a day	L/A
		*Frequently used, not all inclusive.	**L/A (look-alike), S/A (sound-alike)

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.
[3] COMIS, The Established Evaluation System (EES), the Labeling and Nomenclature Committee (LNC) database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.
[4] WWW location http://tess.uspto.gov/bin/gate.exe?f=tess&state=k0n826.1.1.
[5] Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at http://www.thomson-thomson.com.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

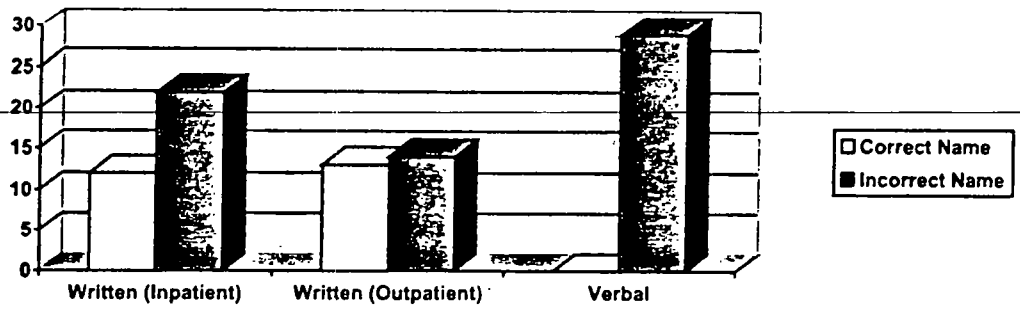
Studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of "[redacted]" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 113 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. A DMETS staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and a prescription for "[redacted]" (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one DMETS staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient: [redacted] 60 mg QD	*Outpatient:* [redacted] 60 mg Take one tablet daily. Dispense thirty with no refills.
Outpatient: [redacted] 60 mg 1 po QD #30	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted [redacted]	Incorrectly Interpreted
Written: Inpatient	40	34 (85%)	12 (35%)	22 (65%)
Outpatient	39	27 (69%)	13 (48%)	14 (52%)
Verbal: Outpatient	34	29 (85%)	0 (0%)	29 (100%)
Total	113	90 (80%)	25 (28%)	65 (72%)

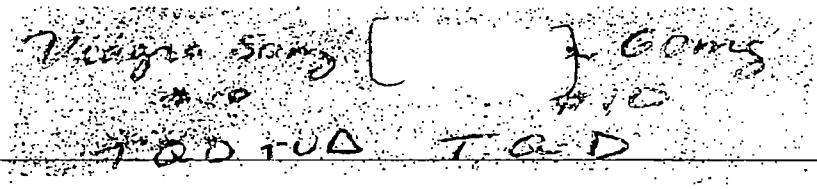


Among the written outpatient prescriptions, 14 out of 27 (52%) respondents interpreted "[redacted]" incorrectly. The majority of the interpretations were phonetic/misspelled variations of the name, such as Marphelan, Marphalan, Marphelon, and Morpheran.

	[redacted]	Vicodin	LA; One written inpt participant responded Vicodin
		Verelan	LA; Similarities btwn Vindara and Verelan include: oral dosing, once daily dosing, 120 mg strength, capsules
10/11/01	[redacted]	Vi-Zac	SA/LA
		Tiazac	SA/LA; Many similarities btwn Vinzak & Tiazac: once daily dosing, 120 mg strength, capsules, similar quantities dispensed (#30); many drug intx with Tiazac
		"Vin" Stem	As per USAN Guidelines, the use of the stem "vin" is associated with the class of drugs known as Vinca Alkaloids. The proposed drug is not a Vinca Alkaloid.
12/27/01	[redacted]	Melphalan	SA/LA; One respondent interpreted the drug to be Melphalan but a higher dose; Increase potential for confusion due to placement of decimal point in strength (Melphalan 6.0 mg (which is the usual daily dose), Morphelan 60 mg) especially if "use as directed" provided as the directions
		Marplan	SA
		Naprelan	LA

