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RESEARCH**

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PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

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Product: Morphine Sulfate oral solution (20 mg/mL)

Indication: Relief of moderate to severe acute and chronic pain where an opioid analgesic is appropriate.

Applicant: Lannett Holdings, Inc.

Review Division: Division of Anesthesia and Analgesia Products (DAAP)

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1 Executive Summary

1.1 Introduction

Morphine sulfate, a full opioid receptor agonist, is relatively selective for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. It is indicated for the relief of moderate to severe acute and chronic pain where an opioid analgesic is appropriate.

1.2 Brief Discussion of Nonclinical Findings

The Sponsor did not submit any new nonclinical studies in this NDA. The Sponsor is relying up the Agency’s previous findings of safety and efficacy for morphine sulfate oral solution (Roxane’s NDA 22195). The levels of the impurities and degradants from the drug substance and drug product specifications sent by the Sponsor are deemed adequate. Analysis of the excipients at the maximum theoretical daily dose (MTDD) indicates that the exposures of the excipients do not represent a safety concern in the formulations. From a pharmacology toxicology perspective, the components of the container closure system appear to be appropriately cited in the CRF as indirect food additives and as such there are no safety issues pending CMC issues (see CMC review).

1.3 Recommendations

1.3.1 Approvability

From a nonclinical pharmacology toxicology perspective, NDA 201517 may be approved.

1.3.2 Additional Non Clinical Recommendations

At this time, there are no recommendations for further nonclinical studies.

1.3.3 Labeling

The labeling for Lannett Holdings, Inc’s morphine sulfate oral solution will be the same as the referenced drug product, morphine sulfate oral solution (NDA 22195).

| Applicant’s proposed labeling | Reviewer’s proposed changes | Rationale for changes |
|-------------------------------|-----------------------------|-----------------------|
|-------------------------------|-----------------------------|-----------------------|



(b) (4)

2 Drug Information

2.1 Drug

Morphine sulfate

CAS Registry Number

6211-15-0

Generic Name

Morphine sulfate

Code Name

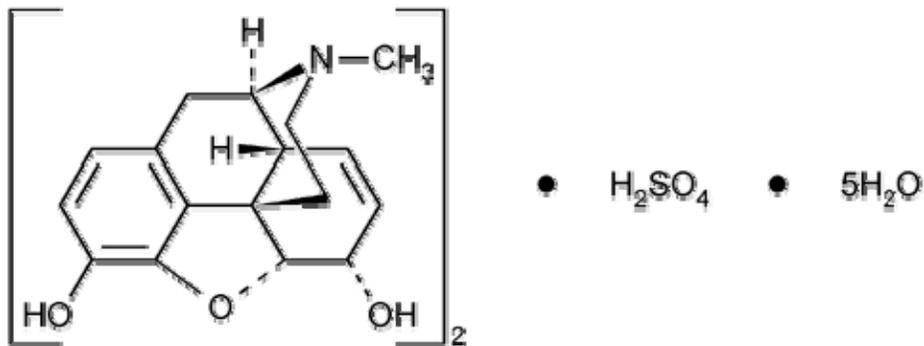
Chemical Name

Morphine sulfate is 7,8-didehydro-4,5 alpha-epoxy-17 methyl-morphinan-3,6 alpha-diol sulfate (2:1) (salt), pentahydrate or morphinan-3,6-diol, 7,8-didehydro-4,5-epoxy-17-methyl, (5 alpha,6 alpha)-, sulfate (2:1) (salt), pentahydrate.

Molecular Formula/Molecular Weight

$(C_{17}H_{19}NO_3)_2 \cdot H_2SO_4 \cdot 5H_2O$ / 758.83 g/mol

Structure or Biochemical Description



Pharmacologic Class

Opioid agonist (FDA established pharmacological class)

2.2 Relevant INDs, NDAs, BLAs and DMFs

The referenced drug for this 505(b)(2) NDA is morphine sulfate oral solution (NDA 22195; Roxane Laboratories, Inc.).

| <i>NDA#</i> | <i>Drug Name</i> | <i>Div</i> | <i>Strength (route)</i> | <i>Marketing Status</i> | <i>AP Date</i> | <i>Indication</i> | <i>Company</i> |
|-------------|--------------------------------|------------|---------------------------|-------------------------|----------------|---|---------------------------|
| 22195 | Morphine sulfate oral solution | DAAP | 2, 4, and 20 mg/mL (oral) | AP | 3/17/2008 | Relief of moderate to severe acute and chronic pain | Roxane Laboratories, Inc. |

| <i>IND#</i> | <i>Status</i> | <i>Division</i> | <i>Indication</i> | <i>Stamp Date</i> | <i>Sponsor</i> |
|-------------|---------------|-----------------|-------------------|-------------------|----------------|
|-------------|---------------|-----------------|-------------------|-------------------|----------------|



(b) (4)

| | | | | | |
|--------|---------------|------|------------------|-------------|----------------|
| 105256 | Presubmission | DAAP | For chronic pain | May 6, 2009 | Lannett Co Inc |
|--------|---------------|------|------------------|-------------|----------------|



(b) (4)

| <i>DMF#</i> | <i>Subject of DMF</i> | <i>Holder</i> | <i>Submit Date</i> | <i>Reviewer's Comment</i> |
|-------------|-----------------------|---------------|--------------------|---------------------------|
|-------------|-----------------------|---------------|--------------------|---------------------------|



(b) (4)

2.3 Drug Formulation

The following table is the final formulation of morphine sulfate oral solution:

Morphine Sulfate Oral Solution

| Ingredient | mg/mL | % (w/w)* | Functionality |
|---------------------------------|-------|----------|-------------------|
| Morphine Sulfate, USP | 20.0 | (b) (4) | Active ingredient |
| Propylparaben, NF | | | (b) (4) |
| Methylparaben, NF | | | (b) (4) |
| Sodium Benzoate, NF | | | (b) (4) |
| Sorbitol USP | | (b) (4) | (b) (4) |
| Glycerin, USP | | | (b) (4) |
| Citric Acid Anhydrous, USP | | | (b) (4) |
| Edetate Disodium Dihydrate, USP | | | (b) (4) |
| Purified Water, USP | | | (b) (4) |

All of the excipients are listed in the Inactive Ingredient Guide (IIG) and are found in other approved products. It is noted that there are no novel excipients.

The clinicians of DAAP have established a maximum theoretical daily dose (MTDD) of morphine for a controlled release drug product to an opioid tolerant individual is 2 g/day. This drug product contains 20 mg/mL of morphine. Accordingly, an opioid tolerant individual may take 100 mL of the drug product to achieve the MTDD. The following table quantifies each excipient at the MTDD:

| Ingredients | Exposure in 20 mg/mL strength oral solution at the MTDD of 2 g/day (mg) | IIG maximum potency (in oral products) |
|-------------------------|---|--|
| No. of doses to MTDD | 100 | |
| Morphine Sulfate | 2000 | N/A |
| Propylparaben | (b) (4) | 0.21 mg |
| Methylparaben | | 50 mg |
| Sodium Benzoate | | 60 mg |
| Sorbitol Solution (70%) | | 97 mg |
| Glycerin | | 223.8 mg |
| Citric Acid Anhydrous | | 1.50% (oral solution); 500 mg (oral bar chewable) |

| | | |
|----------------------------|---------|------|
| Edetate Disodium Dihydrate | (b) (4) | 5 mg |
| Purified Water* | | N/A |
| Total (mg) | | |

* The percentage of water in the morphine sulfate oral solution formulation is estimated to be (b) (4)

The exposure levels of all of the excipients are above the IIG maximum potency limits for oral products at the MTDD of 2 g/day morphine. Therefore, a safety assessment was completed for these excipient levels.

