CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-260

MEDICAL REVIEW(S)

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857
Tel:(301) 827-7410

DIVISION DIRECTOR'S REVIEW

DATE:	March 20, 2002
DRUG PRODUCT:	**Avinza®** Morphine Sulfate Extended Release Capsules
SPONSOR:	Elan Pharmaceuticals/Ligand Pharmaceuticals
SUBMISSION:	NDA # 21-260
DRUG CLASS:	Opioid analgesic
PROPOSED INDICATION:	for the management of patients requiring continuous opioid analgesia
DATE RECEIVED:	July 2, 2001
REVIEWED BY:	Cynthia G. McCormick, MD Director, Division of Anesthetic, Critical Care and Addition Drug Products, ODE II, CDER, FDA

Background

Refer to Division Director's supervisory review dated March 30, 2001 which reviewed the basis for the prior Approvable action and the basis for the finding of efficacy and safety of morphine sulfate extended release capsules. This review summarizes the final successful resolution of the issues that were pending at the time of the previous action.

Basis for Approval

This application was submitted under 505(b)(2) of the Act, referencing the Agency's finding of safety and efficacy for MS Contin. The additional positive efficacy trial in patients with moderate to severe pain associated with [redacted] is additional support for the efficacy of Morphine sulfate in this formulation. Additional studies supported the product's safety.

The development plan consisted of a safety database with exposure of 560 patients with chronic pain to doses up to >400 mg/day. There were no unexpected adverse events and overall the adverse event profile was similar to that of MS Contin.

In the response to the Approvable letter the sponsor provided some [redacted] of the doses proposed for Avinza, taking into account the dose of the excipient fumarate that is present in a 1:1 ratio with morphine in this formulation. Preclinical information was conflicting regarding the potential for fumaric acid in high doses to result in renal toxicity to the proximal tubules. Support for dosing up to 1600 mg was supplied by the sponsor. The actual exposure of patients in clinical trials to doses >400mg was limited to 21 patients. There is expected to be a segment of the patient population for whom this drug is targeted who will require doses in excess of 1 or 2 grams per day. The safety of these very high doses has not been fully evaluated. Therefore the labeling will reflect the upper limit of dosing as 1600 mg. until further data are generated. In addition nonclinical studies will be performed as a postmarketing commitment to help characterize the safety profile of fumarate in high doses.

The CMC deficiencies that were identified at the time of the previous action and during this review cycle have been resolved satisfactorily.

Labeling

Labeling negotiations took place, working from the sponsor's draft labeling. The changes that were agreed to by the sponsor included a change in the indication section, reflecting the chronicity of treatment, the clinical trials section, including only the positive placebo controlled trial which demonstrated an statistically significant analgesic effect. Clarification was added to the description of the trial, which, in conjunction with the finding of Safety and Efficacy for MS Contin, provided the basis for approval. [redacted] There was stronger labeling in the drug abuse section, a box warning to alert prescribers to the dangers associated with crushing the tablet. There was a warning limiting dosing to less than 1600 mg. Pediatric Use indicated that the safety and efficacy of Avinza in pediatric patients has not been demonstrated. Strong warnings about the abuse potential of this product were included.

The sponsor developed a PPI for distribution as a mechanism to educate families about the potential risks associated with this product.

Phase 4 Commitments

The sponsor has agreed to the following phase 4 commitments:

1. Carcinogenicity Studies in two species, with a commitment to submit the protocols to FDA for review by the CAC committee.
2. Evaluation of the toxicity of fumaric acid in two animal species evaluating the NOAEL for nephrotoxicity.

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
3/20/02 07:21:32 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
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Tel: (301) 827-7410

Division Director's Review

DATE: March 30, 2001

FROM: Cynthia G. McCormick, MD, Director
Division of Anesthetic, Critical Care and Addiction Drug Products
Office of Drug Evaluation II, CDER, FDA

TO: DFS, NDA #21-260 ——— (morphine sulfate) capsules

RE: Basis for Action

Elan Pharmaceuticals has submitted a new drug application for a modified release formulation of morphine sulfate in capsule strengths of 30, 60, 90 and 120 mg tablets. In support of this application there were two adequate and well-controlled studies in patients with malignant and nonmalignant pain. There was literature provided to support nonclinical safety, biopharmaceutics studies designed to characterize the pharmacokinetic profile of the formulation, and information on the manufacture and controls of the drug substance and drug product. The application was submitted under section 505(b)(2) of the Act and the reference-listed drug was MS Contin against which a relative bioavaiablity study was performed as required.

The basis for the finding of clinical efficacy was provided through two adequate and well-controlled studies in malignant and nonmalignant pain in opiate tolerant patients, and in osteoarthritis in patients who were opiate naiive. One of these studies provided evidence of morphine's efficacy delivered by this formulation in the treatment of pain. The other demonstrated differences in performance across treatment arms but failed to produce convincing evidence of efficacy.

In the first study TRG004-002 patients with chronic malignant and nonmalignant pain were stabilized on an individualized regimen of MS Contin during a prerandomization baseline. They were then randomized to one of four treatments based on their previous dose of MS Contin: 100% MS Contin 100%, [redacted], 50% [redacted] and 133% [redacted] The primary outcome measures included both change in rescue medication and change in VAS pain intensity and Pain Descriptor Score. The designs and conduct of this trial, the results and FDA analysis of the data are carefully reviewed by Drs Hertz and Hartwell and the statistical analysis by Dr. Hoberman. I concur with the review team that there was a statistically significant difference in all outcomes when the 50% [redacted] and 133% [redacted] group were compared. However as the medical team points out there was an increase in pain in all groups as well as a corresponding increase in the use of rescue medication. I differ with the team's conclusion about this trial only in one respect. I do not view the statistically significant difference between treatment arms necessarily as evidence of analgesic efficacy. Clearly there was less deterioration in the highest dose group of [redacted] compared to the lowest, that is incontrovertible. However no improvement in pain was noted in any group, and thus an analgesic effect was not really demonstrated. There are many factors that could have contributed to the worsening of pain across all groups, however these remain speculative.

The second study in patients with osteoarthritis was more clear and I concur with the findings of the review team that in this randomized double-blind fixed dose study comparing two regimens of [redacted] 30 mg qd, MS Contin bid, and placebo there was a statistically significant difference between the [redacted] 30 mg qd and placebo. This effect was diluted by the fourth treatment period where the placebo group continued to demonstrate improvement in WOMACK pain VAS scales and in % change from baseline (the primary out come variables) while the three active treatment arms began to show a decline in performance. This might be attributable to tolerance, again, unproven and a longer duration study might have provided clearer assessment of this. Nevertheless on the primary presepecified endpoints the study demonstrated the desired result.

The overall safety profile of this product is not unlike other drugs in this class and demonstrates no improvement over MS Contin. Typical opiate side effects were manifested, as described by Dr.Hertz and Hartwell in their review.

The agency's previous finding of safety and efficacy of morphine as MS Contin combined with at least one positive efficacy study should provide the clinical basis for the finding of safety and efficacy in this 505(b)(2) application.

The chemistry, manufacturing and controls were thoroughly reviewed by Dr. Harpanhali. He has determined that the information that was submitted is inadequate to ensure the safety and efficacy of the drug product. [redacted]

/s/

Cynthia McCormick
3/30/01 08:31:17 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	**21-260**
Sponsor	Elan Pharmaceutical Research Corporation
Generic Name	Morphine Sulfate
Proprietary Name	Avinza
Pharmacologic Class	Opioid narcotic
Proposed Indication	Relief of chronic moderate to severe pain
Submission Date	July 26, 2001
Type of Submission	Response to Approvable Letter
Dosage forms	Capsules
Strengths	30 mg, 60 mg, 90 mg, 120 mg
Route	Oral
Clinical Reviewer	Sharon Hertz, M.D.
Completion Date	February 28, 2002

TABLE OF CONTENTS

Executive Summary

NDA 21-260 was originally submitted on May 31, 2000. An approvable letter dated March 30, 2001 was sent to the sponsor detailing clinical and CMC issues requiring further information and discussion before the Avinza could be approved. The current submission, the sponsor's complete response to the approvable letter, fails to adequately address the clinical issues raised in the approvable letter. I recommend this application remain approvable pending the adequate resolution of the outstanding questions concerning the safety of exposure to fumaric acid in doses greater than 500 mg/day. Alternatively, an approvable action could be considered in the setting of appropriate labeling that limited the use of this product to a maximum daily dose of 500 mg/day, with a commitment by the sponsor to pursue the information needed to determine the safety of higher doses.

The following comments summarize the review of the Sponsor's response to issues detailed in the Approvable letter:

- The Agency requested support of the safety of exposure to large doses of fumaric acid, an excipient with a 1:1 ratio by weight to morphine sulfate. As there are chronic pain patients requiring very large doses of morphine for adequate pain control, the sponsor was asked to provide evidence that exposure to doses over 500 mg per day was safe given preclinical and clinical reports that suggest such doses of fumaric acid were potentially toxic in humans. The sponsor provided a literature review that failed to provide adequate clinical or preclinical evidence to support the use of such a dose. The Agency did perform an evaluation of the renal function in all patients receiving more than 400 mg of Avinza per day, but the number of patients receiving more than 500 mg/day was too small to support any conclusions on the safety of these doses. A preclinical study or studies demonstrating an acceptable safety margin for toxicity will be required to adequately address this concern.

  The sponsor adequately addressed the issue of a failure to provide unique patient ID numbers across studies by providing an appendix.

  The risk management plan submitted by the sponsor was in an expanded outline format. The sponsor will need to provide additional information and detail.

  The Agency requested the sponsor conduct a study to evaluate the presence of insoluble excipients to assess health risks posed by intravenous abuse of Avinza. The study conducted and submitted provided information on the extractability of morphine but failed to address the primary question concerning insoluble excipients.

- The sponsor was required under 21 CFR 314.50(d)(5)(vi)(*b*) to submit an update to the Integrated Summary of Safety. The safety update provided failed to adequately integrate new data into the safety database and present this information in the manner requested. A review of the submitted information in conjunction with material submitted during the original NDA review cycle did not reveal any new safety signals of concern.

Background

The original review of NDA 21-260, submitted on May 31, 2000, found the submission to be approvable based on outstanding clinical and CMC issues. The following clinical points, excerpted from the approvable letter, will be addressed in order:

1. Because of the one-to-one by weight ratio of fumaric acid to morphine in the formulation of your morphine sulfate extended-release capsule you must determine the risk of toxicity due to the intake of fumaric acid in those patients requiring doses of your morphine sulfate extended-release capsule exceeding 500 mg per day. Additional risk by concurrent use of other medications containing fumaric acid, commonly used by patients receiving your morphine sulfate extended-release capsule, will also need to be assessed. You should develop appropriate recommendations describing the maximum safe dose of your morphine sulfate extended-release capsule both with and without concurrent use of other fumaric acid containing drug products.

2. In the clinical studies, the use of patient ID numbers that were not unique for each patient precludes the adequate evaluation of clinical efficacy and safety data. You will need to rectify the redundancy in patient ID numbers by determining some manner of uniquely identifying all patients and resubmit all data from patients who did not have unique ID numbers. This includes the patients assigned two different numbers and those patients with one ID number that was not unique to that patient.

3. Design and submit a risk management program to ensure the safe and effective use of your morphine sulfate extended-release capsule, and to identify trends in inappropriate use that might have adverse effects on the public health.