As per USAN guidelines, the use of the stem "vin" is reserved for the class of drugs known as vinca alkaloids. Due to the fact that the proposed drug is not a vinca alkaloid, the following proposed tradenames are not acceptable: [redacted]

In addition, there are numerous issues regarding the potential for medication errors with the proposed tradenames and various marketed drug products. [redacted] is not an acceptable tradename due to the fact that it has look alike potential to Viagra. Three respondents interpreted [redacted] to be Viagra and one noted the similarity in appearance to Viagra. Both drugs have once a day oral dosing, with an increased risk of confusion due to the fact that the strengths (50 mg and 60 mg, respectively) may appear similar when scripted.



[redacted] is not an acceptable name due to the fact that it has look alike potential with Verelan. Both Verelan and [redacted] share the same rote of administration (oral), the same dosage form (capsule), the same dosing schedule (once a day), and also have one strength in common (120 mg). One inpatient study participant interpreted the name to be Vicodin.

Verelan-120mg [redacted] 120mg

BEST POSSIBLE COPY

——— is not an acceptable name in that it has sound and look alike similarities with Tiazac. Tiazac and ——— share an overlapping dosing regimen (once daily), strength (120 mg), and dosage form (capsule). Furthermore, both may be prescribed in similar quantities (#30). The inadvertent confusion of these two drugs could potentially be life threatening.

——— 120mg #30 TID Tiazac 120mg #30 TID

——— is also not an acceptable proposed tradename because of its look alike similarities with the marketed drug, Exelon. Two respondents interpreted the name to be Exelon. Both drug products have the same dosage form (capsule) and route of administration (oral). Exelon is usually given twice a day while ——— is given once daily. Even though these two drug products have different directions of use, the prescriber can give the directions "use as directed". There are no overlapping strengths, but there are overlapping numbers in the strengths supplied. Exelon can be written as "Exelon 3.0 mg" with a trailing zero which may look similar to "——— 30 mg" if the decimal point in the "3.0" is not seen.

[ ] 30mg Exelon 3.0mg

One respondent commented that ——— reminded her of Theo-Dur, where ——— may be written as 30.0 mg and misinterpreted as Theo-Dur 300 mg.

Avinza and Albenza not only sound similar but also look similar when scripted, both having similar character lengths (6 vs. 7). When scripted, the "b" in Albenza can look like a "v" if the loop in the letter "b" is not completely connected. Yet, the two drugs lack similarities other than being solid oral dosage forms, and there was no confirmation from the studies that Avinza could be confused with any marketed drug products.

Avinza Albenza

~~Thus, DMETS recommends the use of the proposed proprietary name Avinza.~~

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

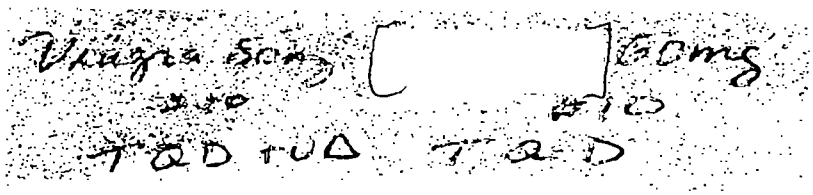
Please refer to DMETS Consult 01-0029.

IV. COMMENTS TO THE SPONSOR:

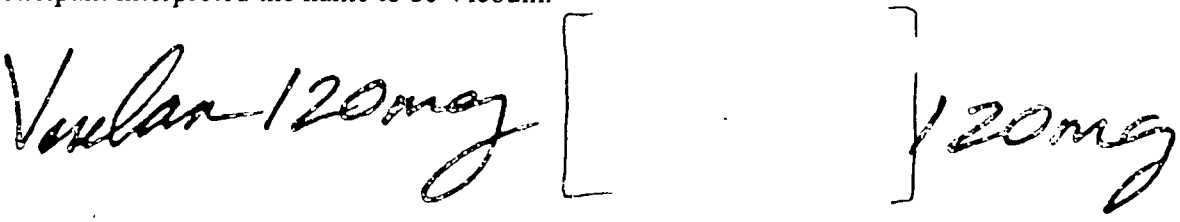
DMETS does not recommend the use of the proprietary name '——— In reviewing the proprietary name '———', the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. The products considered having the greatest potential for name confusion with ——— were *Melphalan, Marplan, and Naprelan.*

