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RESEARCH**

APPLICATION NUMBER:
201517Orig1s000

MEDICAL REVIEW(S)

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Sharon Hertz, M.D.
Subject	Deputy Division Director Summary Review
NDA/BLA #	201517/000
Supplement #	
Applicant Name	Lannett Holdings, Inc.
Date of Submission	March 1, 2010
PDUFA Goal Date	January 1, 2011
Proprietary Name / Established (USAN) Name	NA/Morphine Sulfate Oral Solution
Dosage Forms / Strength	Oral solution/ 100 mg per 5 mL (20 mg/mL)
Proposed Indication(s)	For the management of moderate to severe acute and chronic pain in opioid-tolerant patients.
Action/Recommended Action for NME:	Complete Response

Material Reviewed/Consulted	
OND Action Package, including:	
Pharmacology Toxicology Review	Carlic Huynh, Ph.D.; R. Daniel Mellon, Ph.D.
CMC Review/OBP Review	Arthur B. Shaw, Ph.D.; Prasad Peri, Ph.D.
Microbiology Review	Bryan S. Riley, Ph.D.; Stephen E. Langille, Ph.D.
Clinical Pharmacology Review	Sheetal Agarwal, Ph.D.; Suresh Doddapaneni, Ph.D.
DDMAC	Mathilda K. Fienkeng; Twyla N. Thompson
DSI	N/A
CDTL Review	Sharon H. Hertz, M.D.
OSE/DMEPA	Anne Crandall, Pharm.D., Melina Griffis, R.Ph.; Carol Holquist, R.Ph.
OSE/DDRE	N/A
OSE/DRISK	Steve L. Morin, Ph.D.; LaShawn Griffiths, R.N., MSHS-PH, B.S.N.; Barbara Fuller, R.N., M.S.N., CWOCN; Claudia Karwoski, Pharm.D.
Controlled Substance Staff	Alicja Lerner, M.D., Ph.D., Lori Love, M.D., Ph.D., Michael Klein, Ph.D.

OND Office of New Drugs
DDMAC Division of Drug Marketing, Advertising and Communication
OSE Office of Surveillance and Epidemiology
DMEPA Division of Medication Errors Prevention
DSI Division of Scientific Investigations
CDTL Cross Discipline Team Leader

Signatory Authority Review Template

1. Introduction

The applicant has submitted one pharmacokinetic study and is relying on the Agency's prior findings of safety and efficacy for Morphine Sulfate Oral Solution (Roxane, NDA 22-195), 20 mg/ 5 mL to support this 505(b)(2) application.

2. 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 to support continued marketing of these products. The current application is for a product that has been marketed, although previously unapproved, morphine sulfate oral solution.

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 one clinical pharmacology study. 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 oral solution, NDA 22-195, Roxane Laboratories, Inc.

For immediate-release morphine sulfate products, such as the subject of this NDA, 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 product's pharmacokinetic characteristics and how these relate to the product referenced in the NDA. In this NDA there is also a drug-related area of concern based on the presence of an (b) (4) impurity with a structural alert for mutagenicity, a finding common to thebaine-based opioids. The substance is (b) (4) which can be present as an impurity in the drug substance and as a degradant in the drug product. Based on the results of qualifying nonclinical studies, this impurity has been found not to be genotoxic and can therefore be controlled as an ordinary impurity.

The applicant had requested a priority review stating that the product was medically necessary and needed to treat a serious condition. However, morphine sulfate oral solution 100 mg per 5

mL (20 mg/mL), Roxane, NDA 22-195, S-002, was approved on January 25, 2010, prior to the submission of the current application. Furthermore, while morphine sulfate oral solution 100 mg per 5 mL (20 mg/mL) had been in a shortage situation, Roxane was able to meet the demands of the market, and the product was no longer in short supply at the time NDA 201-517 was submitted.

