CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-195 & 22-207

SUMMARY REVIEW

FDA Center for Drug Evaluation and Research
Division of Anesthesia, Analgesia and Rheumatology Products

DEPUTY DIVISION DIRECTOR REVIEW AND BASIS FOR RECOMMENDATION

DATE:	**March 16, 2007**
FROM:	**Sharon Hertz, M.D.**
NDA:	**22-195 (b)(2)** **22-207 (b)(2)**
APPLICANT:	**Roxane Laboratories, Inc.**
LETTER DATE:	**May 16, 2007** **June 8, 2007**
PDUFA GOAL DATE:	**March 16, 2008** **April 8, 2008**
PROPRIETARY NAME:	**Morphine Sulfate Oral Solution** **Morphine Sulfate Tablet**
ESTABLISHED NAME:	**Morphine Sulfate Oral Solution** **Morphine Sulfate Tablet**
DOSAGE STRENGTH:	**Oral Solution 10 and 20 mg/5 mL** **Oral Tablet 15 and 30 mg**
INDICATION:	b(4)

RECOMMENDATION
Approval

INTRODUCTION and BACKGROUND

Numerous unapproved narcotic analgesics are currently marketed, many under the mistaken belief that as very old products, it was not necessary for applications to be

submitted for review under the Drug Efficacy Study Implementation in support of the continued marketing of these products. The current applications are for two products that have been marketed, although previously unapproved, morphine sulfate (MS) oral solution (NDA 22-195) and morphine sulfate oral tablet (22-207).

Morphine was isolated from opium as early as 1806. Opiate receptors were first identified in the early 1970's followed by the discovery of the first endogenous opiate-like substance, enkephalin. The existence of mu, delta and kappa sub-types of opiate receptors was also confirmed in the 1970's. Morphine, along with most of the clinically used opioids, is relatively selective for the mu receptor and it is through the mu receptor that it exerts its clinical effects.

In support of this 505(b)(2) application, the applicant has submitted findings from three clinical pharmacology studies. No new clinical efficacy or safety studies and no new nonclinical studies were performed in support of this application. The applicant cites their pharmacokinetic data, published, peer-reviewed literature, and the Agency's previous findings of efficacy and safety for morphine sulfate for two referenced products:

- Avinza, modified-release morphine sulfate; NDA 21-260, approved in 2002
- Duramorph, morphine sulfate injection; NDA 18-565, approved in 1984

For immediate-release morphine sulfate products, such as the subjects of these two NDAs, there is clear evidence of efficacy and safety based the Agency's prior findings from other products. Therefore, the focus of this type of 505(b)(2) application is the chemistry, manufacturing and controls information, and the individual products' pharmacokinetic characteristics and how these relate to the products referenced in the NDA. In these NDAs there is also a drug-related area of concern based on the presence of an impurity with a structural alert for mutagenicity, a finding common to thebaine-based opioids. In this case, the substance is which can be present as an impurity in the drug substance and as a degradant in the drug product. In the absence of qualification in nonclinical studies, it is necessary to limit the amount of in the drug product. b(4)

CHEMISTRY, MANUFACTURING AND CONTROLS

The review of the CMC section of NDA 22-195, morphine sulfate oral solution, was performed by Dr. Craig Bertha. The CMC section of NDA 22-207, morphine sulfate tablet, was reviewed by Dr. Arthur Shaw. Excerpts of Dr. Bertha's review and Dr. Shaw's review are included in this memo.

The drug substance suppliers for these two products are the same. The review of the drug substance was based on DMFs from the suppliers, . The ICH Q3A Guidance defines a qualification threshold of NMT 0.05% for impurities in a drug substance for a drug product whose maximum daily dose is greater than 2 g per day. The specification for drug products with a total daily dose of less than 2 grams is 0.15%. As there is no prespecified maximum total daily dose b(4)

for morphine, a specification of not more than (NMT) has been requested of manufacturers of morphine based on ICH Q3A. The DMF from lists a specification for in the drug substance of up to The applicant has provided a clinical justification for applying the higher drug substance qualification threshold of NMT for these particular products based on the impracticality of dosing an immediate-release 15 mg or 30 mg tablet to a daily dose of more than 2 g. This is in contrast to modified-release formulations which are available in strengths as high as 200 mg. b(4)

The facilities inspections have been completed and found to be acceptable for both applications.