As per USAN guidelines, the use of the stem "vin" is reserved for the class of drugs known as vinca alkaloids. Due to the fact that the proposed drug is not a vinca alkaloid, the following proposed tradenames are not acceptable: [redacted]

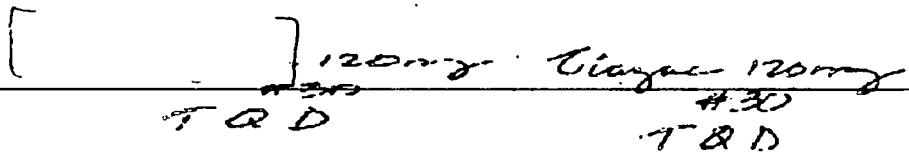
In addition, there are numerous issues regarding the potential for medication errors with the proposed tradenames and various marketed drug products. [redacted] is not an acceptable tradename due to the fact that it has look alike potential to Viagra. Three respondents interpreted [redacted] to be Viagra and one noted the similarity in appearance to Viagra. Both drugs have once a day oral dosing, with an increased risk of confusion due to the fact that the strengths (50 mg and 60 mg, respectively) may appear similar when scripted.



[redacted] is not an acceptable name due to the fact that it has look alike potential with Verelan. Both Verelan and [redacted] share the same rote of administration (oral), the same dosage form (capsule), the same dosing schedule (once a day), and also have one strength in common (120 mg). One inpatient study participant interpreted the name to be Vicodin.



[redacted] is not an acceptable name in that it has sound and look alike similarities with Tiazac. Tiazac and [redacted] share an overlapping dosing regimen (once daily), strength (120 mg), and dosage form (capsule). Furthermore, both may be prescribed in similar quantities (#30). The inadvertent confusion of these two drugs could potentially be life threatening.



[redacted] is also not an acceptable proposed tradename because of its look alike similarities with the marketed drug, Exelon. Two respondents interpreted the name to be Exelon. Both drug products have the same dosage form (capsule) and route of administration (oral). Exelon is usually given twice a day while [redacted] is given once daily. Even though these two drug products have different directions of use, the prescriber can give the directions "use as directed". There are no overlapping strengths, but there are overlapping numbers in the strengths supplied. Exelon can be written as "Exelon 3.0 mg" with a trailing zero which may look similar to "[redacted] 30 mg" if the decimal point in the "3.0" is not seen.

One respondent commented that [redacted] reminded her of Theo-Dur, where [redacted] may be written as 30.0 mg and misinterpreted as Theo-Dur 300 mg.

Avinza and Aibenza not only sound similar but also look similar when scripted, both having similar character lengths (6 vs. 7). When scripted, the "b" in Albenza can look like a "v" if the loop in the letter "b" is not completely connected. Yet, the two drugs lack similarities other than being solid oral dosage forms, and there was no confirmation from the studies that Avinza could be confused with any marketed drug products.

Thus, DMETS recommends the use of the proposed proprietary name Avinza.

APPEARS THIS WAY
ON ORIGINAL

IV. RECOMMENDATIONS:

DMETS does not recommend the use of the proprietary name ~~[redacted]~~.

DMETS has provided a re-review of the previously reviewed tradenames and recommends the use of the proposed proprietary name, Avinza.