3. CMC/Device

According to Dr. Shaw's reviews, the drug substance is supplied by (b) (4) under DMF (b) (4). In the initial review, there were concerns regarding the starting material and (b) (4) submitted another DMF, (b) (4) covering preparation of the starting material. A list of potential process impurities was provided in the application. A DMF deficiency letter for DMF (b) (4) was filed in DARRTS on September 14, 2010 and the holder notified again on December 2, 2010. An adequate response to these deficiencies has not been received. The manufacturing site was found acceptable based on CGMP standards on March 10, 2010. The applicant's specifications include all of the USP tests and additional tests for related substances and residual solvents. The applicant relies on validation information in the DMF for these additional tests and has also performed verification experiments to show that these tests are valid when performed by the applicant. All impurities, including the potentially genotoxic impurity, (b) (4), are well-controlled. The results of batch analysis (three batches) are satisfactory.

The drug product is an oral liquid manufactured by Cody Laboratories. The excipients are compendial.

The specifications for the level of (b) (4) an impurity in the drug substance and drug product and also an (b) (4) NMT (b) (4) was found acceptable.

Stability data was submitted for six batches of drug product, but only one batch was tested in all three packaging configurations. Two batches were out of specification (OOS) at 18 months for sodium benzoate, (b) (4). An unqualified degradant eluting at RRT (b) (4) was found to increase over time. The applicant proposed an expiration date of 18 months. Statistical analysis of the stability data for this impurity supports an expiry of only (b) (4) months using an acceptance criterion of NMT (b) (4). Statistical analysis of the stability data for sodium benzoate support an expiry of only (b) (4) months, based on an acceptance criterion of NLT (b) (4). The antimicrobial effectiveness testing proposed by the applicant for values of preservative between (b) (4) is not applicable for determining an expiration date.

The applicant has included an oral dosing syringe to ensure accurate dosing by patients and caregivers.

Additional outstanding issues that should be addressed, but would not preclude approval are described in Dr. Shaw's review as follows:

1. Provide the source and qualification procedures for the (b) (4) reference standards.
2. Submit a revision to Section 3.2.P.5.6 to include the revised acceptance criterion for (b) (4).
3. Explain why the (b) (4) for the Oral Doser Barrel is different for the 30 mL package size (b) (4) from the (b) (4) for the 120 mL and 240 mL package sizes (b) (4).
4. Explain why the CFR citations for the Colorant used in the Oral Dosers include sections that are not usually associated with colorants for plastics:
176.170 Components of paper and paperboard in contact with aqueous and fatty foods
175.105 Adhesives
175.300 Resinous and polymeric coatings
175.320 Resinous and polymeric coatings for polyolefin films

Lannett Company, Inc. is the site of final testing prior to release of the drug product. Inspection of Lannett found significant GMP violations related to inadequate quality assurance, process validation procedures and practices, and inadequate investigations for out of specification results. The FDA District Office recommended a Withhold on November 10, 2010 and the Office of Compliance has agreed with this recommendation.

I concur with the conclusions reached by the chemistry reviewer regarding the recommendation of complete response due to problems identified at Lannett Holdings, Inc. and pending resolution of the deficiencies in DMF (b) (4) for the morphine sulfate drug substance.

4. Nonclinical Pharmacology/Toxicology

The applicant has referenced the Agency's prior findings of safety and efficacy for the referenced product. No new nonclinical studies were conducted as there are no novel excipients not found in the Inactive Ingredients Guide, nor excipients at levels that require additional qualification. Initially, the justification for the proposed acceptance criterion of NMT (b) (4) for the level of (b) (4) impurity in the drug substance and drug product was unacceptable, since it is potentially genotoxic. In response, the applicant submitted final study reports for an Ames assay and for a Chromosomal Aberration Assay that were negative for mutagenicity and clastogenicity. Therefore its acceptance criterion was set as an ordinary impurity at NMT (b) (4).

Insufficient information was submitted for the possible leachables and extractables for the container closure system. The applicant did submit in vitro biological test USP <87>, which is applicable, but an extraction study was never done. Therefore, the applicant was asked to submit the appropriate CFR citations for indirect food contact material. Review of the response to this request found that the components of the container closure system were appropriately cited in the CFR as indirect food additives.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

The applicant has submitted one pharmacokinetic study in support of this application. The study was intended to assess the relative bioavailability of the product compared to the listed product referenced in this 505(b)(2) application, Morphine Sulfate Oral Solution (Roxane, NDA 22-195), 20 mg/ 5 mL, and to assess the effect of food. The 3-period crossover study in naltrexone-blocked healthy volunteers demonstrated bioequivalence to the referenced drug under fasting conditions and a modest food effect characterized by a 25% lower C_{max}, a 16% higher AUC and an approximately 40 minute delay in peak absorption. These food effects are not expected to have great clinical impact and do not necessitate dosing instructions depending on fasting or fed status.