Morphine Sulfate Oral Solution NDA 22-195

Two strengths of oral morphine sulfate solution were submitted for review, 10 mg/5 mL and 20 mg/5 mL. The low strength will be packaged in bottles with child resistant closures containing 100 and 500 mL of formulation or in 30 mL unit dose cups containing 5 mL of formulation. The high strength will only be packaged in the 100 and 500 mL filled bottles with child resistant closures. b(4)

The drug product contains only known, compendial excipients in amounts present in other oral drug products. The two strengths of MS oral solution are not compositionally proportional. The 10 mg/5 mL formulation contains glycerin and sorbitol and the 20 mg/5 mL formulation contains glycerin and sorbitol The 10 mg/5 mL formulation contains sodium benzoate and the 20 mg/5 mL formulation contains sodium benzoate, propyl paraben, and methyl paraben. b(4)

A discipline review letter and two information requests were sent to the applicant. Adequate responses were received to address the concerns noted. There are no pending concerns about leachables from the bottles as the holder of DMF and the applicant has adequately responded to the associated deficiency comments. b(4)

The methods used for determination of the degradants were clarified and the applicant confirmed that the value for Total Degradants is the sum of both known and unknown degradants and clarified the reporting of the degradant data.

As morphine sulfate degrades when exposed to light, the applicant provided data from light test studies to support the adequacy of the bottle packages with regard to light.

The stability data support the requested 36-month expiry.

The microbiology consultation found the product to be acceptable.

To minimize the risk for variability in dosing, the applicant was asked to add a dosage mechanism with the packaging of the 100-mL and 500-mL filled multi-use bottles. No measuring device had been included with this product previously and patients would have

had to rely on their own measures or whatever was supplied by the pharmacy. A [redacted] dosing cup with graduation marks of 5-, 10-, 15-, and 20-mL volume was proposed by the applicant and reviewed by Dr. Bertha. As this dosing cup will have limited contact with the formulation and is in conformance with food contact regulations, there are no concerns about leachables or compatibility with the drug product. The precision of drug delivery was assessed by the applicant. According to Dr. Bertha, (email dated Feb. 1, 2008) the acceptance criteria are applied in two-tiers such that in the first tier, eight of 10 tested cups have average delivery (triplicate) at each of the marks that is within ±10% with two allowed to ±15%. Individual determinations are held to ±25%. If only seven of the 10 cups tested achieve the tier-one acceptance criterion, an additional 20 cups are tested. Again, for the total of 30 tested cups, no individual results are allowed to exceed ±25% of the intended volume. And, in tier 2, the average for 24 of 30 cups (80% of cups from both tiers) should still be within ±10% for each calibration mark in terms of the triplicate measurements. But six of the 30 are allowed to have average delivery not exceeding ±20%. Based on this, it is possible to have an individual dose that was ±25% of what was intended on occasion. b(4)

Although the precision of this cup could be improved upon, patients who take morphine are generally fairly tolerant of their dose and can tolerate small variations in the amount delivered such as might be expected with the proposed cup. The variations are far less than would be expected were the patient to dose using a household teaspoon. This cup appears to be similar to the cup dispensed by some pharmacies.

Morphine Sulfate Tablets NDA 22-207

Two tablet strengths were submitted in this application, 15 mg and 30 mg.

The DMFs for the container closure system were not reviewed as there was sufficient information provided in the NDA.

[redacted] b(4)

A number of comments were conveyed to the applicant requesting additional information for the drug substance specifications and batch analysis, test procedures, reference standards, and impurities. Comments were also conveyed concerning the drug product composition, manufacturing procedure, excipients, specifications, analytical procedures and validation report, stability data and labeling. These have all been adequately addressed.

There is one outstanding concern, the proposed expiry. As noted above, ICH Q3A defines the qualification thresholds for impurities for the drug substance. ICH Q3B defines thresholds for the drug product and for a product with a 2 g maximum daily dose limit, the qualification threshold level is NMT 0.2%. The applicant proposed a b(4)

expiry, with a specification for [redacted] in the oral tablet drug product which exceeds ICH Q3B. This specification appears to have been proposed because there is a trend for accumulation of [redacted] over time. However, with an expiry of 18 months for the oral tablet, the specification can be set at [redacted] b(4)

There is one final amendment to the NDA that has been requested by Drs. Shaw and Bertha that has been agreed to by the applicant. It is acceptable for this agreement to be submitted post-approval .