4. Clinical reports suggest that intravenous abuse of oral formulations which contain talc or other insoluble elements may cause pulmonary pathology. Provide results of an appropriate *in vitro* test of the extraction of your morphine sulfate extended-release capsule crushed in a manner intended to simulate intravenous abuse of the product.

5. Your product label directly or indirectly references data and language from the labels of products other than MS Contin® (which is the only product for which you have established relative bioavailability). This is most prominent in the Clinical Pharmacology, Clinical Trials, Carcinogenicity, and Pregnancy portions of the label. You must rewrite the product label based only on data for which you have a right of reference, or on data that is generally accepted by the scientific community and that is not based on underlying, proprietary data.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. The safety update should

include data from all nonclinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

    a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

    b. Present tabulations of the new safety data combined with the original NDA data.

    c. Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

    d. For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

Review Items

1. Fumaric Acid

Concern has been raised over the potential for exposure to large amounts of fumaric acid when large doses of Avinza are utilized. Fumaric acid is an excipient in Avinza, present in a 1mg:1mg ratio with morphine. The NOAEL of fumaric acid in humans is reported to be 500 mg/day[1]. Fumaric acid is a common ingredient in many pharmaceutical products and as a food additive. As a pharmaceutical excipient, it is generally recognized a safe. Fumaric acid has been prescribed in high doses as a treatment for severe psoriasis. In this context, there have been numerous well documented reports of dose dependent adverse events in humans including nausea, diarrhea, lymphopenia, and renal toxicity. As a result of this toxicity, fumaric acid esters have replaced fumaric acid as a treatment of psoriasis.

The sponsor has responded to the Agency's request for information supporting the safe use of fumaric acid in doses of more than 500 mg/day in the Approvable letter with the following three arguments (Attachment 51, Vol. 4.11, P. 216).

1. The sponsor first addressed this issue by commenting that patients are unlikely to use doses of Avinza high enough to expose them to fumaric acid in amounts greater than 500 mg/day. However, in the Avinza clinical trials, 42 patients received doses of more than 400 mg/day, 33 of whom remained on more than 400 mg/day for over 90 days. (Vol. 4.13, P. 21, Table 8-2, Duration of Exposure vs. Categorized Dose). In addition, it is generally known that patients with severe chronic pain, particularly those with cancer, may require and tolerate doses of morphine in excess of 500 mg/day. Many of these patients require treatment with morphine for an extended period of time. These are the patients with potential for toxicity due to exposure to high doses of fumaric acid.

2. The sponsor next addressed this issue by reviewing the use of fumaric acid in other pharmaceutical preparations and in non-carbonated fruit juice drinks. As a food additive, fumaric acid is used in concentrations ranging up to 3600 PPM. A review of other products formulated with fumaric acid revealed an important difference between these products and Avinza. As an opioid, unlike many other pharmaceutical agents, there is no upper limit to the dosing of Avinza. Other products formulated with fumaric acid have specific upper limits to dosing.

3. According to the sponsor, literature reports support the proposed doses of fumaric acid. Copies of references were obtained from the sponsor (Appendix A).

- In a case report by Raschka and Koch (1), a patient receiving fumaric acid 420 mg BID for four months for the treatment of psoriasis developed proximal renal tubular damage with glycosuria, hypophosphatemia, proteinuria and hypuricemia. This

[1] Fumaric Acid. HSDB - Hazardous Substances Data Bank, National Library of Medicine, Dept. HHS

damage persisted for at least six months following medication discontinuation and was ongoing at the time of the case report.

- A repeated dose study was performed by Levey et. al. (1946). Seventy five hospitalized patients were given compressed tablet of 500 mg fumaric acid daily. Fifty six of the patients received the fumaric acid for ten months or longer. There were no consistent effects noted on hemoglobin levels, RBC or WBC counts, non-protein nitrogen or creatinine. Eleven of 70 patients with repeated urine examinations had albuminuria of 1+ noted. Renal function was evaluated by the phenosulfonphthalien test and was performed in 70 of 75 patients. Thirteen subjects had a decrease in function that was not quantitated in this article. Liver function was evaluated by the bromsulfalein test, with one of 73 subjects showing a decline in function. No quantitation was provided. The authors conclude that no apparent adverse effects resulted from prolonged oral administration of small amounts of fumaric acid to human subjects.

- The TNO BIBRA International Toxicity profile describes single oral doses of 83-500 mg/kg resulting in nothing worse than nausea, stomach cramps and diarrhea. This source also cites the article by Levey et. al.(2) described above.

- A prospective study of fumaric acid esters in patients with psoriasis (4) did not demonstrate renal toxicity, although there were frequent changes in lymphocyte and eosinophil counts. A review of therapy with fumaric acid derivatives found reversible renal dysfunction with monethylfumaric ester in oral doses of 720 mg/day (5). Unlike fumaric acid, fumaric acid esters are resorbed by the intestine in a manner similar to bile salts. The metabolism and excretion are therefore different. Reports of exposure to other fumaric acid derivatives are also cited, some of which report renal and hepatic toxicity, but the relevance to fumaric acid exposure is unknown.

A review of the dosing of the 42 patients identified as having received 400 mg/day or greater was performed. Twenty one patients actually received doses of 500 mg or greater. The average dose over 500 mg/day was 601 mg/day with a range of 510 mg/day to 1020 mg/day. The average length of time on a dose over 500 mg/day was 191 days. For this limited group of patients and for all patients with dosing of 400 mg/day, the lab results were reviewed. None of these patients had evidence of renal toxicity.

In summary, the sponsor has not provided sufficient clinical information supporting the safe use of more than 500 mg/day of Avinza. The available clinical experience from the safety database is very limited. The published literature lacks relevant studies.

2. Patient ID numbers

Patients were not given unique ID numbers that spanned their double-blind and open-label study participation. The numbering system was different for all 5 originating protocols, so that for several patients, the ID number from the double-blind study

changed to an ID number the open-label study that was assigned to another patient during that patient's double-blind study participation. This has resulted in the need to use a variety of combinations of screening number, randomization number, patient initials and protocol number to identify patients and follow them through the ISS. A 115 page appendix was provided by the sponsor as a guide to identifying the patients in the ISS.

This appendix provides the means needed to adequately identify all patients.

3. Risk Management Plan

The sponsor has provided a brief proposed Risk Management Plan (RMP). There are deficiencies, particularly several areas which require greater detail and others which require some reorganization. The sponsor identifies five main components in this plan: Analysis of Misuse\ Abuse Risk, Communication of Appropriate Use, Post Marketing Surveillance- Phase 4 Study, Monitoring and Tracking, and Program Evaluations.

Section 1.
Under Section 1, Analysis of Misuse\Abuse Risk, the sponsor describes using the sources described to determine a baseline of the "current" risks associated with the use of morphine for future reference. This would include spontaneous reports of adverse events and any information on the potential for misuse and abuse. The sponsor would accomplish this through a review of spontaneous reports of adverse events followed by an analysis of any trends linking the events with a "biological plausibility" for causality from the drug exposure. Periodic review of information from the same sources would contribute to updates to the RMP as indicated. In subsection 1 a., the sponsor reports plans to review spontaneous reporting of adverse events for information on misuse or abuse of Avinza.

It is necessary for the sponsor to differentiate issues related to morphine and the many products containing morphine from Avinza specific issues. As a sustained-release product, the amount of morphine in Avinza tablets is greater than for most immediate-release products. This results in greater appeal for abuse and greater potential for harm with misuse. Does the sponsor plan to establish baseline morphine abuse and misuse risk prior to launching Avinza for later comparison with Avinza, or will a baseline Avinza risk assessment be established over a specified period of time after launch? As there would be a delay prior to the start of spontaneous adverse events reports referable to Avinza following the initial release, timeframes for completing the assessments would need to be specified.

Section 1 b.
In Section 1 b., the sponsor describes reviewing the world literature pertaining to Avinza for inclusion in period safety reports.

Section 1 c.
In Section 1 c., Community Benefit/Risk, the sponsor describes determining an acceptable level of benefit/risk by, "seeking the opinion of those with a vested interest in

the effective and safe use of the product..." The risk/benefit ratio of Avinza would be determined by a review of relevant efficacy data relative to the risks demonstrated in the accumulated safety data.

The sponsor's approach for a benefit/risk assessment using individuals with a vested interest in this product can be, by definition, considered biased by utilizing an appropriate group for making this determination. The approval of the product will require the determination of an acceptable risk/benefit ratio based on the databases in the NDA. Ongoing, post-marketing review of adverse events by the Agency and the sponsor would then contribute to an ongoing risk/benefit assessment.

As another aspect of assessing risk, the sponsor proposes to become a corporate member in related medical professional societies. It is unclear how this would provide information concerning the monitoring of risk or misuse/abuse. The sponsor should provide greater detail on how this will be accomplished.

Section 1 d.
In Section 1 d., the sponsor describes the creation of an internal Advisory Committee for yearly review of the RMP and outcome measures.

Section 1 e.
In this section, the sponsor describes ongoing plans to update the label as needed and for a Patient Information Brochure. The development of a Patient Information Brochure is important and should be made available at the time of initial marketing, but is not relevant to the assessment of risk/benefit. This section should be moved to Section 2, Appropriate Use Communication Program. A draft patient information brochure should be submitted for review.

Section 2
Section 2 describes the Appropriate Use Communication Program. The stated objectives are the communication of appropriate patient selection, proper product usage, awareness and management of adverse events, and the risks of inappropriate usage. The sponsor describes fair and balanced communication targeted to specific physicians, pharmacists, managed care organizations, medical associations, sales representatives, and patients.

The sponsor also has plans to develop a corporate statement on the risk/benefit of opioids and states that no television or radio direct-to-consumer advertising will be undertaken for Avinza. This is important to reduce the risk of inappropriate requests for the product by patients, but should also clearly indicate that written media for the general population are included.

Sections 2 a. and b.
These sections describe the sponsor's plan to create a Dear Healthcare Provider letter and Patient Selection Insert for prescribers for use at product launch, with a similar letter for pharmacists. Continuing education programs for physicians and pharmacists will be sponsored. Paid speakers will be trained and given slides for use prepared by the sponsor

with post-meeting questionnaires to monitor the message received. The sponsor is also planning preprinted, non-abusable prescription pads.

The Patient Information Brochure as described above, will be made available to pharmacists who wish to distribute it to patients.

Sections 2 c. and d.
These sections describe the intent of the sponsor to provided information to Federal and local agencies, and medical associations including Appropriate Use Materials.

Section 2 e.
This section describes the training of sales representative emphasizing the appropriate use of the product.

Section 2 f.
This section describes the development of a patient starter kit that will be made available to physicians consisting of the patient information brochure, a sample coupon, and a patient diary.

Section 3.
This section is titled, "Post Marketing Surveillance-Phase IV Study." This study will include an assessment of misuse and abuse potential. While this may be a useful approach, post marketing surveillance characteristically covers much more as described in Section 4 Monitoring and Tracking. The terminology should be clarified to avoid confusion.

Section 4
Section 4, Monitoring and Tracking, will include monitoring of reports in a safety database from calls to a staffed toll free number.

Section 4b. describes periodic review of the literature.

Section 4c.
This section describes the sponsor's efforts to work with DAWN to develop a program to receive reports on a bi-weekly basis, to no longer categorize morphine and heroin together, and if possible, to get Avinza specific data. The sponsor also mentions obtaining data from the Office of Applied Studies of SAMHSA.

Subsection d. describes use of the MedWatch reports.