DMETS recommends implementation of the labeling changes outlined in DMETS Consult # 01-0029 to improve the safe use of this product and in order to minimize the potential for medication errors. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam at 301-827-3231.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Nora L. Roselle
1/7/02 04:08:54 PM
CSO

Carol Holquist
1/7/02 04:10:08 PM
PHARMACIST

Jerry Phillips
1/8/02 08:37:46 AM
DIRECTOR

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kimberly Compton
11/8/01 02:25:01 PM

APPEARS THIS WAY
ON ORIGINAL

Original

Copy of 356 H for NDA 21-260

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 21-260

APPLICANT INFORMATION

NAME OF APPLICANT
Elan Pharmaceutical Research Corporation

DATE OF SUBMISSION
May 25, 2000

TELEPHONE NO. (*Include Area Code*)
(770) 534-8239

FACSIMILE (FAX) Number. (*Include Area Code*)
(770) 531-0835

APPLICANT ADDRESS (*Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued*):
1300 Gould Drive
Gainesville, GA 30504

AUTHORIZED U.S. AGENT NAME & ADDRESS (*Number, Street, City, State, ZIP Code, telephone & FAX number*) IF APPLICABLE
Same

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued)
21-260

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)
morphine sulfate

PROPRIETARY NAME (*trade name*) IF ANY
~~™ (morphine sulfate) Extended-Release~~ Capsules

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)
morphine sulfate

CODE NAME (*If any*)

DOSAGE FORM:
Capsules

STRENGTHS:
30 mg, 60 mg, 90 mg and 120 mg

ROUTE OF ADMINISTRATION:
Oral

(PROPOSED) INDICATION(S) FOR USE:
Relief of chronic moderate to severe pain

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
MAY 30 2000
CDR

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☒ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug

TYPE OF SUBMISSION
(check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
☐ OTHER

REASON FOR SUBMISSION Original New Drug Application

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 287

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or ty of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, wh it will be ready.
See attached

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application) See enclosed list.

This application contains the following items: (*Check all that apply*)	
X	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
N/A	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
X	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
X	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
X	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
X	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k) (1)) (coming → they forgot)
X	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for b regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 and 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to marke the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best o f my knowledge are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense, U.S Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Roger Wayne Wiley, R.Ph. Director, North America Regulatory Affair	May 25, 2000
ADDRESS (*Street, City, State, Zip Code*) 1300 Gould Drive Gainesville, GA 30504		TELEPHONE NO. (Include Area Code) (770) 534-8239

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing
instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address

FORM FDA 356h (4/97)

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 08/31/01	DUE DATE: 11/01/01	OPDRA CONSULT: 01-0195

TO:

Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Kim Compton
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

PRODUCT NAME:	**MANUFACTURER:** Elan Holdings, Inc. (Pharmaceutical Division)
[redacted] (Morphine Sulfate Extended-Release Capsules) 30 mg, 60 mg, 90 mg, and 120 mg **NDA #:** 21-260	

SAFETY EVALUATOR: Alina Mahmud, R.Ph.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA conducted a review of the proposed proprietary name "[redacted]" to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use the proprietary name "[redacted]".

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 11, 2001

NDA NUMBER: 21-260

NAME OF DRUG: ———————
(Morphine Sulfate Extended-Release Capsules)
30 mg, 60 mg, 90 mg, and 120 mg

NDA HOLDER: Elan Holdings, Inc. (Pharmaceutical Division)

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for assessment of the tradename ———— regarding potential name confusion with other proprietary/generic drug names.

' ———— ' is the new proprietary tradename submitted by the sponsor. Prior proprietary tradename submissions by the sponsor for this product included "Avinza" (OPDRA Consult 00-0264), ———— (OPDRA Consult 01-0049) and ———————— (OPDRA Consult 01-0105); all names were found unacceptable by OPDRA. Labeling comments for this product was provided by OPDRA in OPDRA Consult 01-0029.

PRODUCT INFORMATION

———— is the proposed name for morphine sulfate extended-release. It is formulated as a once-a-day capsule, which contains both immediate-release and extended-release beads of morphine sulfate for oral administration. ———— ' is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. ———— will be supplied as 30 mg, 60 mg, 90 mg, and 120 mg capsules and will be available in both blister pack cartons and bottles of 30, 100, 250, and 500 count.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to ———— to a degree where potential confusion between drug names could occur under

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.
[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database[5] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[6] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name ——— Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

- Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with '———'. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.
- In addition, the Panel found the prefix "Vin" misleading in that "Vin" is a USAN (United States Adopted Name) stem for a class of drugs known as the Vinca Alkaloids.
- DDMAC did not have any concerns with the name in regard to promotional claims.