- Amend your NDA with a commitment to submit a data to show the accuracy, linearity, precision, and limit of quantitation for [redacted] in the first Annual Report. b(4)

NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

Dr. Belinda Hayes has performed the nonclinical pharmacology and toxicology review for these two NDAs. Excerpts of Dr. Hayes' review are included in this memo. No new nonclinical studies were conducted in support of this 505(b)(2) application. The nonclinical labeling sections have been constructed from reference to the Avinza and Duramorph package inserts and publicly available literature.

As noted by Dr. Hayes, several of the impurity levels in the referenced DMFs exceed current ICH thresholds for safety qualification. They have, however, been present in morphine products for decades and have no known associated safety risk. The identified impurities are [redacted] is a metabolite of morphine and is considered to be qualified. [redacted] are well known degradant products of morphine. [redacted] is an oxidation product of morphine and a morphine metabolite in several species. The minor impurity, [redacted] has been detected in morphine products for almost two decades and appears to have similar binding and potency as morphine itself. The impurities [redacted] have been used therapeutically for years and are well characterized. See Dr. Hayes' review for the pertinent literature citations. b(4)

According to Dr. Hayes, a review of the existing data on [redacted] indicates that the compound is not a completely benign substance. [redacted] is a minor metabolite of morphine in several species. Results from *in vitro* studies have shown that [redacted] is a toxic metabolite of morphine and is linked to the liver toxicity of morphine. The mechanism of [redacted]-induced hepatoxicity involves the ability of [redacted] to covalently bind to hepatic glutathione (GSH). The [redacted] group of [redacted] nonezymatically reacts with GSH to form [redacted]-GSH. It has also been demonstrated that isolated rat hepatocytes incubated with morphine induced a marked decrease in GSH that resulted in cell death and these effects correlated with the formation of [redacted] . b(4)

[redacted] is also a potential metabolite of morphine in humans. Hence, the potential of [redacted] to induce liver toxicity in humans exists. While [redacted] has not been identified in the urine of humans following the administration of morphine, the metabolism of morphine [redacted] has been demonstrated *in vitro*. Isolated human hepatocytes metabolized morphine t [redacted] in a fashion similar to that reported for rats. Dr. Hayes concludes that following the administration of morphine in high doses, a significant elevation in [redacted] level may occur and could result in morphine-induced toxicity. However, of note, with the extensive clinical use of morphine, there has not been a hepatotoxicity signal for these products. b(4)

There are a limited number of genotoxicity studies that evaluate the mutagenic potential of morphine reported in the published literature which suggest that morphine has mutagenic potential. Results from the *in vivo* chromosomal aberration assay and the *in vivo* micronucleus assay suggest that morphine is a potential clastogen. Carcinogenicity studies have not been conducted with morphine by the applicant. There are several studies in the literature as reviewed by Dr. Hayes that do not demonstrate any direct carcinogenicity, but some studies suggest possible indirect involvement. Dr. Hayes has recommended that a postmarketing commitment be made to provide for additional studies, specifically:

> A minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:
>
> [redacted] b(4)

Reproductive toxicology studies were not conducted by the applicant. There are studies in the published literature that were used to support the labeling for Avinza and Duramorph and additional literature available subsequent to the approval of those NDAs was cited by the applicant. Morphine is classified as Pregnancy Category C. While teratogenicity has not been specifically studied, there is evidence that early gestational exposure to morphine in rodents has produced neurological, soft tissue and skeletal abnormalities. In addition, nonteratogenic effects have been noted with early exposure to morphine including reduced embryo and fetal viability, reduced birth weight and developmental delays. These findings occurred with doses that produced maternal toxicity.

It is known that babies born to mothers chronically administered opioids will exhibit a neonatal withdrawal syndrome, may suffer from small birth weight, and may be at risk for sudden infant death syndrome.