Section 5.
Section 5, Program Evaluations, describes patient and physician post-market analyses using message testing of the target audiences. The feedback will be used to modify educational information as needed. An internal evaluation will also be undertaken as part of the periodic safety reporting.

In summary, the sponsor has proposed a Risk Management Plan that encompasses many of the important and necessary areas of such a plan. However, it is important that several features proposed be clarified. The sponsor should specify what is meant by the baseline proposed in Section 1a, specifically whether it refers to a general morphine or modified-release morphine baseline assessment of misuse and abuse, or an interval of time following marketing to establish some type of Avinza baseline for future comparison.

The determination of an acceptable risk/ benefit ratio for this product will be determined by the Agency through review of the materials submitted in the NDA, rather than by individuals with a vested interest in this product as proposed in Section 1c. Ongoing, post-marketing review of adverse events by the Agency and the sponsor would then contribute to an ongoing risk/benefit assessment. The sponsor should provide greater detail on how becoming a corporate member in related medical professional societies will be utilized as a means of providing information concerning the monitoring of risk or misuse/abuse.

Section 1e, describing the development of a Patient Information Brochure should be moved to Section 2, Appropriate Use Communication Program. This brochure should made available at the time of initial marketing, and a draft should be submitted for Agency review.

The phase 4 post-marketing surveillance study to assess misuse and abuse potential mentioned in Section 3 and should be submitted for further review and to clarify how this post-marketing surveillance approach will differ from the usual monitoring of post-marketing adverse events.

4. Assessment Of The Extractability Of Insoluble Excipients

As part of the approvable letter for Avinza, the Agency requested that the sponsor conduct an assessment of the extractability of insoluble excipients from Avinza. This was intended to assess the potential for pulmonary pathology resulting from intravenous abuse.

The sponsor has submitted the results of this study on page 125 of volume 4.1. The protocol for this study was submitted in Attachment 53, which can be found in volume 4.13, page 233.

The results of the study submitted provide information on the extractability of morphine from the crushed tablet, but provides no comment on the talc or other insoluble excipients.

5. Product Label

The Agency requested that the sponsor include references to data and language only resulting from clinical trials conducted with this product and from the no labels of products other than MS Contin® (which is the only product for which they have

established relative bioavailability). This was most prominent in the Clinical Pharmacology, Clinical Trials, Carcinogenicity, and Pregnancy portions of the label. The reader is referred to the reviews by the biopharmaceutics and the pharmacology/ toxicology reviewers.

6. Updated ISS

In the Approvable letter, the Agency requested that the sponsor provide an updated Integrated summary of safety. The sponsor was specifically requested to incorporate new safety data describing discontinuations due to adverse events, serious adverse events, and common adverse events as follows:

a. Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.

b. Present tabulations of the new safety data combined with the original NDA data.

c. Include tables that compare frequencies of adverse events in the original NDA with the re-tabulated frequencies described in the bullet above.

d. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

The sponsor failed to provide the safety data as requested. The sponsor reports that this ISS includes data integrated from the five clinical Avinza studies: TRG004-01, TRG004-02, TRG004-04, TRG004-05, TRG004-06, and the two open label extensions TRG004-03, TRG004-04OL. All of these studies have been completed as of the date of this report and all but study TRG004-03 were complete at the time of the 120-day safety update for the original NDA submission On review of the material provided, however, the data reflect only an update of the open-label studies. The Duration of Exposure tables, Tables 8-1 and 8-2, p. 21, have a total number of patients of 558 representing double-blind and open-label patients, while the Disposition table, 9.1 p. 22, and the Patient Characteristics table, 10.1-1 p. 23, have a total of 465 patients representing just open-label patients. Discontinuations due to adverse events, serious adverse events, adverse events, vital signs, physical exam, and laboratory tables and data are provided only for the open-label studies. No comparison to prior data from the original NDA or the 120-day safety update was provided. During the original review cycle, the sponsor was requested to submit an integrated database of all the safety data rather than separate analyses for the open-label and double-blind studies as was initially submitted. A similar integration of the overall safety database was again requested of the sponsor throughout the review cycle, but was never received. Following numerous telephone conversations requesting an integrated safety update, the sponsor did submit tables of adverse events, serious adverse events, and adverse events leading to study discontinuation. These tables consisted of data for a combined population encompassing double-blind and open-label patients, with patients enrolled in more than one trial counted only once for the total number of subjects, a total number of 560. This was different from the format submitted during the NDA review.

The integrated tables submitted in response to the Agency's requests at that time counted patients who participated in both double-blind and open-label studies for each study participation resulting in a total number of 866. The current submissions also failed to provide columns of data from the original NDA or 120-day safety update for comparative purposes.

Clinical Trials

During the clinical trials, Avinza carried a working trade name of Morphelan. In order to permit ready comparison with the original NDA review and data submitted in support of this ISS update, the name Morphelan is maintained during discussions of data resulting from the clinical trials.

Study TRG004-02 was a multicenter, randomized, double-blind, double-dummy study of Morphelan in patients with chronic, moderate to severe pain. Patients with chronic malignant or non-malignant pain were randomized to four treatment groups based on the open-label stabilization period dose of MS Contin. The four treatment groups were Morphelan 50%, Morphelan 100%, Morphelan 133%, and MS Contin 100%. The randomization period was conducted for a total of 7 days, during which time patients were also allowed to take oxycodone as a rescue medication.

TRG001, TRG004-05, and TRG004-06 evaluated the pharmacokinetics and pharmacodynamics of Morphelan in patients with chronic moderate to severe pain of malignant and non-malignant origins. The two-period crossover design was used to establish a PK/PD relationship for once daily Morphelan and twice daily MS Contin.

Study TRG004-03 was a multicenter, open-label, extension study of Morphelan in patients with chronic, moderate to severe pain who had completed a prior Morphelan clinical trial. Patients who had completed TRG004-01, TRG004-02, TRG004-05, or TRG004-06 were eligible for enrollment in this study. Patients initially received Morphelan once a day at a dose closest to the 100% morphine equivalent daily dose that provided stable pain relief during the pre-randomization period of the double-blind studies. Patients without adequate pain relief or with unacceptable adverse events could titrate their dose upward or downward. Rescue medication use was permitted at a dose equivalent to approximately 10% of the initial daily Morphelan dose. Safety and efficacy follow-up evaluations were performed every 30 days for one year.

Study TRG004-04 was a double-blind, placebo-controlled, study in patients with severe osteoarthritis of the knee and/or hip. Patients were randomized into four treatment groups: Morphelan 30mg qam, Morphelan 30mg qpm, MS Contin 15mg bid, and placebo. The double-blind period lasted for a total of four weeks.

Study TRG004-04OL was an open-label extension for osteoarthritis patients from Study TRG004-04. Treatment with Morphelan was discontinued at the end of week 30 (including the 4-week double-blind trial). Efficacy and safety were evaluated at Weeks 5, 8, 12, 18, 24, and 30 (after entry into the double-blind phase).

The sponsor summarized the safety assessments from the open-label studies in the following table. Any treatment-emergent AE, new intercurrent illness, or clinically significant laboratory finding from treatment onset through 5 days post study drug were defined as study events. AEs were coded using the COSTART dictionary.

Table 1 Safety Variables, Open-Label Long-Term Studies

Protocol	Pain Etiology	Planned Duration of Treatment	Safety Assessments	Assessment Times'
TRGO04-03	Chronic, moderate to severe pain of malignant and non-malignant origin	1 year	Hem., chem., u/a PE Vital signs AEs	Baseline, every 90 days Baseline, every 90 days Baseline, every 90 days Throughout study
TRGO04-04 Open-Label Phase	Osteoarthritis with inadequate pain control with NSAIDs and other conventional treatments	26 weeks (30 weeks including DB treatment)	Hem., chem., u/a PE Vital signs EKG AEs	Weeks 4, 18, 31 Weeks 4, 31 Weeks 4, 5, 8, 12, 18, 24, 30, 31 Weeks 4, 18, 31 Throughout study

a. If a patient dropped out of the study, the end-of-study measurement was made at the time of termination.
Source: Sponsor's Table 2-1, P. 17, Vol. 4.13

Extent of Exposure

A total of 465 patients were enrolled in the open-label studies, 284 in Study 03 and 181 in 04OL. In the 120-day safety update submitted October 12, 2000, there were already 461 patients enrolled in the open-label trials, the difference being 4 additional patients enrolled into study TRG004-03. There were 560 unique patients enrolled in double-blind studies and open-label studies, with patients rolling over from the former into the latter counted once.

Patients in TRG004-03 were chronic opioid users and were permitted to continue the Morphelan dose established during the double-blind study, along with subsequent adjustments as needed. The dose range was 61-200 mg/d, with a median dose by body weight of 1.6 mg/kg. For the chronic opioid patients using >400 mg/d, the dose by body weight was 5.3 mg/kg. The patients in TRG004-04OL had osteoarthritis. They were required to start treatment in this open-label study with Morphelan 30 mg/d and were permitted to titrate the dose if needed. The dose range was 30-60 mg and the median dose by body weight was 0.3 mg/kg. Dosing increased over time to a median of 0.4 mg/kg for the osteoarthritis patients.

The mean duration of treatment was 235 days for study TRG004-03 (planned duration of 1 year) compared with 175 days from the 120-day safety update. The mean duration of treatment was 116 days for study TRG004-04OL (planned duration 30 weeks including 4 weeks of double-blind study), unchanged from the safety update. Patients with chronic pain remained on Morphelan longer than the osteoarthritis patients. To some extent, this was due to the different planned study durations. But even within the time constraints imposed by the protocols, the chronic pain patients still can be seen to have remained on study drug relatively longer than the osteoarthritis patients. Table 2 demonstrated that 50% of the patients with chronic pain remained on study drug for at least 275 of the possible 365 days of study participation, 43% completed at least 336 days, and 22% went on to remain on study drug for longer than one year. Among the osteoarthritis patients, 50% had withdrawn by weeks 9-13 out of the possible 30 weeks of study participation, 38% remained on study drug for up to 26 weeks, and 11% reached 30-35 weeks.

Table 2 Extent of Exposure

Days	Morphelan TRG004-03 (N=284)	Morphelan TRG004-04OL (N=181)	Total
≤14	316*	242*	558*
15-30	266	174*	440*
31-61	255	150	405
62-91	229	120	349
92-122	209	107	316
123-152	194	97	291
153-183	185	93	278
184-213	174	68	242
214-244	170	27	197
245-274	161	2	163
275-304	155	-	155
305-335	149	-	149
336-365	137		137
≥366	68	-	68

*Includes duration of exposure to Morphelan during the double-blind and open-label phase, so some patients are counted twice
Source: Table 8-1, Vol. 4.13, p. 21

Another way to explore this is demonstrated in Table 3. The majority of patients in the Morphelan 30-60 mg group (242 of 259, 93%) were from the osteoarthritis study, TRG004-04OL. Patients using higher doses of Morphelan, primarily reflecting the chronic pain patients, remained on study drug for longer durations.

Table 3 Duration of Exposure versus Categorized Dose

Days	Morphelan 30-60 mg	Morphelan 61-200 mg	Morphelan 201-400 mg	Morphelan >400 mg	Total
≤14	259	172	85	42	558
15-30	173	150	78	39	440
31-61	147	144	76	38	405
62-91	118	130	65	36	349
92-122	103	120	60	33	316
123-152	93	109	59	30	291
153-183	88	108	55	27	278
184-213	63	103	49	27	242
214-244	28	96	46	27	197
245-274	10	84	43	26	163
275-304	9	78	43	25	155
305-335	8	75	42	24	149
336-365	7	67	41	22	137
≥366	3	32	23	10	68

Includes duration of exposure to Morphelan during the double-blind and open-label phase.
Source: Table 8-2, Vol. 4.13, p. 21

N=21 750mg Limited to 21 pts

Disposition

The most common reason for study discontinuation was adverse events, but more so from study TRG004-04OL with the osteoarthritis patients (33%) than from TRG004-04OL with the chronic pain patients (15%).