Propylparaben, under 21 CFR §582.3670, is listed as GRAS and may be used in foods at levels not to exceed good manufacturing practices (NMT 0.1%). Accordingly, at the MTDD of 2 g/day morphine, the exposure of propylparaben is (b) (4), which accounts for (b) (4) of the formulation. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of propylparaben and has concluded that an acceptable daily intake (ADI) is 0-2 mg/kg or 120 mg/60 kg adult (WHO Food Additives Series 67.29). Accordingly, at the MTDD of 2 g/day morphine, this formulation contains (b) (4) of propylparaben and an average human weighing 60 kg would be exposed to (b) (4) of propylparaben, which is below the ADI. Therefore, the proposed level of propylparaben in this product does not appear to represent a safety concern.

Methylparaben, under 21 CFR §582.3490, is listed as GRAS and may be used in foods at levels not to exceed good manufacturing practices (NMT 0.1%). Accordingly, at the MTDD of 2 g/day morphine, the exposure of methylparaben is (b) (4) which accounts for (b) (4) of the formulation. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of methylparaben and has concluded that an acceptable daily intake (ADI) is 0-2 mg/kg or 120 mg/60 kg adult (WHO Food Additives Series 67.29). Accordingly, at the MTDD of 2 g/day morphine, this formulation contains (b) (4) of methylparaben and an average human weighing 60 kg would be exposed to (b) (4) of methylparaben, which is below the ADI. Therefore, the proposed level of methylparaben in this product does not appear to represent a safety concern.

Sodium benzoate, under 21 CFR §582.3733, is listed as GRAS and may be used in foods at levels not to exceed good manufacturing practices (NMT 0.1%). Accordingly, at the MTDD of 2 g/day morphine, the exposure of sodium benzoate is (b) (4) which accounts for (b) (4) of the formulation. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of sodium benzoate and has concluded that an acceptable daily intake (ADI) is 0-5 mg/kg or 300 mg/60 kg adult (WHO Food Additives Series 18). Accordingly, at the MTDD of 2 g/day morphine, this formulation contains (b) (4) of sodium benzoate and an average human weighing 60 kg would be exposed to (b) (4) of sodium benzoate, which is below the ADI. Therefore, the proposed level of sodium benzoate in this product does not appear to represent a safety concern.

Sorbitol (b) (4) under 21 CFR §184.1835, is listed as GRAS and may be used in foods at levels not to exceed good manufacturing practices (up to 99%). The amount

of sorbitol (b) (4) in the 20 mg/mL strength oral solution is (b) (4) at the MTDD, which meets good manufacturing practices. Sorbitol is a sugar alcohol that is used as a sugar substitute. As per 21 CFR §184.1835, "The label and labeling of food whose reasonably foreseeable consumption may result in daily ingestion of 50 grams of sorbitol shall bear the statement: 'Excess consumption may have a laxative effect'." The 20 mg/mL strength morphine sulfate oral solution contains (b) (4) of sorbitol at the MTDD, which is less than what could be consumed in foods. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of sorbitol and has concluded that an acceptable daily intake (ADI) does not need to be specified. Thus, the proposed level of sorbitol (b) (4) in this product does not appear to represent a safety concern.

Glycerin is listed as GRAS for human foods under 21 CFR §178.3500 and 21 CFR §182.1320 when used in accordance with good manufacturing practices. The amount of glycerin in this product is (b) (4) at the MTDD of 2 g/day morphine. Moreover, there are approved products whose daily use will expose a patient to more glycerin than this formulation. Hine et al. (1953) conducted a 2-year feeding study of natural and synthetic glycerin in Long-Evans rats. The diet was prepared to contain 5, 10, or 20% natural or synthetic glycerin (equivalent to 50,000, 100,000, and 200,000 mg/kg, respectively). Although there were organ/body weight ratio and histopathological changes, these changes were sporadic and did not demonstrate a clear dose-dependency. The liver/body weight ratio was significantly lower in males (- 10.3%) and higher in females (+ 11.1%) than control in rats that were fed 20% synthetic glycerin. There were changes in the other organ/body weight ratios (lungs, heart, kidneys, and spleen) but these changes were sporadic and not dose-dependent. Regarding the histopathological changes, spontaneous disease was observed in 68 out of 157 rats used in the study; however the lowest incidence of the observation was in the rats fed 20% natural or synthetic glycerin and 5% synthetic glycerin. There were inflammatory lesions observed in the rats in all groups including the control and there was no dose dependency to the finding. Regarding tumors that were formed, malignant tumors were observed in all groups including the control and there was no dose-dependency to the findings. Benign tumors were observed in all natural and synthetic glycerin groups but not in the control; however, there was no dose-dependency observed in the glycerin treatment groups. Other observable changes include albuminuria and glycosuria; however the incidences of these changes were sporadic throughout the treatment groups. Liver glycogen and lipid were also observed; however, these changes were not considered significant. Thus, there was no clear toxicity that could be attributed to glycerin treatment. The lowest dose of glycerin given to the rats in this study, 5%, is equivalent to 50,000 mg/kg. At this rat dose of glycerin, there is an exposure margin of 48.65 at the human dose of 10 g glycerin given to an average human weighing 60 kg. Therefore, the proposed level of glycerin in this product does not appear to represent a safety concern.

Citric acid anhydrous is listed as GRAS for human foods under 21 CFR §184.1033 without limitations other than current good manufacturing practices. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) has reviewed the safety of

citric acid anhydrous and has concluded that citric acid anhydrous does not constitute a significant toxicological hazard to man and that an acceptable daily intake (ADI) in man is not limited. Furthermore, there are approved oral drug products whose daily use will expose a patient to the same amount of citric acid anhydrous as in this formulation. Thus, the proposed level of citric acid in this product does not appear to represent a safety concern.

Edetate disodium dihydrate is listed as GRAS for human foods under 21 CFR §172.135 with the limitation of between at least 75 and up to 500 parts per million (ppm) in foods. At the MTDD of 2 g/day morphine, (b) (4) of edetate disodium dehydrate is present and the average human weighing 60 kg is exposed to (b) (4) of edetate disodium dehydrate per day. One ppm is equal to 1 mg/kg. Accordingly, the exposure of edetate disodium dehydrate from the 20 mg/mL morphine sulfate formulation at the MTDD of 2 g/day morphine does not exceed the limitations set forth in 21 CFR §172.135. Moreover, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) determined that the acceptable daily intake of edetate disodium dehydrate is 0-2.5 mg/kg or 150 mg/60 kg adult. At the MTDD of 2 g/day morphine, the average human is exposed to (b) (4) of edetate disodium dehydrate per day. Thus, the proposed level of edetate disodium dihydrate in this product does not appear to represent a safety concern.

The sponsor has proposed the following drug substance specifications:

| Impurity | Proposed Specification | ICH Q3A(R2) qualification threshold (MTDD 2 g) | Reviewer's Assessment |
|----------|------------------------|--|-----------------------|
| (b) (4) | | | |