Appears This Way
On Original

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS

Much is known about MS. The major metabolic pathway for morphine is glucuronidation to morphine-6-glucuronide which is pharmacologically active, and morphine-3-glucuronide which is not pharmacologically active. Morphine-6-glucuronide can accumulate in the setting of impaired renal function. The effective half-life of morphine is about two to four hours although the terminal half-life is as long as 15 hours based on sampling time. The half-life of morphine-6-glucuronide is approximately 9 hours. Morphine is primarily renally excreted as morphine-3-glucuronide. Morphine undergoes a substantial amount of first-pass metabolism in the liver following oral administration resulting in an oral bioavailability of about 25%. About 33% of morphine is protein bound.

The clinical pharmacology review was performed by Sayed Al Habet, R. Ph., Ph.D. Three studies were conducted in support of these applications. The same studies were submitted in support of NDAs 22-195 and 22-207.

Study MORP-T30-PLFS-1 was a single-dose, 3-period crossover study evaluating the absolute bioavailability of 30 mg of the morphine sulfate 10 mg/5 mL oral solution, a 30 mg tablet and 10 mg of intravenous Duramorph, the parenteral MS referenced by the applicant. Seventeen normal healthy volunteers were enrolled and were dosed with oral naltrexone before and after dosing with MS. According to Dr. Al Habet's review there was a substantial amount of variability in the results of this study. The total exposure ($AUC_{0-\infty}$) was 40% higher following administration of the tablet compared to the solution (181±73 ng.h/mL vs. 131±23.7 ng.h/mL, respectively), although the variability in the study results makes this calculation unreliable. The AUC_{0-t} was comparable for the two oral dosing forms (111±35 ng.h/mL vs. 117±21 ng.h/mL, tablet and oral solution, respectively). The absolute bioavailability compared to the IV MS was 30-35% for the tablets and oral solution. The C_{max} was higher following administration of the tablet as compared to the oral solution (44.8±21.3 ng/mL vs. 36.9±12.7 ng/mL, respectively), and was outside the 90% CI for the bioequivalence limits of 80-125%.

Study MORP-T30-PVFS-2 was a single-dose, 3-period crossover study evaluating dose proportionality between the 15 mg and 30 mg oral tablets and the effect of food prior to a 30 mg tablet. Thirty-two normal healthy volunteers were enrolled and were dosed with oral naltrexone before and after dosing with MS. Both C_{max} and AUC were dose proportional following the 15 mg and 30 mg tablet fasting doses. Elimination half-life was approximately 10 hours. While outside of the 90% CI for the bioequivalence limits of 80-125% for C_{max}, the values from fasting and fed dosing of the 30 mg dose were similar (32.8±14 ng/mL vs. 30.9±21 ng/mL, respectively). $AUC_{0-\infty}$ were bioequivalent for fasting and fed doses. Glucuronide metabolite formation was also dose proportional.

Study MORP-T30-PVFS-3 was a multiple-dose, 3-period crossover study evaluating the steady-state PK characteristics of 30 mg of 10 mg/5mL MS oral solution, 30 mg of MS tablet, and 120 mg of Avinza, the modified-release oral morphine tablet referenced by the applicant. The immediate-release products were dosed every six hours for five days

while the Avinza was dosed once daily for five days. There were no washouts between study periods. Twenty-seven normal healthy volunteers were enrolled and were dosed with oral naltrexone before and after dosing with MS. The C_{max} was approximately 25% higher for the 30 mg immediate-release tablet than for the 30 mg does of oral solution and AUC_{0-24} was approximately 10% higher for the tablet. The C_{max} values for the immediate-release tablet and the oral solution were notably higher than the C_{max} for Avinza, while the AUC was within the 90% CI for the 80-125% bioequivalence criteria for the immediate-release formulations as compared to Avinza.

No studies of special populations or drug-drug interactions were performed. The applicant has referenced two approved products and the labeling for special populations and drug-drug interactions from the Duramorph and Avinza labels will be used to inform the labels for the MS tablet and MS oral solution.

Biowaiver Request

No studies were conducted with the MS oral solution 20 mg/5mL concentration product. This is potentially problematic as the formulations for the 20 mg/mL and the 10 mg/5 mL products are not compositionally proportionate. The applicant has submitted a request for a biowaiver for the higher concentration product. The difference between the formulations is a result of more glycerin and less sorbitol in the 20 mg/5 mL formulation compared to the 10 mg/5 mL formulation b(4)
. As noted by Dr. Al Habet, the amount of sorbitol in a formulation could impact the absorption of a low permeability drug, specifically, the more sorbitol, the less absorption, however, the permeability of morphine is not known. As the relative amounts of sorbitol are not substantially different, in the higher and lower concentrations, respectively, it is unlikely that this would appreciably impact the relative bioavailability of these two formulations. According to Dr. Al Habet, based on its wide use in pharmaceutical products, there is no evidence to suggest that the different amounts of glycerin would have an effect on either permeability or p-glycoprotein activity.