Table 4 Patient Disposition, Open-Label Studies.

	Number (%) of Patients			
	TRG004-03	TRG004-04OL		
	Morphelan 100%	Morphelan QAM	Morphelan QPM	Total
Entered	284	91	90	465
Completed Study	137 (48%)	42 (46%)	44 (49%)	223 (48%)
Discontinued	147 (52%)	49 (54%)	46 (51%)	242 (52%)
Adverse Event	43 (15%)	33 (36%)	27 (30%)	103 (22%)
Unable to Return	7 (3%)	1 (1%)	3 (3%)	11 (2%)
Patient request	19 (7%)	3 (3%)	4 (4%)	26 (6%)
Non-Compliant	18 (6%)	1 (1%)	1 (1%)	20 (4%)
Lost to Follow-up	13 (5%)	-	2 (2%)	15 (3%)
Death	5 (2%)	-	-	5 (1%)
Lack of Efficacy	33 (12%)	10 (11%)	6 (7%)	49 (11%)
Other	9 (3%)	1 (1%)	3 (3%)	13 (3%)

Source: Table 9-1, Vol. 4.13, P. 22.

Note: Table reflects the primary reason for discontinuation given by the Investigator in the "Study Termination" page of the patient's CRF. Patients may have discontinued for more than one reason.

Deaths

There were three deaths during the double-blind studies reported during the original review cycle, all of whom had metastatic cancer. During the open-label studies, there were 14 deaths, 13 of which were reported and reviewed during the original review cycle. Twelve of these 13 patients had advanced or metastatic cancer, while the last patient, who had a history of spinal cord injury, diabetes and aortic rupture, died suddenly 16 days after discontinuing study drug. Four of these reports were lacking in detail, but study drug did not appear to be a likely contributing factor to the patients' deaths.

The one additional death reported in the current safety update was patient RLM, ID 103-017. This was a 66 year old woman with a history of ovarian carcinoma, small bowel obstruction, and colostomy. The patient began study participation in August of 1999. The patient had been taking Morphelan 180 mg/d. On March 3, 2000, the patient was diagnosed with Bacteriodes fragilis sepsis which responded to five days of intravenous antibiotics. The patient was then diagnosed with "terminal disseminated intra-abdominal carcinomatois" on April 18, 2000 with symptoms of intractable nausea and vomiting. The patient had a mental status change resulting in the Morphelan being temporarily held. The patient was admitted to hospice care on May 5, 2000 and was unable to take oral medications due to bowel obstruction on May 10. The Morphelan was discontinued and the patient died six days later. There is no information concerning the events around this patient's death to suggest any contribution by the Morphelan.

Serious Adverse Events

There were five SAEs reported from the double-blind trials and 67 in the open-label trials which were reviewed during the original review cycle. In this safety update, there were 77 patients with treatment-emergent SAEs in the open-label trials, ten more than reported in the original NDA submission.

The sponsor has provided tabulations of serious adverse events by body system for the open-label trials. Individual SAEs felt to be treatment related were provided in a table with 12 patients identified. A full table integrating all of the clinical trials using individual SAEs has been requested, but the sponsor failed to provide comparisons with the original database information. The submitted table is presented in Appendix B.

The most common serious adverse events were vomiting (1.4%), nausea (1.3%), death (1.1%), dehydration (1.1%), and dyspnea (1.1%). There was one report each of apnea and hypoxia. These events are not surprising given the nature of the drug product and the population studied. There were also reports of confusion, thinking abnormal, and encephalopathy. There was no pattern of events to suggest a serious adverse event specific to Morphelan.

The serious adverse events reported in this safety update were compared to those reported during the original NDA review (Appendix L, P. 90). There were no changes to the pattern or type of events reported.

Adverse Events Leading To Discontinuation

The sponsor has provided tabulations of adverse events leading to discontinuation by body system for the open-label trials with a breakdown of the most common AEs leading to discontinuation: constipation, nausea, and somnolence. A full table integrating all of the clinical trials using individual AEs leading to discontinuation has been requested, but the sponsor failed to provide comparisons with the original database information. The submitted table is presented in Appendix C. Table 5 represents those events occurring in $\geq$ 0.9% of patients. The distribution of events leading to study discontinuation in Table 5 below, and in Appendix C is not unexpected in this patient population which includes cancer patients.

Table 5 Adverse Events Leading To Discontinuation in $\geq$ 0.9% of Patients

Body System, Adverse Event	Combined Double-blind and Open-label Population [a]
Number Of Patients Dosed	560
Number Of Patients With Any Event Causing Discontinuation	148 (26.4%)
Constipation	35 (6.3%)
Nausea	32 (5.7%)
Somnolence	17 (3.0%)
Vomiting	14 (2.5%)
Dizziness	9 (1.6%)
Asthenia	8 (1.4%)
Confusion	8 (1.4%)
Abdominal Pain	6 (1.1%)
Dyspnea	6 (1.1%)
Death	5 (0.9%)
Headache	5 (0.9%)
Diarrhea	5 (0.9%)

A If a patient had more than one adverse event for a table entry, that patient is counted once. The denominator of the percentage is the number of Morphelan patients.
Source: Table 3, Fax submission dated January 29, 2002

As demonstrated in the Sponsor's Table 6 below, the incidence of AEs resulting in discontinuation were more common in patients taking doses in the range of 30-60 mg. These were primary osteoarthritis patients, many of whom were new to opioids during the double-blind studies. The chronic pain patients previously treated with opioids represented a smaller proportion of patients who discontinued due to adverse events.

Table 6 Most Frequently Reported AEs Resulting in Discontinuation, ≥ 2% of Total Population

		Number (%) of Patients		
	TRG004-03	TRG004-04OL		
AE	Morphelan 100%	Morphelan QAM	Morphelan QPM	Total
Constipation	5 (2%)	13 (14%)	5 (6%)	23 (5%)
Nausea	3 (1%)	4 (4%)	7 (8%)	14 (3%)
Somnolence	5 (2%)	1 (1%)	4 (4%)	10 (2%)
	TRG004-03	TRG004-04OL		
AE	30-60 mg	61-200 mg	201-400 mg	>400 mg
Constipation	18 (10%)	4 (3%)	-	1 (3%)
Nausea	10 (5%)	3 (2%)	1 (1%)	-
Somnolence	6 (3%)	3 (2%)	1 (1%)	-
Source: Appendix 2, Statistical Table 19 D.				

Source: Table 12.5-2, Vol. 4.13, P. 30

The adverse events resulting in study discontinuation reported in this safety update were compared to those reported during the original NDA review (Appendix M, P 91). There were no changes to the pattern or type of events reported.

Adverse Events

As noted above, in this safety update, the sponsor provided the adverse events only for the open-label trials. Integrated tables with data from all of the clinical trials have been requested, but the sponsor failed to provide comparisons with the original database. The submitted table is presented in Appendix D.

Table demonstrates adverse events occurring in more than 5% of patients in the open-label trials with and a column was added representing data from the combined open-label and double-blind population from Appendix D. The incidence of adverse events was high, 85% overall for patients receiving Morphelan. The top four adverse events, constipation, nausea, somnolence and vomiting, can be considered expected for an opioid. Headache was next most common in the combined group and may reflect the occurrence of a frequent background event. None of the adverse events listed in Table 7 were particularly unexpected in the population studied. A review of the adverse event table for events occurring in at least 1% of patients in Appendix D revealed no pattern of adverse events that could be considered specific to Morphelan.

Table 7 Incidence of AEs Which Occurred in ≥ 5% of Patients

Adverse Event	Open-Label Trials, ISS Update				Combined Open-label/ Double-blind, ISS Update
	TRG004-03 Morphelan 100%	TRG004-04OL Morphelan QAM	Morphelan QPM	Total	
	(N=284)	(N=91)	(N=90)	(N=465)	560
Any Event	242 (85%)	75 (82%)	72 (80%)	389 (84%)	479 (85%)
Constipation	53 (19%)	34 (37%)	29 (32%)	116 (25%)	182 (32%)
Nausea	57 (20%)	11 (12%)	18 (20%)	86 (19%)	136 (24%)
Somnolence	28 (10%)	14 (15%)	9 (10%)	51 (11%)	83 (15%)
Vomiting	38 (13%)	4 (4%)	7 (8%)	49 (11%)	75 (14%)
Headache	32 (11%)	9 (10%)	5 (6%)	46 (10%)	65 (12%)
Pain	33 (12%)	5 (6%)	10 (11%)	48 (10%)	58 (10%)
Asthenia	34 (12%)	4 (4%)	2 (2%)	40 (9%)	56 (10%)
Dizziness	22 (8%)	5 (6%)	11 (12%)	36 (8%)	55 (10%)
Peripheral Edema	34 (12%)	4 (4%)	7 (8%)	45 (10%)	52 (9%)
Diarrhea	21 (7%)	14 (15%)	9 (10%)	44 (10%)	52 (9%)
Abdominal Pain	23 (8%)	7 (8%)	8 (9%)	38 (8%)	51 (9%)
Infection	26 (9%)	6 (7%)	7 (8%)	39 (8%)	46 (8%)
UTI	34 (12%)	2 (2%)	3 (3%)	39 (8%)	44 (8%)
Accidental Injury	34 (12%)	2 (2%)	5 (6%)	41 (9%)	42 (8%)
Flu Syndrome	30 (11%)	3 (3%)	2 (2%)	35 (8%)	37 (7%)
Back Pain	29 (10%)	1 (1%)	3 (3%)	33 (7%)	37 (7%)
Rash	24 (9%)	2 (2%)	2 (2%)	28 (6%)	37 (7%)
Sweating	18 (6%)	2 (2%)	1 (1%)	21 (5%)	36 (6%)
Fever	26 (9%)	-	2 (2%)	28 (6%)	35 (6%)
Insomnia	19 (7%)	5 (6%)	6 (7%)	30 (7%)	31 (6%)
Depression	23 (8%)	2 (2%)	2 (2%)	27 (6%)	31 (5%)
Paresthesia	25 (9%)	1 (1%)	1 (1%)	27 (6%)	30 (5%)
Anorexia	18 (6%)	1 (1%)	2 (2%)	21 (5%)	30 (3%)
Dry Mouth	6 (2%)	3 (3%)	5 (6%)	14 (3%)	27 (5%)
Dyspnea	15 (5%)	2 (2%)	2 (2%)	19 (4%)	25 (5%)
Rhinitis	30 (11%)	3 (3%)	1 (1%)	34 (7%)	21 (4%)
Sinusitis	19 (7%)	1 (1%)	-	20 (4%)	21 (4%)
Cough Increased	15 (5%)	-	1 (1%)	16 (3%)	21 (4%)
Gastroenteritis	15 (5%)	-	-	15 (3%)	16 (3%)

Source: Table 12.1-1, vol. 4.13, P. 25, Table 1, Fax submission dated January 29, 2002

The adverse events reported in this safety update were compared to those reported during the original NDA review (Appendix N, P. 94). There were no changes to the pattern or type of events reported.