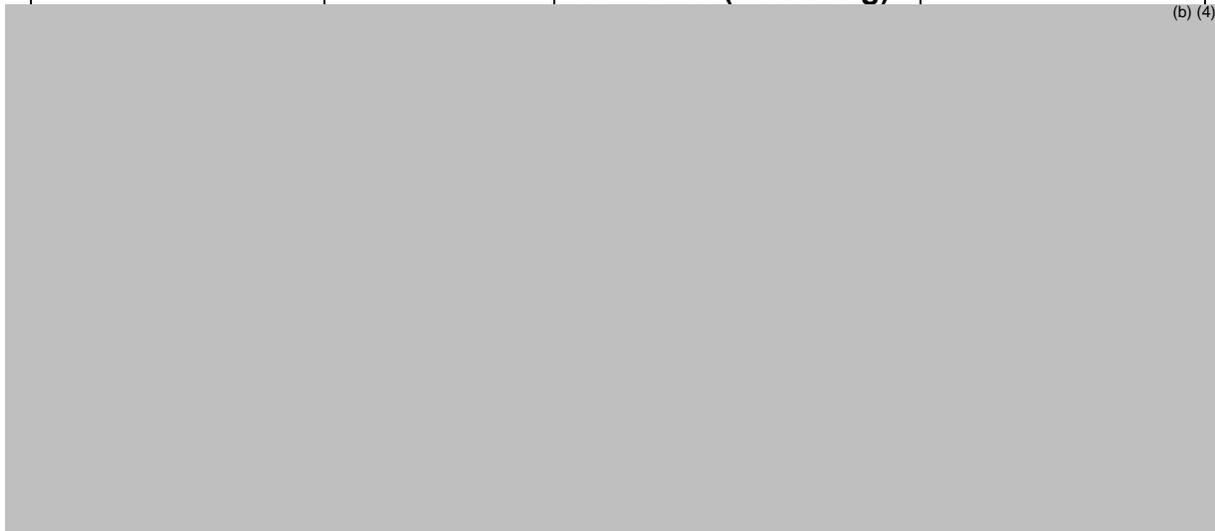


(b) (4)

The sponsor has proposed the following drug product stability specifications:

| Impurity | Proposed Specification | ICH Q3B(R2) qualification threshold (MTDD 2 g) | Reviewer's Assessment |
|-----------------|-------------------------------|---|------------------------------|
|-----------------|-------------------------------|---|------------------------------|

(b) (4)



(b) (4) which is present in both the drug substance and drug product, contains a structural alert for genetic toxicity and as such must be reduced to below ICHQ3A(R2) and ICHQ3B(R2) qualification thresholds. Therefore, (b) (4) must be below (b) (4) (b) (4) qualified via the standard battery of genetic toxicity testing, or otherwise justified. The Sponsor has submitted the final study reports for the Ames and chromosomal aberrations assays using (b) (4) in SDN 11 and a review of those studies can be found in Section 7 Genetic Toxicology below.

The Sponsor has proposed using 30, 120, and 240 mL bottles to store the morphine sulfate formulation and has proposed the following components for the container closure system (Table 1):

Table 1: Container Closure System

| Bottle Information | | | | | | | |
|---------------------------|--|--------------|-----|-------|--------|--------|---|
| | Type | Manufacturer | DMF | 30 mL | 120 mL | 240 mL | Justification in the CFR |
| Size | (b) (4) | | | | | | 21 CFR §177.1520; §174.5; §178.2010; §178.3297; and §178.3400 |
| | | | | | | | Same as above |
| | | | | | | | 21 CFR §177.1520; §178.3860; and 178.3297 |
| (b) (4) | | | | | | | 21 CFR §177.1520 |
| | | | | | | | 21 CFR §177.1520 |
| | | | | | | | 21 CFR §177.1520 |
| Colorant | | | | | | | 21 CFR §174.5; §177.1520; §178.2010; §178.3297; and §178.3400 |
| | 21 CFR §177.1520; §178.3860; and §178.3297 | | | | | | |

Cap Information

| | Type | Manufacturer | DMF | 30 mL | 120 mL | 240 mL | Justification in the CFR |
|--------------------------------|------|--------------|-----|-------|--------|--------|---|
| Size | | | | | | | 21 CFR §177.1520; §178.3860; §178.3297; §178.2010; and §176.170 |
| Outer Cap Colorant | | | | | | | 21 CFR §177.1520; §178.3860; and §178.3297 |
| Inner and Outer Cap (b) (4) | | | | | | | 21 CFR 177.1520; §178.2010; and §176.170 |
| Primary Liner | | | | | | | 21 CFR §177.1520 |
| | | | | | | | Same as above |

Oral Doser Information

| | Type | Manufacturer | DMF | 30 mL | 120 mL | 240 mL | Justification in the CFR |
|-------------------------|------|--------------|-----|-------|--------|--------|--------------------------|
| Size | | | | | | | See text below |
| Barrel HDPE (b) (4) | | | | | | | 21 CFR §177.1520 |
| | | | | | | | 21 CFR §177.1520 |
| Plunger HDPE (b) (4) | | | | | | | 21 CFR §177.1520 |
| Wrap | | | | | | | N/A |
| | | | | | | | N/A |
| Colorant | | | | | | | 21 CFR |

| | | |
|-----|---------|---|
| | (b) (4) | §178.3297; §178.2010; §177.1520; §181.28; §178.3295; §175.105; §175.300; §175.320; §176.180; §177.1200; §177.1210; §177.1350; §177.1400; §178.3260; and §179.45 |
| Ink | | 21 CFR §174.5; §175-178; §176.170; and §182.90 |

As shown in the table above, not all of the components of the container closure system have DMFs except for all cap components. The Sponsor has submitted the compliance of all of the components of the container closure system to the appropriate CFRs for indirect food additives in SDN 13 (see CMC review). As seen in the table above, all of the components of the container closure system have been cited in the CFR for indirect food additives. DMF (b) (4) was previously deemed acceptable for (b) (4).

It is noted that the wrap used for the oral doser will not be in contact for the drug product and as such, the appropriate CFR compliance for indirect food additives is not needed. Therefore, from a pharmacology toxicology perspective, there are no safety concerns with the components of the container closure system pending CMC issues (see CMC review).

2.4 Comments on Novel Excipients

There are no novel excipients in the drug product.

2.5 Comments on Impurities/Degradants of Concern

(b) (4) in the drug substance and drug product contains a structural alert for genetic toxicity and as such must be below (b) (4) qualified via the standard battery of genetic toxicity testing, or otherwise justified. The Sponsor has submitted the final study reports for the Ames and chromosomal aberrations assays using (b) (4) in SDN 11 and a review of those studies can be found in Section 7 Genetic Toxicology below. Based on the results of these studies, the impurity was deemed nongenotoxic and can be regulated as per standard ICH guidelines.

2.6 Proposed Clinical Population and Dosing Regimen

The proposed clinical population is patients in need of relief of moderate to severe acute and chronic pain where an opioid analgesic is appropriate. Due to the development of tolerance, there is no maximum daily dose of morphine. A maximum theoretical daily dose (MTDD) has been established by the Division for morphine at 2 g/day.

2.7 Regulatory Background

There was a preIND meeting held with the Sponsor on July 1, 2009 (PIND 105,256). At the preIND meeting, the Sponsor was told to provide a quantitative listing of the drug product formulation. The Sponsor was also told that they may need to conduct 90-day toxicity studies on any impurity or degradant of the drug product that exceeds the NMT (b) (4) qualification threshold.

3 Studies Submitted

3.1 Studies Reviewed

The Sponsor submitted the final study reports for an Ames Assay and for the Chromosomal Aberrations Assay for (b) (4). There were no other nonclinical toxicology studies submitted.

3.2 Studies Not Reviewed

All nonclinical toxicology studies submitted were reviewed.

3.3 Previous Reviews Referenced

The Sponsor is relying upon the Agency's previous findings of safety and efficacy for morphine sulfate oral solution (NDA 22-195).

4 Pharmacology

4.1 Primary Pharmacology

The following information on the mechanism of action of morphine sulfate is taken from the approved label for morphine sulfate oral solution (NDA 22195):

Morphine sulfate, a pure opioid agonist, is relatively selective for the mu receptor, although it can interact with other opioid receptors at higher doses. In addition to analgesia, the widely diverse effects of morphine sulfate include drowsiness, changes in mood, respiratory depression, decreased gastrointestinal motility, nausea, vomiting, and alterations of the endocrine and autonomic nervous system.

4.2 Secondary Pharmacology

The following information on drug interactions is taken from the approved label for morphine sulfate oral solution (NDA 22195):

... **CNS Depressants**

Other central nervous system (CNS) depressants including sedatives, hypnotics, general anesthetics, antiemetics, phenothiazines, or other tranquilizers or alcohol increases the risk of respiratory depression, hypotension, profound sedation, or coma. Use morphine sulfate with caution and in reduced dosages in patients taking these agents.