CLINICAL EFFICACY AND SAFETY

No new efficacy or safety studies were conducted or submitted in support of this application. The safety data from the clinical pharmacology studies do not provide useful information about the safety of morphine sulfate as subjects were all pretreated with an opioid antagonist, naltrexone, for subject safety. This memo will serve as the clinical review for these applications.

Efficacy and safety for these immediate-release oral morphine products is supported by the Agency's prior findings of efficacy and safety for the two reference products, Duramorph, a parenteral formulation of morphine sulfate approved for the management of pain and Avinza, a modified-release formulation of morphine sulfate approved for the management of chronic pain. The applicant has provided support for the use of the referenced products through relative bioavailability studies.

Compared to an IV administration of 10 mg of Duramorph, a 30-mg dose of the oral tablet and a 30-mg dose of the oral solution resulted in relatively lower concentrations of morphine and higher concentrations of morphine-3-glucuronide and morophine-6-glucuronide. This is consistent with the known hepatic metabolism of morphine and the earlier exposure to the liver via the oral route. The two oral formulations demonstrated comparable exposures (AUC_{0-t}), but C_{max} was higher for the tablet.

Compared to an oral administration of 120 mg of Avinza, morphine sulfate tablet and oral solution dosed as 30 mg every 6 hours were demonstrated comparable exposures (AUC_{0-24}), and as expected, higher C_{max} and lower C_{max}.

These results are adequate to support the use of the Agency's prior findings of safety and efficacy for the reference products for this application.

CONTROLLED SUBSTANCES STAFF

A review was performed by Dr. Lori Love of the Controlled Substance Staff. Dr. Love requested that the following comments be sent to the applicant:
1. As a Schedule II drug under the CSA, all Schedule II regulations and procedures regarding manufacture, distribution, dispensing, storage, recordkeeping, and disposal of study drug should be in place and strictly followed.
2. Information and data related to abuse, misuse, diversion and overdose should be provided to the Agency. Specifically, the sponsor should submit descriptions of all reports and details, including narratives, of an incident of abuse, overuse, or overdose (intentional or unintentional), or drug that is lost, stolen, missing or unaccounted for in all clinical studies. Additionally, the sponsor should provide any available epidemiological data on abuse, misuse, diversion and overdose on their currently marketed, but unapproved morphine products.

These comments were not sent to the applicant because there were no clinical studies performed other than the clinical pharmacology studies conducted under direct supervision and with naltrexone blockade of all subjects. Also, the Agency has been following the data on abuse, misuse, and diversion of all narcotic analgesics including morphine. This product has had no trade name, and given the large number of unapproved products, there is no mechanism for identifying reports specific to this product in the AERS or MedWatch systems. As there is no request by the applicant to alter the category of scheduling for these products under CSA, there is adequate information known to the Agency concerning abuse liability of morphine without an additional submission by the applicant.

PEDIATRICS

The applicant has submitted a pediatric plan that begins with a statement saying that the indication and treatment of pain is the same between adult and pediatric patients. The

applicant requests deferral of studies in patients of three to 17 years of age and waiver for studies of patients less than three. The safety and effectiveness in pediatric patients in the age group 0-3 years will be extrapolated from the demonstration of safety and effectiveness in age range of 3-17 years and adults. The applicant proposed only to perform two open-label studies in which patients will receive an immediate-release morphine product, will be dosed based on body weight and titrated based on clinical effect. One study would be performed in pediatric patients ages three to 12 years, the second in pediatric patients ages 12 to 17 years.

A deferral of pediatric studies is acceptable. The products are already marketed and it is very important to have these products under NDA without any delay and the applications are ready for approval. It is not acceptable to waive studies in pediatric patients under three years of age. These patients are very different than older patients with regard to maturation of metabolic pathways and development of the central nervous system. Hence, it is acceptable at this time to defer studies of pediatric patients from birth to 17 years of age. The applicant has certified that pediatric studies have not been initiated.