Vital Signs

An update was provided for the open-label studies, but as above, no integrated data for the entire clinical database was provided. There were no consistent trends in blood pressure, heart rate, respiratory rate, temperature, or weight for the open-label patients.

Laboratory Tests

The sponsor reports that across all sites in the double-blind studies investigators were not consistent in their reporting of lab abnormalities as adverse events. The sponsor also notes that laboratory test abnormalities were inconsistently and at times incorrectly

recorded as adverse events, reflecting abnormalities predating study entry, explicable changes on the basis of concomitant medications (thiazide diuretics and hypokalemia), or condition of specimen (hemolyzed specimens and hyperkalemia). Some lab results were incorrectly interpreted by the investigator (mild hypocalcemia in the setting of hypoalbuminemia).

The review of lab results presented in this safety update is limited to the results from Study TRG004-003. The sponsor generated a table of statistically significant laboratory findings from baseline-to-final results, using a range of defined upper and lower limits of acceptable values. The sponsor further indicates that because of the frequency of antihypertensive drug usage and poorly controlled diabetes mellitus, detailed evaluations of abnormalities in basic serum chemistries including BUN and creatinine, were not performed. Emphasis was placed on low total WBC and unexplained elevations in hepatic enzymes. This was an unfortunate choice given the Agency's concerns about renal toxicity from exposure to high doses of fumaric acid described in the Approvable letter.

Seven patients with abnormal hematologic parameters were reviewed by the sponsor. In all cases, the abnormalities could be explained by underlying illness or treatment with cancer chemotherapeutic agents. Of the 284 patients in study TRG004-003 with liver function tests, 25 abnormal findings were reviewed by the sponsor. Twenty four of these patients either entered the study with the abnormality, had only transient changes, or the abnormality could be attributed to underlying illness. The one patient for whom the sponsor could not exclude a relationship with study drug and abnormal values had an AST that rose from 38 at baseline to 89 at Visit 12 and declined to 38 after six additional weeks. The ALT values were 65, 192, and 68, respectively. No explanation for these changes could be determined.

There were 42 patients who were exposed to Morphelan in doses of 400 mg/day or greater during the clinical trials. The chemistry laboratory results for all of these patients were reviewed. No abnormal BUN or creatinines were found. (Listing 17.2, Vol. 7.45, P. 286).

Drug-drug interactions
There were no special studies to evaluate the occurrence of drug-drug interactions with Avinza.

Drug Abuse, Overdose and Dependence.
The sponsor identified six patients who experienced symptoms of opiate withdrawal following abrupt discontinuation or rapid taper of Avinza. Review of these brief narratives did not reveal any point for further comment.

Drug abuse was reported in two study patients and one non-study individual. The family of patient 116-015 (Study 3), a 49 year old with history of chronic migraine headaches, reported to the study site that the patient was visiting several physicians and pharmacies to obtain medications including lorazepam and MSIR. The patient also had a history of

ethanol abuse. Patient 153-002 (Study 03), a 42 year old nurse with breast cancer, reported that she had been dissolving and injecting 45-90 mg of study drug. She was voluntarily hospitalized for detoxification.

The third report of abuse was identified when the mother of an individual called the study site to inform them her child had bought study drug from someone described as a patient of the investigator. The study site contacted a study patient who then reported that her medication had been stolen by a person who had previously been terminated from the study and the investigator's practice due to suspected substance abuse. It is unclear how the site knew which patient to contact about this incident, but that patient was subsequently terminated from the study.

In summary, there were two reports of abuse of Avinza during the clinical trials. This underscores the potential for abuse of Schedule II opioids including the study formulation.

Appendix A

Reverences

1. Raschka C, H Koch. Long-term Treatment of Psoriasis using Fumaric Acid Preparations can be Associated with Severe Proximal Tubular Damage. Human &Exp. Tox. 18:738-739, 1999.
2. Levey S, Lasichak A, Brimi R, Orten J, Smyth C, and A Smith. A Study to Determine the Toxicity of Fumaric Acid. J of the Am. Pharm. Assoc., 35:298-304, 1946.
3. TNO BIBRA International Toxicity profile. Fumaric acid and its common salts. Charshalton, UK, 1991.
4. Mrowietz U, Christophers E, and P Altmeyer. Treatment of Psoriasis with Fumaric Acid Esters: Result of a Prospective multicenter Study. Br. J of Derm. 138:456-460, 1998.
5. Nieboer C, de Hoop D, et. al. Systemic Therapy with Fumaric Acid Derivatives: New Possibilities in the Treatment of Psoriasis. J Am Acad. Derm, 20(4):601-608, 1989.

Source: Fax dated 1/8/02, Vol. 4.11, Attachment 51.

Appendix B

Treatment Emergent Serious Adverse Events, Combined Population [a]

Body System, Adverse Event	Total
Number Of Patients Dosed	560
Number Of Patients With Any Event	83 (14.8%)
Body As A Whole - General Disorders	34 (6.1%)
Abdominal Pain	2 (0.4%)
Accidental Injury	2 (0.4%)
Back Pain	1 (0.2%)
Cellulitis	4 (0.7%)
Chest Pain	4 (0.7%)
Chills	2 (0.4%)
Death	6 (1.1%)
Fever	3 (0.9%)
Hernia	1 (0.2%)
Infection	2 (0.4%)
Mucous Membrane Disorder	1 (0.2%)
Neck Pain	1 (0.2%)
Pain	1 (0.2%)
Reaction Unevaluable	1 (0.2%)
Sepsis	6 ((1.1%)
Suicide Attempt	1 (0.2%)
Viral Infection	2 (0.4%)
Cardiovascular System Disorders	14 (2.3%)
Angina Pectoris	1 (0.2%)
Atrial Fibrillation	1 (0.2%)
Bradycardia	2 (0.4%)
Cardiomyopathy	1 (0.2%)
Congestive. Heart Failure	1 (0.2%)
Deep Vein Thrombosis	2 (0.4%)
Heart Arrest	1 (0.2%)
Hemorrhage	1 (0.2%)
Hypotension	1 (0.2%)
Migraine	1 (0.2%)
Myocardial Infarction	1 (0.2%)
Palpitation	1 (0.2%)
Tachycardia	1 (0.2%)
Thrombophlebitis	2 (0.4%)
Digestive System Disorders	23 (4.1%)
Cholecystitis	3 (0.5%)
Cholelithiasis	2 (0.4%)
Colitis	1 (0.2%)
Constipation	3 (0.5%)
Diarrhea	3 (0.5%)
Duodenal Ulcer Hemorrhage	1 (0.2%)
Enteritis	1 (0.2%)
Gastritis	1 (0.2%)
Gastroenteritis	2 (0.4%)
Gastrointestinal Hemorrhage	1 (0.2%)
Hepatic Failure	1 (0.2%)
Ileus	1 (0.2%)

Table continues

Treatment Emergent Serious Adverse Events, continued

Nausea	7 (1.3%)
Vomiting	8 (1.4%)
Endocrine System Disorders	2 (0.4%)
Thyroid Carcinoma	2 (0.4%)
Hemic And Lymphatic System Disorders	2 (0.4%)
Leukopenia	2 (0.4%)
Metabolic And Nutritional Disorders	11 (2.0%)
Acidosis	1 (0.2%)
Dehydration	6 (1.1%)
Electrolyte Abnormality	1 (0.2%)
Hyponatremia	1 (0.2%)
Obesity	1 (0.2%)
Peripheral Edema	2 (0.4%)
Respiratory Acidosis	1 (0.2%)
Musculoskeletal System Disorders	3 (0.5%)
Bone Disorder	2 (0.4%)
Tendionous Contracture	1 (0.2%)
Nervous System Disorders	17 (3.0%)
Anxiety	1 (0.2%)
Aphasia	1 (0.2%)
Catatonic Reaction	1 (0.2%)
Confusion	2 (0.4%)
Depression	3 (0.5%)
Drug Dependence	2 (0.4%)
Encephalopathy	1 (0.2%)
Multiple Sclerosis	1 (0.2%)
Nervousness	1 (0.2%)
Neuropathy	4 (0.7%)
Psychotic Depression	1 (0.2%)
Thinking Abnormal	1 (0.2%)
Tremor	1 (0.2%)
Withdrawal Syndrome	1 (0.2%)
Respiratory System. Disorders	13 (2.3%)
Apnea	1 (0.2%)
Dyspnea	6 (1.1%)
Hypoxia	1 (0.2%)
Pneumonia	3 (0.5%)
Pulmonary Embolus	2 (0.4%)
Respiratory Congenital Anomaly	1 (0.2%)
Skin And Appendages Disorders	3 (0.5%)
Skin Ulcer	1 (0.2%)
Sweating	2 (0.4%)
Urogenital System Disorders	9 (1.6%)
Kidney Calculus	1 (0.2%)
Kidney Function Abnormal	1 (0.2%)
Metrorrhagia	1 (0.2%)
Prostatic Carcinoma	1 (0.2%)
Pyelonephritis	2 (0.4%)
UTI	1 (0.2%)

Table continues

Treatment Emergent Serious Adverse Events, continued

Urogenital Disorder	1 (0.2%)
Uterine Fibroids Enlarged	1 (0.2%)
Vaginal Hemorrhage	1 (0.2%)

(A) If a patient had more than one serious adverse event for a table entry. that patient is counted once. The denominator of the percentages is the number of Morphelan treated patients.
(b) Adverse events are sorted first alphabetically by body system, and then alphabetically by adverse event name within body system.
Source: Table 3, Fax submission dated January 29, 2002

Appendix C

Treatment Emergent Adverse Events Causing Discontinuation, Combined Population [a]

Body System, Adverse Event	Total
Number Of Patients Dosed	560
Number Of Patients With Any Event Causing Discontinuation	148 (26.4%)
Body As A Whole, General Disorders	33 (5.9%)
Abdominal Pain	6 (1.1%)
Accidental Injury	1. (0.2%)
Asthenia	8 (1.4%)
Back Pain	3 (0.5%)
Chest Pain	2 (0.4%)
Chills	1 (0.2%)
Death	5 (0 9%)
Face Edema	1 (0.2%)
Fever	3 (0.5%)
Halitosis	1 (0.2%)
Headache	5 (0 9%)
Hernia	2 (0.4%)
Lab Test Abnormal	1 (0.2%)
Pain	2 (0.4%)
Sepsis	1 (0.2%)
Viral Infection	1 (0.2%)
Cardiovascular System Disorders	5 (0 9%)
Congestive Heart Failure	1 (0.2%)
Myocardial Infarction	1 (0.2%)
Syncope	1 (0.2%)
Tachycardia	1 (0.2%)
Thrombophlebitis	1 (0.2%)
Digestive System Disorders	83 (14.8%)
Anorexia	3 (0.5%)
Colitis	1 (0.2%)
Constipation	35 (6.3%)
Diarrhea	5 (0 9%)
Dyspepsia	3 (0.5%)
Dysphagia	2 (0.4%)
Enteritis	1 (0.2%)
Flatulence	1 (0.2%)
Gastritis	2 (0.4%)
Gastrointestinal Hemorrhage.	1 (0.2%)
Ileus	1 (0.2%)
Intestinal Obstruction	1 (0.2%)
Liver Function Tests Abnormal	3 (0.5%)
Melena	1 (0.2%)
Nausea	32 (5.7%)
Stomatitis	1 (0.2%)
Vomiting	14 (2.5%)
Hemic And Lymphatic System Disorders	3 (0.5%)
Anemia	1 (0.2%)
Coagulation Disorder	1 (0.2%)
Leukopenia	1 (0.2%)