... Muscle Relaxants

Morphine sulfate may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

... Mixed Agonist/Antagonist Opioid Analgesics

Do not administer mixed agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, and butorphanol) to patients who have received or are receiving a course of therapy with a pure opioid agonist analgesic such as morphine sulfate. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect and/or may precipitate withdrawal symptoms.

... Cimetidine

Concomitant administration of morphine sulfate and cimetidine has been reported to precipitate apnea, confusion, and muscle twitching in an isolated report. Monitor patients for increased respiratory and CNS depression when receiving cimetidine concomitantly with morphine sulfate.

... Monoamine Oxidase Inhibitors (MAOIs)

MAOIs markedly potentiate the action of morphine sulfate. Allow at least 14 days after stopping treatment with MAOIs before initiating treatment with morphine sulfate.

... Anticholinergics

Anticholinergics or other medications with anticholinergic activity when used concurrently with opioid analgesics may result in increased risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

... P-Glycoprotein (PGP) Inhibitors

Based on published reports, PGP inhibitors (e.g. quinidine) may increase the absorption/exposure of morphine sulfate by about two fold. Therefore, exercise caution when morphine sulfate is co-administered with PGP inhibitors.

4.3 Safety Pharmacology

No safety pharmacology studies were submitted, as the effects of morphine on critical organ systems are well known. The following information on the pharmacodynamic effects of morphine sulfate was taken from the approved label for morphine sulfate oral solution (NDA 22195):

Effects on the Central Nervous System (CNS)

The principal therapeutic action of morphine sulfate is analgesia. Other therapeutic effects of morphine sulfate include anxiolysis, euphoria and feelings of relaxation. Although the precise mechanism of the analgesic action is unknown, specific CNS opiate receptors and endogenous compounds with morphine sulfate-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression and perception of analgesic effects. In common with other opioids, morphine sulfate causes respiratory depression, in part by a direct effect on the brainstem respiratory centers. Morphine sulfate and related opioids depress the cough reflex by direct effect on the cough center in the medulla.

Morphine sulfate causes miosis, even in total darkness.

Effects on the Gastrointestinal Tract and on Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine sulfate. Morphine sulfate causes a reduction in motility and is associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result may be constipation. Morphine sulfate can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi. Morphine sulfate may also cause spasm of the sphincter of the urinary bladder.

Effects on the Cardiovascular System

In therapeutic doses, morphine sulfate does not usually exert major effects on the cardiovascular system. Morphine sulfate produces peripheral vasodilation which may result in orthostatic hypotension and fainting. Release of histamine can occur, which may play a role in opioid-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes and sweating.

Endocrine System

Opioid agonists have been shown to have a variety of effects on the secretion of hormones. Opioids inhibit the secretion of ACTH, cortisol, and luteinizing hormone (LH) in humans. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon in humans and other species, rats and dogs. Thyroid stimulating hormone (TSH) has been shown to be both inhibited and stimulated by opioids.

Immune System

Opioids have been shown to have a variety of effects on components of the immune system in *in vitro* and animal models. The clinical significance of these findings is unknown.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The following information on the pharmacokinetics/ADME of morphine sulfate is taken from the approved label for morphine sulfate oral solution (NDA 22195):

Absorption

Morphine sulfate is about two-thirds absorbed from the gastrointestinal tract with the maximum analgesic effect occurring 60 minutes post-administration. The oral bioavailability of morphine sulfate is less than 40% and shows large inter-individual variability due to extensive pre-systemic metabolism.

Food Effects

Although the presence of a food effect was not assessed with morphine sulfate oral solution, significant food effect is not expected with a solution formulation.

Steady-State

Administration of the 30 mg Morphine Sulfate Tablet and 30 mg of Morphine Sulfate Oral Solution every six hours for 5 days resulted in a comparable 24-hour exposure (AUC). The steady-state levels were achieved within 48 hours for both tablets and solution. The mean steady state C_{max} values were about 78 and 58 ng/mL for tablet and solution, respectively.

Distribution

Once absorbed, morphine sulfate is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen and brain. Although the primary site of action is the CNS, only small quantities cross the blood-brain barrier. Morphine sulfate also crosses the placental membranes and has been found in breast milk. The volume of distribution of morphine sulfate is approximately 1 to 6 L/kg, and morphine sulfate is 20 to 35% reversibly bound to plasma proteins.

Metabolism

The major pathway of morphine sulfate detoxification is conjugation, either with D-glucuronic acid to produce glucuronides or with sulfuric acid to produce morphine-3-etheral sulfate. While a small fraction (less than 5%) of morphine sulfate is demethylated, virtually all morphine sulfate is converted by hepatic metabolism to the 3- and 6-glucuronide metabolites (M3G and M6G; about 50% and 15%, respectively). M6G has been shown to have analgesic activity but crosses the blood-brain barrier poorly, while M3G has no significant analgesic activity.

Excretion

Most of a dose of morphine sulfate is excreted in urine as M3G and M6G, with elimination of morphine sulfate occurring primarily as renal excretion of M3G. Approximately 10% of the dose is excreted unchanged in urine. A small amount of glucuronide conjugates are excreted in bile, with minor enterohepatic

recycling. Seven to 10% of administered morphine sulfate is excreted in the feces.

The mean adult plasma clearance is approximately 20 to 30 mL/min/kg. The effective terminal half-life of morphine sulfate after IV administration is reported to be approximately 2 hours. In some studies involving longer periods of plasma sampling, a longer terminal half-life of morphine sulfate of about 15 hours was reported.

Race

There may be some pharmacokinetic differences associated with race. In one published study, Chinese subjects given intravenous morphine sulfate had a higher clearance when compared to Caucasian subjects (1852 +/- 116 mL/min compared to 1495 +/- 80 mL/min).

5.2 Toxicokinetics

(If not included in toxicity studies)

6 General Toxicology

The following adverse reactions were listed in the approved label for morphine sulfate oral solution (NDA 22195):

Serious adverse reactions associated with morphine sulfate use include: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock and cardiac arrest.

The common adverse reactions seen on initiation of therapy with morphine sulfate are dose-dependent and are typical opioid-related side effects. The most frequent of these include constipation, nausea, and somnolence. Other commonly observed adverse reactions include: lightheadedness, dizziness, sedation, vomiting, and sweating. The frequency of these events depends upon several factors including clinical setting, the patient's level of opioid tolerance, and host factors specific to the individual. Anticipate and manage these events as part of opioid analgesia therapy.

Other less frequently observed adverse reactions expected from opioid analgesics, including morphine sulfate include:

Body as a Whole: malaise, withdrawal syndrome

Cardiovascular System: bradycardia, hypertension, hypotension, palpitations, syncope, tachycardia

Digestive System: biliary pain, dyspepsia, dysphagia, gastroenteritis, abnormal liver function tests, rectal disorder, thirst

Hemic and Lymphatic System: anemia, thrombocytopenia

Metabolic and Nutritional Disorders: edema, weight loss

Musculoskeletal: skeletal muscle rigidity

Nervous System: abnormal dreams, abnormal gait, agitation, amnesia, anxiety, ataxia, confusion, convulsions, coma, delirium, hallucinations, lethargy, nervousness, abnormal thinking, tremor, vasodilation, vertigo, headache

Respiratory System: hiccup, hypoventilation, voice alteration

Skin and Appendages: dry skin, urticaria, pruritus

Special Senses: amblyopia, eye pain, taste perversion

Urogenital System: abnormal ejaculation, dysuria, impotence, decreased libido, oliguria, urinary retention, anti-diuretic effect

6.1 Single-Dose Toxicity

The Sponsor did not submit any single-dose toxicity studies in this NDA.

6.2 Repeat-Dose Toxicity

The Sponsor did not submit any repeat-dose toxicity studies in this NDA.