Table 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
———	Morphine Sulfate Extended-Release (Rx) Capsule: 30 mg, 60 mg, 90 mg, 120 mg	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Benza	Benzalkonium chloride 1:750 solution (otc)	Applied topically for skin antisepsis as needed	S/A, L/A per OPDRA
Benzac AC Benzac W	Benzoyl Peroxide Gel and Wash: 2 ½%, 5% and 10% (Rx)	Apply to affected areas once of twice daily.	S/A, L/A per OPDRA
Prozac	Fluoxetine Hydrochloride (Rx) Pulvules: 10 mg, 20 mg and 40 mg Tablet: 10 mg Oral Solution: 20 mg/5 mL Weekly: 90 mg	*Depression*: 20 mg once daily or divided in two doses. *Obsessive Compulsive Disorder*: 20 mg to 80 mg/day *Bulimia Nervosa*: 60 mg/day	S/A per OPDRA
Tiazac	Diltiazem Hydrochloride Extended-Release (Rx) Capsules: 120 mg, 180 mg, 240 mg,	*Hypertension*: 120 mg to 540 mg once daily Angina: initial dose of	S/A, L/A per OPDRA

[5] Http://tess.uspto.gov/bin/gate.exe?f=tess&state=ggdukv.1.1.

[6] WWW location http://www.thomson-thomson.com.

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
[redacted]	Morphine Sulfate Extended-Release (Rx) Capsule: 30 mg, 60 mg, 90 mg, 120 mg	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
	300 mg, 360 mg and 420 mg	120 mg to 180 mg; adjust according to patient's needs.	
Vi-Zac	Multivitamin with Minerals (otc)	One tablet daily.	S/A, L/A per OPDRA
Univasc	Moexipril Hydrochloride (Rx) Tablet: 7. 5 mg and 15 mg	7.5 mg to 30 mg per day in one or two divided doses	L.A. S/A per OPDRA
		*Frequently used, not all-inclusive	**S/A(Sound-alike), L/A (Look-alike

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Studies were conducted within FDA for the proposed proprietary names to determine the degree of confusion of '[redacted] and with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 116 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An OPDRA staff member wrote one inpatient prescription and one outpatient prescription, each consisting of a combination of marketed and unapproved drug products and prescriptions for [redacted] (see below). These written prescriptions were optically scanned and one prescription was delivered via e-mail to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription for each name that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via e-mail.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Inpatient: [redacted] 120 mg po qd	*Outpatient:* [redacted] 120 mg Take 1 capsule by mouth once a day. #15
Outpatient: [redacted] 120 mg Sig: i cap po QD #15	

2. Results:

Results of these exercises are summarized below:

Study	# of Participants	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written: Outpatient	39	24 (62%)	11 (46%)	13 (54%)
Inpatient	38	26 (68%)	23 (88%)	3 (12%)
Verbal	39	27 (69%)	0 (0%)	27 (100%)
Total	116	77 (66%)	34 (44%)	43 (56%)

pain. *Tiazac* is also associated with numerous drug interactions when given concomitantly with other drugs. Such drugs include: cimetadine, digitalis, beta-blockers, carbamazepine, levostatin,

benzodiazepines, cyclosporin, and rifampin. A patient that inadvertently receives ——— instead of *Tiazac* will remain untreated for high blood pressure and also experience respiratory depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine.

——— TIAZAC

——— 120mg Tiazac 120mg
#30 #30
TID TID

The Panel found the prefix "Vin" misleading in that "Vin" is a USAN stem for a class of drugs known as the Vinca Alkaloids. Proprietary names the incorporate a USAN stem will generally be considered misleading if the drug does not have the chemical, therapeutic and/or pharmacologic parameters associated with the USAN stem. Per USAN guidelines, the use of the stem "vin" as a prefix or in the middle of the name is associated with the class known as the Vinca Alkaloids.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

Please refer to OPDRA Consult 01-0029.