Table continues

Treatment Emergent Adverse Events Causing Discontinuation, Combined Population, cont'd

Metabolic And Nutritional Disorders	10 (1.8%)
Acidosis	1 (0.2%)
Dehydration	2 (0.4%)
Edema	1 (0.2%)
Hyponatremia	1 (0.2%)
Peripheral Edema	4 (0.7%)
Respiratory Acidosis	1 (0.2%)
Weight Gain	1 (0.2%)
Weight Loss	2 (0.4%)
Nervous System Disorders	54 (9.8%)
Abnormal Dreams	1 (0.2%)
Abnormal Gait	1 (0.2%)
Confusion	8 (1.4%)
Depression	4 (0.7%)
Dizziness	9 (1.6%)
Drug Dependence	2 (0.4%)
Dry Mouth	4 (0.7%)
Hallucinations	3 (0.5%)
Hypertonia	1 (0.2%)
Insomnia	1 (0.2%)
Nervousness	3 (0.5%)
Neuropathy	1 (0.2%)
Paresthesia	1 (0.2%)
Somnolence	17 (3.0%)
Thinking Abnormal	4 (0.7%)
Tremor	2 (0.4%)
Vasodilatation	3 (0.5%)
Vertigo	3 (0.5%)
Respiratory System Disorders	7 (1.3%)
Dyspnea	6 (1.1%)
Lung Disorder	1 (0.2%)
Pneumonia	1 (0.2%)
Skin And Appendages Disorders	10 (1.8%)
Pruritus	3 (0.5%)
Rash	2 (0.4%)
Sweating	4 (0.7%)
Urticaria	1 (0.2%)
Special Senses Disorders	6 (3.1%)
Deafness	2 (0.4%)
Diplopia	1 (0.2%)
Dry Eyes	1 (0.2%)
Eye Pain	1 (0.2%)
Taste Perversion	1 (0.2%)
Visual Field Defect	1 (0.2%)
Urogenital System Disorders	9 (1.6%)
Dysuria	2 (0.4%)
Impotence	1 (0.2%)
Kidney Calculus	1 (0.2%)
Kidney Function Abnormal	1 (0.2%)

Table continues

Treatment Emergent Adverse Events Causing Discontinuation, Combined Population, cont'd

Metrorrhagia	1 (0.2%)
Pyelonephritis	1 (0.2%)
Sexual Function Abnormal	1 (0.2%)
Urinary Incontinence	1 (0.2%)

A If a patient had more than one adverse event for a table entry, that patient is counted once. The denominator of the percentage is the number of Morphelan patients.

B Adverse events are sorted first alphabetically by body system, and then alphabetically by adverse event name within body system.

Source: Table 3, Fax submission dated January 29, 2002

Appendix D
Treatment Emergent Adverse Events Occurring in ≥1% of Patients, Combined Population

Body System, Adverse Event	Total Morphelan [a]
Number Of Patients Dosed	560
Number Of Patients With Any Event	479 (85.4%)
Body As A Whole - General Disorders	269 (49.0%)
Abdominal Pain	51 (9.1%)
Accidental Injury	42 (7.5%)
Asthenia	56 (10.0%)
Back Pain	37 (6.6%)
Cellulitis	9 (1.6%)
Chest Pain	19 (3.4%)
Chills	33 (2.7%)
Death	6 (1.1%)
Fever	35 (6.3%)
Flu Syndrome	37 (6.6%)
Headache	65 (11.6%)
Infection	46 (8.2%)
Infection Fungal	7 (1.3%)
Malaise	8 (1.4%)
Neck Pain	11 (2.0%)
Pain	58 (10.4%)
Reaction Unevaluable	11 (2.0%)
Sepsis	6 (1.3%)
Cardiovascular System Disorders	59 (10.5%)
Hypertension	12 (2.3%)
Migraine	9 (1.6%)
Digestive System Disorders	327 (58.4%)
Anorexia	30 (3.4%)
Constipation	182 (32.3%)
Diarrhea	52 (9.3%)
Dyspepsia	21 (3.8%)
Flatulence	10 (1.8%)
Gastroenteritis	16 (2.9%)
Gastrointestinal Disorder	12 (2.3%)
Liver Function Tests Abnormal	7 (1.3%)
Nausea	136 (24.3%)
Rectal Disorder	6 (1.1%)
Rectal Hemorrhage	6 (1.1%)
Vomiting	75 (33.4%)
Endocrine System Disorders	10 (1.8%)
Hemic And Lymphatic System Disorders	28 (5.0%)
Ecchymosis	14 (2.3%)
Metabolic And Nutritional Disorders	102 (18.2%)
Dehydration	9 (1.6%)
Edema	13 (2.3%)
Hyperglycemia	7 (1.3%)
Peripheral Edema	52 (9.3%)
Weight Loss	12 (2.1%)

Table continues

Treatment Emergent Adverse Events, Combined Population, Continued

Musculoskeletal System Disorders	66 (11.8%)
Arthralgia	8 (1.4%)
Arthritis	15 (2.7%)
Leg Cramps	10 (1.8%)
Myalgia	9 (1.6%)
Nervous System Disorders	254 (45.4%)
Abnormal Dreams	6 (1.1%)
Anxiety	17 (3.0%)
Confusion	14 (2.3%)
Depression	31 (5.3%)
Dizziness	55 (9.8%)
Dry Mouth	27 (4.8%)
Hallucinations	6 (1.1%)
Hypertonia	19 (3.4%)
Insomnia	31 (5.5%)
Nervousness	16 (2.9%)
Neuralgia	8 (1.4%)
Neuropathy	8 (1.4%)
Paresthesia	30 (5.4%)
Somnolence	83 (14.8%)
Thinking Abnormal	9 (1.6%)
Tremor	11 (2.0%)
Vasodilatation	11 (2.0%)
Respiratory System. Disorders	123 (22.0%)
Asthma	8 (1.4%)
Bronchitis	13 (2.3%)
Cough Increased	21 (3.8%)
Dyspnea	25 (4.5%)
Pharyngitis	15 (2.7%)
Pneumonia	39 (7.0%)
Rhinitis	21 (3.8%)
Sinusitis	21 (3.8%)
Skin And Appendages Disorders	110 (19.6%)
Pruritus	39 (7.0%)
Rash	37 (6.6%)
Sweating	36 (6.4%)
Special Senses Disorders	39 (7.0%)
Amblyopia	6 (1.1%)
Urogenital System Disorders	107 (19.1%)
Albuminuria	6 (1.1%)
Breast Neoplasm	7 (1.3%)
Dysuria	12 (2.1%)
Hematuria	11 (2.0%)
Urinary Frequency	6 (1.1%)
UTI	44 (7.9%)

Note: The 1% rule is applied to body system totals, as well as to individual adverse events. Thus, only those adverse events that meet the 1%) criteria are shown within each body system.

A If a patient had more than one adverse event for a table entry, that patient is counted once. The denominator of the percentage is the number of Morphelan patients.

B Adverse events are sorted first alphabetically by body system, and then alphabetically by adverse event name within body system.

Source: Table 1, Fax submission dated January 29, 2002

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

/s/

Sharon Hertz
3/15/02 03:59:43 PM
MEDICAL OFFICER

Bob Rappaport
3/15/02 06:31:58 PM
MEDICAL OFFICER
I have found this review to be accurate and complete. I concur with the conclusions and recommendations in this review.

FDA Center for drug evaluation and research
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857 (301) 827-7410

ADDENDUM TO THE REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	**21-260**
Sponsor	Elan Pharmaceutical Research Corporation
Generic Name	Morphine Sulfate
Proprietary Name	———— Extended-Release Capsules
Pharmacologic Class	Opioid narcotic
Proposed Indication	Relief of chronic moderate to severe pain
Submission Date	May 31, 2000
Dosage forms	Capsules
Strengths	30 mg, 60 mg, 90 mg, 120 mg
Route	Oral
Clinical Reviewer	Sharon Hertz, M.D.
Date	March 29, 2001

Addendum:
Two additional items are presented in this addendum.

1. Fumaric Acid
Concern has been raised over the potential for the consumption of large amounts of fumaric acid when large doses of ——— are utilized. Fumaric acid is a constituent of ——— in a 1mg:1mg ratio with morphine. The NOAEL of fumaric acid in humans is reported as 500 mg/day. Reported adverse events due to fumaric acid in doses of more than 500 mg/day in humans include nausea, diarrhea, lymphopenia and renal toxicity. In the clinical trials, 39 patients received doses over 400 mg per day (Table 7.1, REVIEW AND EVALUATION OF CLINICAL DATA, p. 51), so the potential for exposure to toxic doses of fumaric acid is clinically relevant.

The ISS was reviewed for reports of clinically significant elevations of lymphopenia, renal function, renal insufficiency and renal failure. Three cases of abnormal renal lab values reported as adverse events were reported and two patients with abnormal renal function were noted among the narratives for deaths. One patient, 126-001, had transient proteinuria while on MS Contin and is not discussed further.

Patient 115-003 was a 53 year old man with diabetic neuropathy an a history of kidney stones. The patient was on multiple concurrent medications including Lotensin, Neurontin, Humulin, Rezulin, Prozac, Trazodone, and MSIR. He enrolled in study TRG004-003 following completion of TRG004-02 during which he received MS Contin. The patient took ——— in doses from 150 to 240 mg per day. The patient was hospitalized 5 months after beginning ——— with the diagnoses of mental status change and renal insufficiency. The creatinine was 4.3 and BUN 75 at that time, they were 1.0 and 24 respectively, at the end of study TRG004-02. No etiology for the renal insufficiency was established, but it resolved with labs returning to a creatinine of 0.9 and a BUN of 18 at the time of hospital discharge. ——— was discontinued upon hospitalization.

Patient 106-006 was a 67 year old female with diffuse metastatic adenocarcinoma of the breast and past medical history of dyspnea, hypertension, edema, anorexia, peripheral neuropathy, nausea, and chest pain. She had received MS Contin in protocol TRG004-02 and began ——— 150mg qd in study TRG004-03. After 9 months of study drug treatment, she had developed encephalopathy, moderate renal failure, and tremors. The study drug regimen was discontinued and she died 3 days after discontinuation of the study drug. Review of the lab values for study TRG004-03, reveal the highest BUN reported as 29 and the highest creatinine as 1.1.

Patient 103-004 was a 78 year old woman with metastatic colon cancer who died from pneumonia 60 days after starting study drug. She received MS Contin in Study TRG004-02 and ——— 120 mg per day in study TRG004-03. Although an adverse event of elevated creatinine and BUN was reported on the CRF by the investigator, no abnormal

values for BUN and creatinine were provided with that report and all scheduled labs reported were normal with respect to BUN and creatinine values.

Patient 104-001 was a 59 year old man with metastatic prostate cancer and diabetes. The patient died and his death was attributed to advanced cancer. The patient had been hospitalized due to infected decubitus ulcers and renal failure. The patient had received ——— 90 mg/d in study TRG004-03. No lab values for creatinine or BUN were reported for this patient during study TRG004-03.

Patient 115-008 was a 48 year old man with a history of pain due to carpal tunnel syndrome, and a past medical history of hypertension, diabetes and hematuria. The patient had a creatinine of 1.1 and BUN of 21 when he started ——— 60 mg per day in study TRG004-03, after receiving MS Contin in study TRG004-02. The ——— dose was increased to 120 mg per day 3 months later. The patient had a BUN of 44 and a creatinine of 2.0 reported six months after beginning ——— One month later, the BUN was 26 and the creatinine was 1.2, while still on ——— At the end of the study, the patient's BUN was 15 and creatinine 1.3.