7 Genetic Toxicology

The following information on the mutagenicity of morphine sulfate is found in the approved label for morphine sulfate oral solution (NDA 22195):

No formal studies to assess the mutagenic potential of morphine sulfate have been conducted. In the published literature, the results of *in vitro* studies showed that morphine sulfate is non-mutagenic in the *Drosophila melanogaster* lethal mutation assay and produced no evidence of chromosomal aberrations when incubated with murine splenocytes. Contrary to these results, morphine sulfate was found to increase DNA fragmentation when incubated *in vitro* with a human lymphoma line. *In vivo*, morphine sulfate has been reported to produce an increase in the frequency of micronuclei in bone marrow cells and immature red blood cells in the mouse micronucleus test and to induce chromosomal aberrations in murine lymphocytes and spermatids. Some of the *in vivo*

clastogenic effects reported with morphine sulfate in mice may be directly related to increases in glucocorticoid levels produced by morphine sulfate in this species.

7.1 *In Vitro* Reverse Mutation Assay in Bacterial Cells (Ames)

Study title: *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay (OECD 471)

Study no.: 10-3639-G1
Study report location: Module 4
Conducting laboratory and location: (b) (4)
Date of study initiation: August 4, 2010
GLP compliance: Yes, signature provided on September 28, 2010
QA statement: Yes, signature provided on September 28, 2010
Drug, lot #, and % purity: (b) (4) lot # RS-02057-3, 99.1% purity

Key Study Findings

- *S. typhimurium* strains (TA98, TA100, TA1535, and TA1537) and *E. coli* strain (WP2 *uvrA*) were incubated in 0.02, 0.061, 0.185, 0.555, 1.666, and 5.0 mg/plate (b) (4) in a definitive study.
- This Ames Assay was deemed valid.
- (b) (4) did not induce mutations in any tester strain in either the presence or absence of metabolic activation and thus is negative in the Bacterial Reverse Mutation Assay.

Methods

- Strains: *S. typhimurium* strains (TA98, TA100, TA1535, and TA1537) and *E. coli* strain (WP2 *uvrA*)
- Concentrations in definitive study: 0.02, 0.061, 0.185, 0.555, 1.666, and 5.0 mg/plate (b) (4)
- Basis of concentration selection: The concentrations used in the definitive study were based on the results of a range finding study. The range finding study used 0.02, 0.061, 0.185, 0.555, 1.666, and 5.0 mg/plate (b) (4) on TA98 and TA100 strains and was used to determine the cytotoxicity of (b) (4). The range finding study showed that there was complete toxicity at 5.0 mg/plate (b) (4) in both TA98 and TA100 strains and partial toxicity at 1.666 mg/plate (b) (4) in TA100 only. The four lower concentrations (0.02, 0.061, 0.185, and 0.555 mg/plate (b) (4)) showed no toxicity in both TA98 and TA100 strains.
- Negative control: DMSO (100 μ L/plate)
- Positive control: Without metabolic activation:
 2-nitrofluorene for TA98 (10 μ g/mL); sodium azide for TA100 (100 μ g/mL) and TA1535 (5 μ g/mL); 9-aminoacridine for TA1537 (800 μ g/mL); and 4-nitroquinoline 1-oxide for WP2 *uvrA* (100 μ g/mL)
 With metabolic activation:
 2-aminoanthracene for all strains (5 μ g/mL for TA98, 10 μ g/mL for TA100, 20 μ g/mL for TA1535, 30 μ g/mL for TA1537, and 200 μ g/mL for WP2 *uvrA*)
- Formulation/Vehicle: The test substance is dissolved in DMSO.
- Incubation & sampling time: Plates containing the appropriate strain of bacteria and test substance or control substance were incubated at $37 \pm 2^\circ\text{C}$ for 48-72 hours with or without metabolic activation. After incubation, the number of revertant colonies was counted on each plate.

Study Validity

The study is considered valid for the following reasons: 1) the appropriate controls were used; 2) the appropriate strains were tested; 3) the positive control substances produced reliable positive results; 4) the highest concentration of [REDACTED]^{(b) (4)} tested reached the maximum recommended concentration of 5.0 mg/plate (5,000 µg/plate); and 5) there was no evidence for a dose-dependent increase in revertants following drug treatment.

Results

The number of revertants/plate in the reverse mutation assay done without metabolic activation using [REDACTED]^{(b) (4)} is shown in figure 1.

Figure 1: Reverse Mutation Assay Without Metabolic Activation

| Revertants/Plate* | | | | | | | | |
|--------------------|------------|-------------|----------------------------------|-----------|-----------|-----------|-----------|-----------|
| Strain | Controls | | Test Substance | | | | | |
| | Positive** | Negative*** | Dosing Concentrations (mg/plate) | | | | | |
| | | | 5.0 | 1.666 | 0.555 | 0.185 | 0.061 | 0.02 |
| TA98 | 264 | 12 | 0 | 5 | 8 | 10 | 8 | 10 |
| | 253 | 9 | 0 | 7 | 9 | 6 | 10 | 10 |
| | 276 | 14 | 0 | 6 | 10 | 8 | 11 | 12 |
| Mean | 264 | 12 | 0 | 6 | 9 | 8 | 10 | 11 |
| SD | 12 | 3 | 0 | 1 | 1 | 2 | 2 | 1 |
| TA100 | 965 | 68 | 0 | 0 | 62 | 67 | 62 | 65 |
| | 978 | 73 | 0 | 0 | 63 | 55 | 60 | 66 |
| | 994 | 65 | 0 | 0 | 58 | 59 | 61 | 60 |
| Mean | 979 | 69 | 0 | 0 | 61 | 60 | 61 | 64 |
| SD | 15 | 4 | 0 | 0 | 3 | 6 | 1 | 3 |
| TA1535 | 192 | 9 | 1 | 5 | 6 | 9 | 8 | 10 |
| | 187 | 11 | 1 | 1 | 3 | 7 | 7 | 5 |
| | 185 | 5 | 0 | 2 | 2 | 5 | 3 | 5 |
| Mean | 188 | 8 | 1 | 3 | 4 | 7 | 6 | 7 |
| SD | 4 | 3 | 1 | 2 | 2 | 2 | 3 | 3 |
| TA1537 | 199 | 3 | 1 | 1 | 2 | 4 | 2 | 6 |
| | 205 | 6 | 0 | 2 | 4 | 5 | 5 | 8 |
| | 200 | 3 | 1 | 0 | 2 | 6 | 2 | 4 |
| Mean | 201 | 4 | 1 | 1 | 3 | 5 | 3 | 6 |
| SD | 3 | 2 | 1 | 1 | 1 | 1 | 2 | 2 |
| WP2 <i>uvrA</i> | 374 | 48 | 24 | 40 | 45 | 45 | 48 | 50 |
| | 362 | 50 | 21 | 31 | 45 | 48 | 49 | 47 |
| | 351 | 43 | 20 | 28 | 46 | 42 | 47 | 42 |
| Mean | 362 | 47 | 22 | 33 | 45 | 45 | 48 | 46 |
| SD | 12 | 4 | 2 | 6 | 1 | 3 | 1 | 4 |

* All plates were applied at 100 µL/plate.

** The positive control used was Sodium Azide for strains TA100 and TA1535, 2-Nitrofluorene for strain TA98, 9-Aminoacridine for strain TA1537, and 4-Nitroquinoline 1-oxide for strain WP2 *uvrA*.

*** The negative control used in the assay was DMSO.

SD = Standard Deviation

Positive controls in the absence of metabolic activation were shared between Main Assay and Confirmatory Assay.