IV. COMMENTS TO THE SPONSOR:

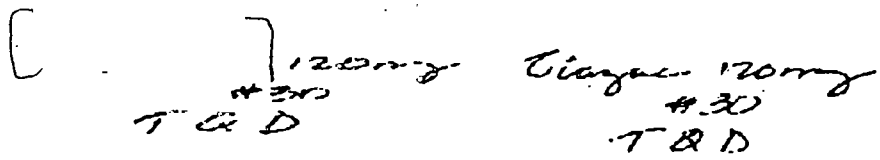
In reviewing the proprietary name ——— the primary concerns raised were related to sound-alike, look-alike names that already exist in the U.S. marketplace. Two products, *Vi-Zac and Tiazac,* were believed to be the most problematic in terms of medication error prevention.

Vi-Zac capsules are over-the-counter multivitamins containing minerals. Not only does ——— and *Vi-Zac* sound similar to one another, the drug names look similar when scripted as well. In addition, they share an overlapping dosing regimen (once daily) and dosage form (capsules). Although *Vi-Zac* is an over-the-counter multivitamin and ——— is a Schedule II controlled substance requiring a written prescription, the possibility does exist where a written prescription for *Vi-Zac* may be presented to the pharmacist. Furthermore, verbal prescription orders for Schedule II controlled substances are communicated in inpatient hospital settings hence adding to the potential for confusion between these two drug names. However, ——— will be available in 30 mg, 60 mg, 90 mg and 120 mg capsules whereas *Vi-Zac* is available without a strength. Therefore, the presence of a strength on a written or verbal prescription will aid in distinguishing ——— from *Vi-Zac.*

Tiazac is the proprietary name for diltiazem and is indicated for the treatment of hypertension and chronic stable angina. *Tiazac* and ——— not only sound similar but the names look similar as well (see prescription below). *Tiazac* and ——— share an overlapping dosing regimen (once

daily), strength (120 mg), and dosage form (capsules). Furthermore both may be prescribed in similar quantities (#30). The inadvertent confusion of these two drugs could potentially be life threatening. For example, a patient receiving *Tiazac* instead of [redacted] may experience decreased blood pressure, dizziness, peripheral edema, headache, pain and other adverse events related to calcium channel blockers. Additionally, the patient will remain untreated for moderate to severe pain. *Tiazac* is also associated with numerous drug interactions when given concomitantly with other drugs. Such drugs include: cimetadine, digitalis, beta-blockers, carbamazepine, levostatin, benzodiazepines, cyclosporin, and rifampin. A patient that inadvertently receives [redacted] instead of *Tiazac* will remain untreated for high blood pressure and also experience respiratory depression and/or the possibility of an allergic reaction if the patient is hypersensitive to morphine.

[redacted] TIAZAC



The prefix "Vin" is also misleading in that "Vin" is a USAN stem for a class of drugs known as the Vinca Alkaloids. Proprietary names that incorporate a USAN stem will generally be considered misleading if the drug does not have the chemical, therapeutic and/or pharmacologic parameters associated with the USAN stem. Per USAN guidelines, the use of the stem "vin" as a prefix or in the middle of the name is associated with the class known as the Vinca Alkaloids.

V. RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name ----------

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Alina Mahmud
10/22/01 04:16:02 PM
PHARMACIST

Jerry Phillips
10/23/01 10:59:02 AM
DIRECTOR

Martin Himmel
10/24/01 09:10:40 AM
MEDICAL OFFICER

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 5/17/01	DUE DATE: 8/17/01	OPDRA CONSULT: 01-0105

TO:

Cynthia McCormick, M.D.
Director, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

THROUGH:

Kim Compton
Project Manager, Division of Anesthetic, Critical Care, and Addiction Drug Products
HFD-170

PRODUCT NAME:	**MANUFACTURER:** Elan Holdings, Inc. (Pharmaceutical Division)
——— (Primary) and ——— (Alternate) (Morphine Sulfate Extended-Release Capsules) 30 mg, 60 mg, 90 mg, and 120 mg NDA #: 21-260	

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170), OPDRA conducted a review of the proposed proprietary names ——— and ——— to determine the potential for confusion with approved proprietary and established names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of both proprietary names, ——— and ———.