Just what the pediatric development program will need to include will require additional discussion. It has historically been very difficult to get data from adequate and well-controlled studies in pediatric patients due, in large part, to difficulty enrolling patients in placebo-controlled trials, even with the availability of rapid rescue. While any superiority-design study would be acceptable, superiority still requires a less effective comparator arm. Consideration will need to be given to whether any of the pediatric age ranges are suitable for an extrapolation of efficacy findings. This will need to begin with a basis for the evidence of efficacy and it seems that the most likely candidate would be the oldest pediatric age range rather than the youngest age range. This will need to be based on, at a minimum, pharmacokinetic data. Consideration may also be given to the applicability of the use of pharmacokinetic/pharmacodynamic relationships, at least for the setting of acute pain.

OTHER REGULATORY ISSUES

There are no outstanding regulatory issues. The regulatory requirements to support this 505(b)(2) application have been adequately addressed.

LABELING

No proprietary names were proposed for these products.

Internal discussion was held regarding whether the oral solution should be described as mg per 5 mL or mg per 1 mL to reduce the risk for medication errors. This was discussed with the CMC team and with the Division of Medication Errors and Technical Support team. The mg per 1 mL concentration is the most straightforward, is consistent with other products, and the easiest designation for calculating doses. The use of a mg per 5

mL concentration has been in place for decades, and is fairly standard. One consideration when expressing the dose as a concentration is that the 10 mg per 5 mL would become 2 mg per 1 mL and 20 mg per 5 mL would become 4 mg per 1 mL. In terms of potential confusion there would still be risk of confusion between [redacted] (a currently unapproved product) and the 2 mg per 1 mL concentration (formerly the 10 mg per 5 mL strength) due to similar numeric overlap. Additionally the new strength expressions of 2 mg per 1 mL and 4 mg per 1 mL would overlap with the injectable dosage form of morphine and further increase the risk of oral solutions being given as injections. There have already been cases of this reported to AERS. Based on the potential for confusion with parenteral morphine and the longstanding use of the mg per 5 mL designation, the concentrations will remain labeled as mg per 5 mL. b(4)

b(4)

A review of the package insert by Dr. Iris Masucci of the Study Endpoints and Label Development team was obtained and recommendations were forwarded to the applicant along with comments from the chemistry, pharmacology and toxicology, and clinical pharmacology reviewers.

A review of labeling was obtained from the Division of Medication Errors and Technical Support. Ms. Felicia Duffy provided a number of comments that were conveyed to the applicant.

Agreement has been reached on the language for the package insert and the carton and container labels have also been reviewed.

POSTMARKETING COMMITMENT

1. A minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) tested up to the limit dose for the assay, for each of the following drug substance impurities that exceed ICHQ3A qualification thresholds of NMT 0.15%:

b(4)

DISCUSSION

The results from the clinical pharmacology studies comparing the MS tablet and MS oral solution to the parenteral Duramorph and modified-release Avinza were as expected. An IV route of administration of morphine would be expected to produce a higher C_{max} and AUC than an oral route of administration. Similarly, immediate-release oral MS formulations would be expected to produce a higher C_{max} and comparable AUC as compared to a modified-release oral morphine formulation. There is no clear explanation for this finding. The extent of difference in the C_{max} is approximately a 20% higher value for the tablet as compared with a comparable dose of oral solution. For patients who are started on either product, dosing begins conservatively and is then titrated to effect. There would be no need to provide different dosing instructions based on the difference in C_{max}. Even for patients who were converted from one formulation to the next, a 20% difference would be expected to have no deleterious effect.

RECOMMENDATIONS/RISK-BENEFIT ASSESSMENT

- Recommended regulatory action - Approval

- Risk Benefit Assessment – The overall benefit associated with immediate-release oral morphine tablets and oral solution outweigh the overall risk associated with this opioid analgesic.

- Recommendation for Postmarketing Risk Management Activities – No risk minimization action plan is recommended at this time. These products have been marketed and this action does not represent any additional or novel products coming to market.

Appears This Way
On Original

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

/s/

Sharon Hertz
3/17/2008 02:52:35 PM
MEDICAL OFFICER