As shown in the figure above, the number of revertants/plate at all concentrations of (b) (4) without metabolic activation was below or similar to the negative control for all tester strains. Interestingly, there was no or a decrease in the number of revertants/plate at 5.0 mg/plate (b) (4) in tester strains TA98, TA1535, and WP2 *uvrA*, demonstrating toxicity at the highest concentration. There was no or a decrease in the number of revertants/plate at 5.0 and 1.666 mg/plate (b) (4) in tester strains TA100 and TA1537.

The number of revertants/plate in the reverse mutation assay done with metabolic activation using (b) (4) is shown in figure 2.

**Figure 2: Reverse Mutation Assay
With Metabolic Activation**

| Strain | Controls | | Test Substance | | | | | |
|---------------------|------------|-------------|----------------------------------|-----------|-----------|-----------|-----------|-----------|
| | Positive** | Negative*** | Dosing Concentrations (mg/plate) | | | | | |
| | | | 5.0 | 1.666 | 0.555 | 0.185 | 0.061 | 0.02 |
| TA98 | 295 | 18 | 0 | 12 | 21 | 23 | 20 | 19 |
| | 316 | 23 | 0 | 7 | 18 | 17 | 21 | 18 |
| | 304 | 16 | 0 | 5 | 15 | 12 | 16 | 15 |
| Mean | 305 | 19 | 0 | 8 | 18 | 17 | 19 | 17 |
| SD | 11 | 4 | 0 | 4 | 3 | 6 | 3 | 2 |
| TA100 | 785 | 81 | 15 | 58 | 78 | 78 | 74 | 80 |
| | 796 | 87 | 10 | 52 | 70 | 65 | 78 | 73 |
| | 803 | 89 | 0 | 49 | 68 | 79 | 75 | 71 |
| Mean | 795 | 86 | 8 | 53 | 72 | 74 | 76 | 75 |
| SD | 9 | 4 | 8 | 5 | 5 | 8 | 2 | 5 |
| TA1535 | 216 | 9 | 0 | 2 | 2 | 8 | 8 | 9 |
| | 208 | 6 | 0 | 4 | 10 | 13 | 14 | 11 |
| | 214 | 10 | 0 | 2 | 9 | 11 | 12 | 12 |
| Mean | 213 | 8 | 0 | 3 | 7 | 11 | 11 | 11 |
| SD | 4 | 2 | 0 | 1 | 4 | 3 | 3 | 2 |
| TA1537 | 210 | 9 | 0 | 6 | 8 | 8 | 8 | 10 |
| | 236 | 11 | 0 | 2 | 7 | 7 | 8 | 5 |
| | 245 | 4 | 0 | 2 | 3 | 5 | 6 | 5 |
| Mean | 230 | 8 | 0 | 3 | 6 | 7 | 7 | 7 |
| SD | 18 | 4 | 0 | 2 | 3 | 2 | 1 | 3 |
| WP2 <i>uvr A</i> | 415 | 53 | 23 | 37 | 53 | 53 | 47 | 48 |
| | 426 | 52 | 12 | 40 | 45 | 52 | 54 | 55 |
| | 408 | 56 | 18 | 35 | 40 | 58 | 52 | 58 |
| Mean | 416 | 54 | 18 | 37 | 46 | 54 | 51 | 54 |
| SD | 9 | 2 | 6 | 3 | 7 | 3 | 4 | 5 |

* All plates were applied at 100 µL/plate.

** The positive control used was 2-Aminoanthracene for all strains.

*** The negative control used in the assay was DMSO.

SD = Standard Deviation

Positive controls in the presence of metabolic activation were shared between Main Assay and Confirmatory Assay.

As shown in the figure above, the number of revertants/plate at all concentrations of (b) (4) with metabolic activation was below or similar to the negative control for all tester strains. Interestingly, there was no or a decrease in the number of revertants/plate at 5.0 and 1.666 mg/plate (b) (4) in all tester strains, demonstrating toxicity at the 2 highest concentrations.

Therefore, (b) (4) did not induce mutations in any tester strain in either the presence or absence of metabolic activation and thus is negative in the Bacterial Reverse Mutation Assay.

7.2 *In Vitro* Assays in Mammalian Cells

Study title: Chromosomal Aberration Assay in Human Peripheral Blood Lymphocytes

Study no.: 10-3639-G2
 Study report location: Module 4
 Conducting laboratory and location: (b) (4)
 Date of study initiation: August 4, 2010
 GLP compliance: Yes, signature provided on September 28, 2010
 QA statement: Yes, signature provided on September 28, 2010
 Drug, lot #, and % purity: (b) (4) lot # RS-02057-3, 99.1% purity

Key Study Findings

- Human peripheral blood cells were incubated in 3.33, 10, and 30 µg/mL (b) (4) in the definitive study.
- This Chromosomal Aberration Assay was deemed valid.
- (b) (4) is negative for the induction of chromosome aberrations with and without metabolic activation in this *in vitro* chromosome aberration assay.

Methods

Cell line: Human peripheral blood from a healthy donor
 Concentrations in definitive study: 3.33, 10, and 30 µg/mL
 Basis of concentration selection: The concentrations used in the definitive study were based on the results of a range finding study. The range finding study used 0.02, 0.061, 0.185, 0.55, 1.66, and 5.0 mg/plate (b) (4) and was used to determine the cytotoxicity of (b) (4). There was toxicity at all concentrations except for 0.020 mg/plate (b) (4).
 Negative control: DMSO
 Positive control: Mitomycin C (MMC) for the non-activated system and cyclophosphamide (CP) for the activated system
 Formulation/Vehicle: The test substance is dissolved in DMSO.
 Incubation & sampling time: Human periphery blood cells (HPBCs) were exposed to the test article, (b) (4) for

5 hours at 37°C in the presence and absence of S9 metabolic activation 48 hours after the initiation of cultures. HPBCs were also exposed to (b) (4) for 21 hours at 37°C in the absence of S9 metabolic activation 48 hours after the initiation of cultures.

Study Validity

The study is considered valid because the positive and the negative controls were used appropriately, the dose selection was based accurately on a 50% reduction in the mitotic index, peripheral blood lymphocytes were used appropriately in the assay, the Sponsor's methods of evaluation of the metaphase cells were appropriate e.g. a sufficient number of metaphase cells were counted/treatment as ensured by the percentage of cells in mitosis/500 cells scored, and a minimum of 200 metaphase spreads were analyzed per treatment group for chromatid-type and chromosome-type aberrations.

Results

HPBCs were exposed to the test article, (b) (4) for 5 hours at 37°C in the presence and absence of S9 metabolic activation 48 hours after the initiation of cultures. The effect of (b) (4) on the formation of aberrations in HPBCs with and without metabolic activation is shown in figure 3.

Figure 3: Summary of Aberrations in Human Peripheral Blood Cells Exposed to Test Substance (b) (4) (Non-Activated and Activated Assays)

Non-Activated Assay

| Treatment | Mitotic Index+ | # Cells Analyzed | Total # Aberrations* | # Aberrations per Cell | % Cells with Aberrations* |
|--|----------------|------------------|----------------------|------------------------|---------------------------|
| Negative Control: DMSO | 7.0% | 200 | 1 | 0.005 | 0.5 |
| Positive Control: Mitomycin C (0.075 µg/mL) | 5.6% | 100 | 63 | 0.63 | 18 |
| Test Substance: 30 µg/mL | 4.0% | 200 | 2 | 0.01 | 1.0 |
| Test Substance: 10 µg/mL | 6.2% | 200 | 1 | 0.005 | 0.5 |
| Test Substance: 3.33 µg/mL | 6.4% | 200 | 2 | 0.01 | 1.0 |

Activated Assay

| Treatment | Mitotic Index+ | # Cells Analyzed | Total # Aberrations* | # Aberrations per Cell | % Cells with Aberrations* |
|--|----------------|------------------|----------------------|------------------------|---------------------------|
| Negative Control: DMSO | 6.2% | 200 | 1 | 0.005 | 0.5 |
| Positive Control: Cyclophosphamide (35 µg/mL) | 3.8% | 100 | 52 | 0.52 | 17 |
| Test Substance: 30 µg/mL | 4.0% | 200 | 1 | 0.005 | 0.5 |
| Test Substance: 10 µg/mL | 6.4% | 200 | 1 | 0.005 | 0.5 |
| Test Substance: 3.33 µg/mL | 6.0% | 200 | 1 | 0.005 | 0.5 |

* Not including Gaps or Polyploid cells.