The patients described above do not appear to have experienced clinically significant renal dysfunction due to exposure to ——— except possibly patient 115-003. While this patient's renal function returned to normal following discontinuation of ———, the ——— dose was only 150 mg per day, so the fumaric acid dose was also 150 mg per day. This is presumably too low a dose for an adverse reaction in humans. There is not adequate information available concerning this patient's clinical situation to determine what caused the transient renal dysfunction.

The exposure to doses over 400 mg per day or ——— was limited in this clinical database. At this time, the question as to whether the presence of fumaric acid in a 1 mg: 1mg ratio in ——— presents a significant clinical risk remains unanswered at this time and will need to be addressed by the sponsor.

2. Duplicate patient ID numbers.
A potential problem with data integrity came to light during the review of the patients noted above. Patient 115-008 in study TRG004-03 had a different number in study TRG004-02, 115-016. There was a different patient assigned to ID number 115-008 in study TRG004-02. This became apparent when the patient profiles for patient 115-008 for these two studies revealed different ages and different initials. The sponsor was questioned about this discrepancy in a telephone call on March 29, 2001. The sponsor indicated that three investigators changed patient ID numbers when enrolling patients into the open-label studies. For patients with serious adverse events, adverse events leading to study discontinuation, and deaths, the two ID numbers were provided in the narratives. However, for patients without one of these events, no notification of these inconsistent numbers was provided by the sponsor prior to the inquiry for this addendum.

In a fax received 3/20/01, the sponsor provided a list of patients who had ID numbers different in the open-label study than in the double-blind study. There are examples of

ID numbers used for different patient sin two studies, not just of individual patients assigned more than one number as in the example above. In addition, what is missing from the information faxed is how many other patients who participated only one study had an ID number that was the same as one of the two numbers assigned for another patient. For example, Patient RKD was assigned ID number 1115-008 in study RG004-02 and number 115-005 in study TRG004-03. It is unknown from the information provided if there was a patient assigned to number 115-005 in study TRG004-02.

This issue could have consequences with respect to data integrity. While the sponsor did provide two ID numbers for patients in the narratives, there was no warning that other patients could have the same numbers in other studies. As a result, when reviewing data line listings, there was no way to know that the individual ID numbers were not unique to single patients. Errors in patient identification could have been made while attempting to review values for any given patient.

The sponsor will need to rectify the redundancy in patient ID numbers by determining some manner of uniquely identifying all patients and resubmit all data from patients who did not have unique ID numbers.

/s/

Sharon Hertz
3/30/01 10:58:34 AM
MEDICAL OFFICER

Bob Rappaport
3/30/01 05:24:52 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

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DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS
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REVIEW AND EVALUATION OF CLINICAL DATA

NDA #	**21-260**
Sponsor	Elan Pharmaceutical Research Corporation
Generic Name	Morphine Sulfate
Proprietary Name	[redacted] Extended-Release Capsules
Pharmacologic Class	Opioid narcotic
Proposed Indication	Relief of chronic moderate to severe pain
Submission Date	May 31, 2000
Dosage forms	Capsules
Strengths	30 mg, 60 mg, 90 mg, 120 mg
Route	Oral
Clinical Reviewer	Patricia Hartwell, M.D., M.B.A Sharon Hertz, M.D.
Statistical Reviewer	David Hoberman, Ph.D.
Completion Date	March 7, 2001

APPEARS THIS WAY
ON ORIGINAL

EXECUTIVE SUMMARY

Executive Summary

1 RECOMMENDATIONS

Based on the clinical studies submitted, I recommend approval for this NDA for ——— Capsules. The sponsor has successfully demonstrated the efficacy in a randomized, double-blind, dose-controlled study in patients with chronic pain of non-malignant and malignant origin, and in a randomized, double-blind, placebo-controlled trial in osteoarthritis. The safety profile of this product consists of findings that are common to the opioid class of analgesics without any risks specific to the formulation.

The sponsor proposes to label ——— Capsules for the following indications:

- Once-daily formulation for the relief of moderate to severe pain
- Intended for use in patients who require repeated dosing with opioid analgesics over periods of more than a few days

2 SUMMARY OF CLINICAL FINDINGS

2.1 Overview of Clinical Program

The information submitted for evaluation and review in this NDA is for ———, a combined immediate release and delayed release oral morphine formulation. Each ———capsule contains 30, 60, 90, or 120 mg of morphine sulfate and has been developed for once daily administration. A total of seven clinical or clinical pharmacology trials and six healthy volunteer trials were submitted in support of this NDA. A total of 866 subjects were exposed to ——— during clinical development, 405 of which were patients in the Phase III clinical trials. Two indications were studied during this development plan: 1) analgesia for moderate to severe (malignant or non-malignant) chronic pain, and ———

2.2 Efficacy

TRG004-02 was a double-blind trial in which patients with chronic malignant or non-malignant pain were randomized to four treatment groups: 1) ———50%, 2) ———100%, 3)———133%, and 4) MS Contin 100%. The dosing was based on the titrated MS Contin dose established during an open-label stabilization period of up to three weeks. The randomized treatment period was seven days in duration. Oxycodone was permitted as rescue medication. The primary efficacy variables were change in total daily rescue medication dose, change in VAS Pain Intensity Score, and change in Pain Descriptor Score.

The pain intensity scores and the use of rescue medication increased during the seven-day randomized treatment period for all treatment groups. While the absolute changes in outcome measures were small, there were many differences between treatment groups that were statistically significant. MS Contin 100% and ———133% were

consistently better in managing pain than [redacted] 50%, as demonstrated by the comparisons across all primary and secondary outcome measures. [redacted] 100% was better than [redacted] 50% as reflected by one primary outcome measure, change in mean PDS score, and by all secondary outcome measures except mean amount of rescue medication. In addition, MS Contin 100% was somewhat more effective than [redacted] 100% as reflected in two primary outcome measures, change in mean VAS score and change in mean PDS score. In no comparison did [redacted] 100% demonstrate superiority over MS Contin 100%.

There are several possible explanations for greater efficacy of MS Contin 100% compared with [redacted] 100% for change in VAS score and change in PDS score and for the more consistent greater efficacy of MS Contin 100% over [redacted] 50% than [redacted] 100% compared with [redacted] 50%. There are differences in PK profiles of the two products. While the overall AUC values from comparable doses are similar, [redacted] results in a lower peak serum concentration than MS Contin and a higher trough concentration. It may be that opioid tolerant patients achieve a greater sense of pain relief from a product which peaks higher even if there is a lower trough later in the dosing interval, and the overall bioavailability is comparable.

There is no apparent explanation for the finding of increased pain intensity scores and the increased use of rescue across all treatment groups over the randomized treatment period. Over a one week period, particularly among non-malignant chronic pain patients, one would not expect progression of underlying disease. These findings might reflect an artifact created by the frequent reporting of pain scores (four times each day) imposed upon patients.

In patients with pain of malignant origin, [redacted] 133% showed the greatest decrease in usage of rescue medication and the smallest increase in the Pain Descriptor Scale Score than all other treatment groups. Conclusions based on this finding must be conservative as patients with pain of malignant origin only constituted 15% of the study population

TRG004-04 was a double-blind trial in which patients with moderate to severe osteoarthritis of the knee or hip were randomized to four treatment groups: 1) [redacted] 30mg qam, 2) [redacted] 30mg qpm, 3) MS Contin 15mg bid, and 4) placebo. The randomized treatment period was of four weeks duration. No rescue medication was permitted. The primary efficacy variables were change in WOMAC Index Pain Subscale Score and Overall Arthritis Pain Intensity VAS Score.

Based on the planned primary outcome measures, [redacted] qam, [redacted] qpm and MS Contin were superior to placebo in the management of pain associated with osteoarthritis. The effects remained statistically significant for all three treatments for 2 weeks, for the two [redacted] treatments for 3 weeks and just for the [redacted] qam group through week 4 according to the analysis of the WOMAC OA Index Pain Subscale. The results were less robust for the Overall Arthritis Pain Intensity VAS score with only [redacted] qam and MS Contin showing statistically significant improvements

compared to placebo at Week 1, and only [redacted] qam continuing to demonstrate statistically significant improvements through Week 3. There was general support for the efficacy of [redacted] from the secondary efficacy variables. These findings suggest that [redacted] qam may be somewhat more effective than [redacted] qpm, and may be somewhat more effective than MS Contin, but it is important to recognize that none of the comparisons between active treatment groups demonstrated any statistically significant differences.

These results are difficult to interpret. The sponsor suggest the influence of baseline differences in use of physical therapy or assistive devices between treatment groups as a possible explanation. When added as a factor in the analysis, the statistically significant findings are more sustained for the two [redacted] and MS Contin treatment groups for the WOMAC OA Index Pain Subscale. This post-hoc analysis did not, however, alter the results for the Overall Arthritis Pain Intensity VAS.

The lack of statistical significance for the comparisons from the later time points may reflect the robust placebo effect. There was no evidence for a loss of efficacy of the active treatments or the development of tolerance as the scores reflecting pain were either stable or improved over time in the setting of a stable morphine dose. Another possibility is that the underlying disorder, osteoarthritis, is not a pain model with a constant level of pain over time and as such, the improvement in pain scores reflects the natural fluctuations of the condition. If enough patients with a flair of symptoms resulting in adequate pain to enroll in study, experienced a reduction of pain because of the natural history of the osteoarthritis, the results could show a trend for improvement in pain symptoms regardless of therapy, as occurred in the placebo group. This would also explain why the number of patients dropping out due to a lack of efficacy was not statistically significantly different between the active and placebo treatment groups.

Given the different study designs and different patient populations of the two efficacy trials, it is difficult to draw many conclusions that can be generalized. It appears that [redacted] is effective in controlling pain in the patient populations studied, chronic pain of malignant and non-malignant origin, and osteoarthritis. It is unclear what is the actual durability of efficacy given the brief duration of study TRG004-02 in chronic pain patients, and the curious results from the Week 4 evaluations TRG004-004 in patients with osteoarthritis. It also remains unclear how [redacted] and MS Contin compare, as MS Contin had an apparent greater efficacy in TRG004-02, but lesser efficacy in TRG004-04.

Subgroup analyses of efficacy based on gender and age group demonstrated widely variable results. Interpretation of these analyses is unwarranted as the subgroups were of insufficient size to permit meaningful statistical comparison.

2.3 Safety

The profile of serious adverse events, discontinuations due to adverse events, and all observed adverse events from the submitted clinical trials was consistent with the known

spectrum of adverse events of opioid analgesics. Of the 16 deaths during the double-blind trials and open-label extensions, all but one of the patients had metastatic cancer. While the possibility exists that the use of morphine and opioid related adverse events may have been a contributory factor to the cause of death in five cases, there was no evidence that the use of ——— per se, was responsible.

Safety concerns for ——— would focus on any results deviating from the expected spectrum of typical opioid-related side effects. Information compiled from the submitted safety database gives no information suggesting such a deviation from the expected safety profile. Nausea and vomiting, constipation, and somnolence were the most frequent adverse events causing discontinuation from both open-label and double-blind populations and are among the most common adverse events associated with opioid use.