Carol Holquist, R.Ph. for
Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: 301-827-3246
Fax: 301-443-5161

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: July 26, 2001

NDA NUMBER: 21-260

NAME OF DRUG: [redacted] (Primary) and [redacted] (Alternate)
(Morphine Sulfate Extended-Release Capsules),
30 mg, 60 mg, 90 mg, and 120 mg

NDA HOLDER: Elan Holdings, Inc. (Pharmaceutical Division)

I. INTRODUCTION:

This consult was written in response to a request from the Division of Anesthetic, Critical Care, and Addiction Drug Products (HFD-170) for assessment of the tradename [redacted]", regarding potential name confusion with other proprietary/generic drug names.

[redacted]" is the new proprietary tradename submitted by the sponsor. Prior proprietary tradename submissions by the sponsor for this product included "Avinza" (OPDRA Consult 00-0264) and "[redacted]" (OPDRA Consult 01-0049); both names were found unacceptable by OPDRA. Labeling comments for this product was provided by OPDRA in OPDRA Consult 01-0029.

PRODUCT INFORMATION

[redacted]" is the proposed name for morphine sulfate extended-release. It is formulated as a once-a-day capsule, which contains both immediate-release and extended-release beads of morphine sulfate for oral administration. [redacted] is indicated for the relief of moderate to severe pain and is intended for the use in patients that require repeated dosing with opioid analgesics over periods of more than a few days. [redacted] will be supplied as 30 mg, 60 mg, 90 mg, and 120 mg capsules and will be available in both blister pack cartons and bottles of 30, 100, 250, and 500 count.

II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts[1,2,3] as well as several FDA databases[4] for existing drug names which sound alike or look alike to "[redacted]" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S.

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

[2] American Drug Index, 42nd Edition, online version, Facts and Comparisons, St. Louis, MO.

[3] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

[4] The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

Patent and Trademark Office's Text and Image Database[5] and the data provided by Thomson & Thomson's SAEGIS™ Online Service[6] were also conducted. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name [redacted]. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Several product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with [redacted]. These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

Table 1

Product Name	Dosage form(s); Generic name	Usual adult dose**	Other**
[redacted]	Morphine Sulfate Extended-Release (Narcotic Analgesic – Rx) Capsule: 30 mg, 60 mg, 90 mg, 120 mg	Once-a-day dosing. Total daily dose depends on patient's tolerance and reaction to morphine.	
Exelon	Rivastigmine Tartrate (Cholinesterase Inhibitor – Rx) Capsule: EQ 1.5 mg base, EQ 3 mg base, EQ 4.5 mg base, EQ 6 mg base Solution: EQ 2 mg base/mL	Initial: 1.5 mg twice a day. Maximum dose: 6 mg twice daily.	L/A per OPDRA
Hexitol Irrigants	Mannitol or Sorbitol (Nonelectrolytic and nonhemolytic urologic irrigation solution) Sorbitol Solution: 1500 mL (165 mOsm/L), 2000 mL (183 mOsm/L), and 3000 mL (165 mOsm/L) Mannitol: 2000 mL (275 mOsm/L) Sorbitol and Mannitol: 1500 mL and 3000 mL (both 178 mOsm/L)	Use as required for irrigation.	S/A per OPDRA
Hexadrol	Dexamethasone (Glucocorticoid -- Rx) Elixir: 0.5 mg per 5 mL Tablet: 1.5 mg, 4 mg	Initial dosage: 0.75 to 9 mg/day	S/A per OPDRA

[5] WWW location http://www.uspto.gov/tmdb/index.html.

[6] WWW location http://www.thomson-thomson.com.