+ Mitotic Index = % of cells undergoing mitosis per total cells examined.

As shown in the figure above, the total number of aberrations, the number of aberrations per cell, and the % cells with aberrations are similar to the negative control and are far below the positive controls for all concentrations of (b) (4) done with and without metabolic activation. In the non-activated assay, there were a total of 2, 1, and 2 cells with aberrations in the 3.33, 10, and 30 µg/mL groups, respectively. The 2 cells with aberrations in the 3.33 µg/mL group have an instance of chromatid gap, chromatid break, chromosome break, and polyploid cells. The 1 cell with aberrations in the 10 µg/mL group has an instance of chromatid gap, chromatid break, and polyploid cells. The 2 cells with aberrations in the 30 µg/mL group have an instance of chromosome gap and polyploid cells as well as 2 instances of chromatid breaks. In the activated assay, there was a total number of 1 cell with aberrations in each dose group. The 1 cell with aberrations in the 3.33 µg/mL group has an instance of chromosome gap and chromosome break as well as 2 instances of polyploid cells. The 1 cell with aberrations in the 10 µg/mL group has an instance of deletion and 3 instances of polyploid cells. The 1 cell with aberrations in the 30 µg/mL group has an instance of chromosome gap, chromatid break, and polyploid cells.

HPBCs were also exposed to (b) (4) for 21 hours at 37°C in the absence of S9 metabolic activation 48 hours after the initiation of cultures. The effect of (b) (4) on the formation of aberrations in HPBCs without metabolic activation is shown in figure 4.

Figure 4: Summary of Aberrations in Human Peripheral Blood Cells Exposed to Test Substance (b) (4) (Non-Activated, Confirmatory Assay)

Non-Activated Assay

| Treatment | Mitotic Index+ | # Cells Analyzed | Total # Aberrations* | # Aberrations per Cell | % Cells with Aberrations* |
|--|----------------|------------------|----------------------|------------------------|---------------------------|
| Negative Control: DMSO | 6.4% | 200 | 0 | 0.0 | 0.0 |
| Positive Control: Mitomycin C (0.075 µg/mL) | 5.6% | 100 | 63 | 0.63 | 18 |
| Test Substance: 30 µg/mL | 3.6% | 200 | 1 | 0.005 | 0.5 |
| Test Substance: 10 µg/mL | 6.0% | 200 | 1 | 0.005 | 0.5 |
| Test Substance: 3.33 µg/mL | 6.0% | 200 | 1 | 0.005 | 0.5 |

* Not including Gaps or Polyploid cells.

+ Mitotic Index = % of cells undergoing mitosis per total cells examined.

As shown in the figure above, the total number of aberrations, the number of aberrations per cell, and the % cells with aberrations are similar to the negative control and are far below the positive controls for all concentrations of (b) (4) done without metabolic activation. In the non-activated assay, there was a total of 1 cell with aberrations in each dose group. The 1 cell with aberrations in the 3.33 µg/mL group has an instance of chromosome break as well as 2 instances of chromosome gap. The 1 cell with aberrations in the 10 µg/mL group has an instance of deletion. The 1 cell with aberrations in the 30 µg/mL group has an instance of chromosome gap and chromosome break as well as 2 instances of polyploid cells.

In conclusion, (b) (4) is negative for the induction of chromosome aberrations with and without metabolic activation in this *in vitro* chromosome aberration assay.

7.3 *In Vivo* Clastogenicity Assay in Rodent (Micronucleus Assay)

The Sponsor did not submit a Micronucleus Assay in this NDA.

7.4 Other Genetic Toxicity Studies

None.

8 Carcinogenicity

The Sponsor did not submit carcinogenicity studies in this NDA. From the approved label for morphine sulfate oral solution (NDA 22195), “[s]tudies in animals to evaluate the carcinogenic potential of morphine sulfate have not been conducted”. These studies were not required for the product as per current OND policy for 505(b)(2) drug applications where the proposed drug product does not exceed the exposures in the referenced drug product given similar routes of administration and patient population to be exposed.

9 Reproductive and Developmental Toxicology

The following information on the reproductive and developmental toxicology of morphine sulfate can be found in the approved label for morphine sulfate oral solution (NDA 22195):

Teratogenic Effects (Pregnancy Category C)

Animal reproduction studies have not been conducted with morphine sulfate. It is also not known whether morphine sulfate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Only give morphine sulfate to a pregnant woman if clearly needed.

In humans, the frequency of congenital anomalies has been reported to be no greater than expected among the children of 70 women who were treated with morphine sulfate during the first four months of pregnancy or in 448 women treated with this drug anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine sulfate and other medication during the first trimester of pregnancy.

Several literature reports indicate that morphine sulfate administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic to those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of maternal toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. Morphine sulfate was not a significant teratogen in the rat at exposure levels significantly beyond that normally encountered in clinical practice. **In one study however, decreased litter size and viability were observed in the offspring of male rats administered morphine at doses approximately 3-fold the maximum recommended human daily dose (MRHDD) for 10 days prior to mating.** In two studies performed in the rabbit, no evidence of teratogenicity was reported at subcutaneous doses up to 100 mg/kg.

Nonteratogenic Effects

Controlled studies of chronic *in utero* morphine exposure in pregnant women have not been conducted. Infants born to mothers who have taken opioids chronically may exhibit withdrawal symptoms following birth, reversible reduction in brain volume, small size, decreased ventilatory response to CO₂ and increased risk of sudden infant death syndrome.

Manifestations of the neonatal withdrawal syndrome include irritability, hyperactivity, abnormal sleep pattern, high-pitched cry, tremor, vomiting, diarrhea, weight loss, and failure to gain weight. The time and amount of the mother's last dose and the rate of elimination of the drug from the newborn may affect the onset, duration, and severity of the disorder. When severe symptoms occur, pharmacologic intervention may be required.

Published literature has reported that exposure to morphine sulfate during pregnancy is associated with reduction in growth and a host of behavioral abnormalities in the offspring of animals. Morphine sulfate treatment during gestational periods of organogenesis in rats, hamsters, guinea pigs and rabbits resulted in the following treatment-related embryotoxicity and neonatal toxicity in one or more studies: decreased litter size, embryo-fetal viability, fetal and neonatal body weights, absolute brain and cerebellar weights, lengths or widths at birth and during the neonatal period, delayed motor and sexual maturation, and increased neonatal mortality, cyanosis and hypothermia. Decreased fertility in female offspring, and decreased plasma and testicular levels of luteinizing hormone and testosterone, decreased testes weights, seminiferous tubule shrinkage, germinal cell aplasia, and decreased spermatogenesis in male offspring were also observed. Behavioral abnormalities resulting from chronic morphine sulfate exposure of fetal animals included altered reflex and motor skill development, mild withdrawal, and altered responsiveness to morphine sulfate persisting into adulthood.

As noted in the labeling recommendations at the beginning of the review, this red statement in the label above must be corrected for this drug product. The statement should also be corrected in the referenced product labeling, as there is no maximum daily dose for either morphine drug product. Review of the literature for morphine suggests that the statement is likely based on data reported by Cicero et al.; however, the details as worded in the reference label are not correct. The study administered morphine (25 mg/kg, IP) to male rats one day prior to mating, not 10 days prior to mating.