In both of the double-blind pivotal trials, patients receiving ——— experienced a greater incidence of adverse events than patients receiving MS Contin. This was true for all ——— treatment groups even though in the chronic pain study, patients receiving ——— 133% and to a large extent those receiving ———, 100% experienced comparable efficacy as patients receiving MS Contin. There is no ready explanation for this finding. There was no focused increase in any particular adverse event or group of adverse events. The studies were not designed to permit meaningful statistical evaluation of the safety findings so it is possible this may not represent a meaningful finding.

There was a greater frequency of adverse events observed among the osteoarthritis patients who were mostly opioid-naïve at study entry than the chronic pain patients who were mostly opioid-tolerant, regardless of the randomization group. This finding is not unexpected, as tolerance to opioid-related adverse events is a known phenomenon among opioid tolerant patients.

Analysis of laboratory results and vital sign changes from both clinical trial patients and healthy volunteers revealed no trends toward abnormalities that could be attributed to the use of ———

2.4 Dosing

The dosage of ——— will be based on the individual patient's requirements for pain control. The formulations available, 30, 60, 90, and 120 mg, will provide adequate flexibility for individual dose adjustment. The pharmacokinetics of the product support the intended regimen of once per day dosing. It can be expected that patients on chronic opioid therapy will develop physical tolerance and require increased dosages over time. No specific upper limit for ——— dosage has been defined.

2.5 Special Populations

Gender

The Phase III clinical trials were well balanced for enrollment of men and women. There were no gender differences in the primary measure for efficacy, however, adverse events were more common among women.

Race/Ethnicity
The majority of the subjects studied during this development plan were Caucasian. The number of non-Caucasian study participants was too small for meaningful comparisons.

Elderly
There was a greater incidence of adverse events among patients over 65 and more so among patients over 75 years of age. These findings are consistent with the known increased sensitivity to opioids that occurs in the elderly.

Renal Insufficiency
The exposure of patients with renal insufficiency during the Phase III trials was inadequate to characterize any effects on efficacy or safety.

Hepatic Insufficiency
The exposure of patients with hepatic insufficiency during the Phase III trials was inadequate to characterize any effects on efficacy or safety.

Pediatric Plan
The sponsor has proposed a pediatric study. As presented the proposal is not designed adequately to provide sufficient information on safety, efficacy or pharmacodynamics. These deficiencies will be addressed at a later date.

2.6 Pharmacokinetics and Pharmacodynamics

According to the Clinical Pharmacology and Biopharmaceutics Review by Dr. Shinja R. Kim, the overall PK evaluation was adequate. Further evaluation of the use of capsule contents sprinkled in applesauce is necessary. There was dose proportionality in the range from 30 to 120 mg following single doses in healthy volunteers, however, dose-proportionality was not demonstrated based on $C_{max, ss}$ or AUC_{ss} in patients whose dose range was 60-840 mg/day. ——— (QD) was BE with oral morphine solution (q4h/day) and MS Contin® (Bid) at steady state. Steady state was achieved by day 3-5 in the majority of patients and healthy volunteers. There was no food effect.

The PK-PD relationship demonstrated supports a tendency for an inverse relationship between VAS scores and morphine dose, but no relationship between "Time-to-rescue" and concentrations was found. An IVIVC was not demonstrated.

Metabolism, distribution, excretion and PK in special populations were not investigated with ——— capsules.

Clinical Review

1 INTRODUCTION AND BACKGROUND

1.1 Proposed Indications

Morphine sulfate is a μ opioid receptor agonist and has been used for its analgesic properties since the early 19th century. Its effect at both supraspinal and spinal receptors apparently accounts for most of the observed analgesic activity although activity at kappa-1 and kappa-3 receptors may contribute to a lesser degree. Activation of the mu receptor may also cause generalized central nervous system depression, nausea and vomiting, peripheral vasodilatation, and diminished gastrointestinal motility.

Opioids are absorbed from the gastrointestinal tract but there is a significant first-pass metabolism in the liver, resulting in a bioavailability of conventional oral morphine preparations of approximately 25%. By combining immediate release morphine with a formulation of extended-release morphine, the sponsor believes that the enhanced bioavailability will be sufficient to achieve adequate analgesia without an increase in opioid-related side effects.

The intended use for [redacted] is for the management of moderate to severe pain when treatment with an opioid analgesic is indicated for more than a few days. The sponsor believes that the use of this agent will result in more predictable analgesia and less breakthrough pain.

1.2 Milestones in Product Development

The initial IND for the [redacted] Capsule formulation was filed on June 20, 1996 under # 50, 825. NDA #21-260 was subsequently filed on May 31, 2000 and this submission is evaluated in the current review. The following table lists other NDA applications that were referenced during investigation for this application.

Table 1.1
Referenced NDA Applications

Form	*Brand Name*	*NDA Number*	*Approval Date*	*Applicant*
Extended Release Tablet	MS Contin	19-516	May 29, 1987	Purdue Frederick
Extended Release Capsule	Kadian	20-616	July 3, 1996	Faulding
Extended Release Tablet	Oramorph SR	19-977	August 15, 1991	Roxane
Tablet	Roxicodone	20-932	October 26, 1998	Roxane
Solution	MSIR			Purdue Frederick

From Sponsor's in-text table, Vol. 2.44, pg. 14.

1.3 Foreign Marketing

Morphine sulfate has been used worldwide in a variety of dosage forms. However, [redacted] (morphine sulfate) Capsules are not commercially available in any foreign market.

2 FINDINGS FROM OTHER REVIEW DIVISIONS OR CONSULTS

2.1 Chemistry

Morphine sulfate is the sulfate salt of morphine, the chief alkaloid of opium, which is the dried or partially dried latex from the capsules of Papaver somniferum. Each [redacted] Capsule contains 30, 60, 90, or 120 mg of morphine sulfate in immediate release and delayed release formulations. Stability, manufacturing procedures, shelf-life considerations, and other related issues have not yet been evaluated at the time of this review. For a full evaluation of these and other issues of the [redacted] formulation, refer to Dr. Pat Matura's Chemistry review.

2.2 Pharmacotoxicology

Morphine has been used for decades in the treatment of moderate to severe pain conditions. When it was initially introduced, formal non-clinical toxicology studies were not performed. However, since that time, there have been published reports in the scientific literature researching various pharmacotoxicology issues. For a full evaluation of the animal pharmacology and toxicology portion of this NDA, refer to Dr Kathleen Haberny's review.

2.3 Division of Scientific Investigations

The Division of Scientific Investigations (DSI) investigated two sites where clinical studies had been conducted:

- [redacted]
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Inspection revealed a few minor violations that would not affect the reliability of the submitted data. For a full evaluation of DSI findings, refer to Dr. Khairy Malik's review.

2.4 Office of Post-Marketing Drug Risk Assessment

The Office of Post-Marketing Drug Risk Assessment does not recommend the use of the proprietary names [redacted] or "Avinza". At the time of this clinical review, the sponsor had not yet submitted an acceptable name. For more complete information on this issue, see Dr. Alina R. Mahmud's review.

3 HUMAN PHARMACOKINETICS AND PHARMACODYNAMICS

[redacted] Capsules contain beads composed of soluble polymers with immediate release and extended release components. Theoretically, this formulation results in rapid

achievement of a therapeutic morphine plasma concentration and maintenance of therapeutic concentrations throughout the 24-hour dosing interval. The morphine is then converted by hepatic metabolism to glucuronide metabolites that are then excreted in the urine.

3.1 Pharmacokinetic/Pharmacodynamic Studies

The individual pharmacokinetic and pharmacodynamic studies submitted with this NDA are summarized below (in addition, see Appendix A).

Bio 0596008
Single-dose study comparing the pharmacokinetics of ——— 50mg formulation with that of 10mg morphine sulfate immediate release oral solution dosed six times daily. In addition the study assessed the effect of a high fat breakfast on ——— . According to the sponsor, bioequivalence for AUC between ——— and the oral solution could not be demonstrated and the high fat meal had no meaningful effect on AUC for either formulation.

Bio 0596009
Single-dose study investigating the in-vivo pharmacokinetics of ———doses from 30 – 120mg. According to the sponsor, doses from 30mg to 120mg were proportional in terms of AUC data for morphine and 90% confidence intervals showed equivalence between all doses in the dose range tested.

Bio 0698002
Single-dose study to assess the relative bioavailability of ——— 60mg formulation when administered in a capsule and in a sprinkle form. According to the sponsor, bioequivalence was demonstrated between the intact ———60mg capsule and the contents of the capsule sprinkled on applesauce in terms of Cmax and AUC.

Bio 0197006
Steady-state comparative study of two 60mg formulations of ——— q24 hrs for 5 days and 10mg oral solution q4 hrs for 5 days. The sponsor states that steady state was attained in 2-3 days and that ——— was bioequivalent to an equivalent total daily dose of oral solution in terms of AUC.

TRG004-01
Steady-state study of ——— in patients with chronic, moderate to severe pain. The sponsor states that ——— was equally bioavailable to MS Contin for morphine in this group of patients. In addition, the plasma concentration of morphine appeared to be proportional to dose.

TRG004-06
Study comparing pharmacokinetic/pharmacodynamic relationships of once daily ———and twice daily MS Contin in patients with chronic moderate to severe non-

malignant pain (for additional information on study design, see Efficacy section). The sponsor states that a significant concentration-response relationship independent of formulation was demonstrated in the analysis using VAS score as the measure of effect.

For a thorough discussion of pharmacokinetic/pharmacodynamic studies, refer to Dr. Shinja Kim's review.

4 REVIEW METHODS

4.1 Conduct of Review

The study protocols, study reports, and tabulated data submitted in support of efficacy were reviewed. The safety summary was reviewed and compared with data in primary tables and case report tabulations. Data for all deaths and serious adverse events were compared between the Integrated Summary of Safety, relevant appendices, case narratives, case report tabulations, and case report forms. Information on specific adverse events and on a random sample of subjects was similarly evaluated. Information concerning several patients, supplied upon request from the sponsor, was consistent with the previously submitted data.

4.2 Materials Consulted

NDA 21-260 (05/30/00)	Volume 1, Volumes 44-135, Volumes 228-287
NDA 21-260 (05/30/00)	Electronic Review Aids Discs 1 & 2
NDA 21-260 (08/29/00)	Additional information requested from sponsor: Exposure update
NDA 21-260 (10/13/00)	120-day safety update, Volumes 1-68
NDA 21-260 (10/30/00)	Additional information requested from sponsor on 2 deaths
NDA 21-260 (11/01/00)	Additional information requested from sponsor: Combined double-blind and open-label safety database
NDA 21-260 (12/16/00) (12/20/00)	Additional information requested from sponsor: Healthy volunteer safety data
NDA 21-260 (01/23/01)	Additional information requested from sponsor Demographics and tabulated lab data
NDA 21-260	Pharmacokinetic evaluation of NDA submission, Shinja Kim Ph.D.
NDA 21-260	Chemistry evaluation of NDA submission, Pat Matura, Ph.D.
NDA 21-260	Pharmacology evaluation of NDA submission, Kathy Haberny, Ph.D.
NDA 21-260	Statistical review of NDA submission, David Hoberman, Ph.D.
NDA 21-260	DSI review of NDA submission, Khairy Malek, MD
NDA 21-260	OPDRA review of NDA submission, Alina Mahmud, RPh
IND [redacted]	Division file
IND [redacted]	Medical officer review of study protocols, Monte Scheinbaum, MD
ICH-E1A, March 1995	Guideline for extent of exposure – safety assessment for chronic use agents