9.1 Fertility and Early Embryonic Development

The Sponsor did not submit any fertility and early embryonic development studies in this NDA. However, information regarding impairment of fertility can be found in the approved label for morphine sulfate oral solution (NDA 22195):

A literature report indicated that morphine sulfate impairs fertility in rats. In a fertility study in which male rats were administered morphine sulfate subcutaneous prior to mating (up to 30 mg/kg twice daily) and during mating (20 mg/kg twice daily) with untreated females, a number of adverse reproductive effects were observed. These included reduction in total pregnancies, higher incidence of pseudopregnancies, and reduction in implantation sites.

9.2 Embryonic Fetal Development

The Sponsor did not submit any embryonic-fetal development studies in this NDA. See above information for reference drug labeling.

9.3 Prenatal and Postnatal Development

The Sponsor did not submit any prenatal and postnatal development studies in this NDA. See above information for reference drug labeling.

10 Special Toxicology Studies

The Sponsor did not submit any special toxicology studies in this NDA.

11 Integrated Summary and Safety Evaluation

The drug product subject in this NDA is morphine sulfate oral solution, 20 mg/mL, from Lannett Holdings, Inc. The Sponsor is relying upon the Agency's previous finding of safety and efficacy for morphine sulfate oral solution (NDA 22195). From a nonclinical pharmacology toxicology perspective, there are no safety concerns and this NDA is recommended for approval.

12 Appendix/Attachments

References

Cicero, T.J., Nock, B., O'Connor, L., Adams, M., and Meyer, E.R. 1995. Adverse effects of paternal opiate exposure on offspring development and sensitivity to morphine-induced analgesia. *JPET* 273:386-392.

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FAO Nutrition Meetings; Report Series No. 40A,B,C; WHO Food Additives Series 67.29 on propylparaben (<http://www.inchem.org/documents/jecfa/jecmono/40abcj06.htm>).

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WHO Food Additives Series 18 on sodium benzoate (<http://www.inchem.org/documents/jecfa/jecmono/v18je04.htm>).

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/s/

CARLIC K HUYNH
11/03/2010

RICHARD D MELLON
11/04/2010

I concur. From the nonclinical pharmacology toxicology perspective, NDA 201517 may be approved with recommended labeling.

PHARMACOLOGY/TOXICOLOGY NDA FILEABILITY CHECKLIST

NDA/BLA Number: 201-517 **Applicant:** Lannett Holdings, Inc. **Stamp Date:** March 1, 2010

Drug Name: Morphine Sulfate Oral Solution **NDA/BLA Type:** 505(b)(2) DAAP/OND/CDER/FDA

On **initial** overview of the NDA application for Refuse to File (RTF): **Fileable**

| | Parameters | Yes | No | Comment |
|---|--|------------|-----------|--|
| 1 | On its face, is the pharmacology section of the NDA/BLA organized (in accord with 21 CFR 314 and current guidelines for format and content) in a manner to allow substantive review to begin? | X | | |
| 2 | Is the pharmacology/toxicology section of the NDA/BLA indexed and paginated in a manner allowing substantive review to begin? | X | | |
| 3 | On its face, is the pharmacology/toxicology section of the NDA/BLA legible so that substantive review can begin? | X | | |
| 4 | Are all required (*) and requested IND studies (in accord with 505(b1) and (b2) including referenced literature) completed and submitted in this NDA (carcinogenicity*, mutagenicity*, teratogenicity*, effects on fertility*, juvenile studies, acute and repeat dose adult animal studies*, maximum tolerated dose determination, dermal irritancy, ocular irritancy, photo co-carcinogenicity, animal pharmacokinetic studies, safety pharmacology, etc)? | | X | The Sponsor did not conduct any new nonclinical studies. The submitted 505(b)(2) New Drug Application (NDA) relies upon the Agency's previous finding of safety for Roxane's Morphine Sulfate oral solution for nonclinical support. The Sponsor did not include the requested literature assessment or justification for the safety of the excipients, nor justification for the safety of the (b)(4) impurity, as requested at the time of PreNDA. |
| 5 | If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies been conducted with the appropriate formulation? | | | Not applicable. At the time of the filing review, the Sponsor is proposing to rely upon the published scientific literature as well as the Agency's previous findings of safety for Roxane's Morphine Sulfate oral solution for toxicology studies. |

| | | | |
|----|--|---|--|
| 6 | Is (are) the excipient(s) appropriately qualified (including interaction between the excipients if applicable)? | X | This NDA contains excipients that are found in the FDA IIG. Examination of the amounts of the excipients in relation to the maximum daily dose was requested but not provided. Therefore, this will be requested in the 74-day letter and become a review issue. |
| 7 | On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the sponsor <u>submitted</u> a rationale to justify the alternative route? | | Not applicable. The Sponsor has not conducted any animal studies in support of this NDA. |
| 8 | Has the sponsor <u>submitted</u> a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) <u>or</u> an explanation for any significant deviations? | | Not applicable. The Sponsor has not conducted any animal studies in support of this NDA. |
| 9 | Has the sponsor submitted all special studies/ data requested by the Division during pre-submission discussions with the sponsor? | X | The Sponsor did not justify the safety of the excipients for an opioid tolerant individual, nor did they justify the safety of the (b) (4) specifications. |
| 10 | Are the proposed labeling sections relative to pharmacology, reproductive toxicology, and carcinogenicity appropriate (including human dose multiples expressed in either mg/m ² or comparative serum/plasma levels) and in accordance with 201.57? | X | The referenced labels do not contain exposure margins; therefore, they will be incorporated into the label during this review cycle based on the dosage form. This need not be a filing issue. |
| 11 | Has the sponsor submitted any toxicity data to address impurities, new excipients, leachables, etc. issues. | X | The Sponsor has submitted specifications for the drug substance and drug product in module 3. Adequate justification for the specification of (b) (4) has not been provided. The specifications for (b) (4) will need to be discussed during review as there is a difference in opinion regarding the maximum daily dose for these products. |
| 12 | Has the sponsor addressed any abuse potential issues in the submission? | X | The Sponsor provides discussion on the addiction potential of morphine sulfate. The information in the label will be the |

| | | | |
|----|---|---|---|
| | | | same as in Roxane's Morphine Sulfate oral solution label. |
| 13 | If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted? | | Not applicable. This is a 505(b)(2) New Drug Application (NDA) submitted to support a Rx. |
| 14 | From a pharmacology/ toxicology perspective, is the NDA/BLA fileable? If ``no`` please state below why it is not. | X | FILING ISSUES: The Agency considers the above deficiencies to be review issues and not necessarily filing issues. |

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? Yes.

Comments to Sponsor:

Following the filing review of you NDA submission, we have identified the following potential approval issues:

1. Your NDA does not contain adequate information to justify the safety of the drug product formulation. Specifically, your NDA must include justification for the safety of each excipient should individuals consume up to 2 grams per day of morphine via this formulation. Please refer to the FDA Guidance for Industry: Nonclinical Studies for Safety Evaluation of Pharmaceutical Excipients (May 2005) which is available on the CDER web page at the following

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

2. Your proposed drug substance specification for (b) (4), an impurity that contains an (b) (4) structural alert for genotoxicity, is not adequately justified for safety. As noted in the preNDA meeting minutes, impurities with structural alerts for genotoxicity must be reduced to NMT (b) (4) mcg/day or adequate safety qualification must be provided. Adequate safety qualification for this impurity must include a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

3. You have not provided adequate justification for the safety of the container closure system in terms of the safety assessment of potential leachables extractables into the drug product solution. The safety assessment should be specifically discussed in module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission.

Reviewing Pharmacologist: _____
Date

Team Leader: _____
Date

| Application Type/Number | Submission Type/Number | Submitter Name | Product Name |
|-------------------------|------------------------|----------------------|---|
| NDA-201517 | ORIG-1 | LANNETT HOLDINGS INC | morphine sulfate oral solution 20 mg/mL |

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/s/

CARLIC K HUYNH
04/26/2010

RICHARD D MELLON
04/26/2010