As noted in Dr. Agarwal's review, a DSI inspection was not requested as the product qualifies for a biowaiver.

I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer that there are no outstanding clinical pharmacology issues that preclude approval.

6. Product Quality Microbiology

A microbiology review by Dr. Riley found that the applicant had not submitted test methods and acceptance criteria to demonstrate that the product is free of *Burkholderia cepacia* and a request was sent to the applicant. Were this the only outstanding issue, a post marketing commitment could have been requested of the applicant, as the testing for and development of acceptance criteria for this bacterium is relatively new. However, as the application cannot be approved at this time, the lack of adequate test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia* is an outstanding deficiency that should be addressed if the applicant chooses to pursue a second review cycle for this product. The following was requested of the applicant:

Provide test methods and acceptance criteria to demonstrate the product is free of the objectionable microorganism *Burkholderia cepacia*. We recommend that potential sources are examined and sampled as process controls, and these may include raw materials and the manufacturing environment. A risk assessment for this species in the product and raw materials is recommended to develop sampling procedures and acceptance criteria. Your test method should be validated and a discussion of those methods should be provided. Test methods validation should address multiple strains of the species and cells that are acclimated to the environments (e.g., warm or cold water) that may be tested.

The applicant submitted a response on December 7, 2010. However, the application cannot be approved until the cGMP deficiencies and the DMF deficiencies are corrected, so the review of this submission will be completed upon resubmission of the application.

I concur with the conclusions reached by the product quality microbiology reviewer there are no outstanding product quality microbiology or sterility issues that, on their own, could not have been addressed as a postmarketing requirement and that would have that precluded approval.

7. Clinical/Statistical-Efficacy

No new clinical safety or efficacy data was submitted in support of this application. The applicant is relying on the Agency's prior findings for morphine sulfate oral solution, NDA 22-195. The clinical pharmacology study was conducted using the opioid antagonist naltrexone for the safety of the subjects so no additional safety information was obtained from these studies.

8. Safety

No new clinical safety or efficacy data was submitted in support of this application. The applicant is relying on the Agency's prior findings for morphine sulfate oral solution, NDA 22-195. The clinical pharmacology study was conducted using the opioid antagonist naltrexone for the safety of the subjects so no additional safety information was obtained from these studies.

To improve the safety and accuracy of dosing, an oral dosing syringe was requested by FDA and added by the applicant. In addition, while this NDA contains only one concentration of morphine oral solution, there are other morphine oral solutions marketed with different concentrations (NDA (b) (4), 20 mg per 5 mL and 10 mg per 5 mL). Therefore, the applicant was told that a medication guide and medication guide only REMS were required to ensure that patients were alerted to the need for care when administering a dose of this product. Labeling recommendations include a boxed warning to alert prescribers to the risk for medication errors as follows:



In addition, the indication for this product, for the management of moderate to severe acute and chronic pain in opioid-tolerant patients, reflects that the 100 mg per 5 mL (20 mg/mL) concentration of morphine sulfate poses greater risks for overdose and should be reserved for use in patients who require doses that cannot be adequately accommodated with 20 mg per 5 mL and 10 mg per 5 mL concentration oral solutions.

9. Advisory Committee Meeting

An advisory committee meeting was not held for this NDA. Morphine sulfate is a long established analgesic and the formulation proposed does not present any novel issues or concerns.

10. Pediatrics

As this application does not represent a change in active ingredient, dosage form, route of administration, indication or dosing regimen, the requirements under the Pediatric Research Equity Act were not applicable.

11. Other Relevant Regulatory Issues

The Controlled Substances Staff was consulted and had the following recommendation:

Conduct routine pharmacovigilance of this drug and report all cases of potential abuse, misuse or overdose (intentional or unintentional and leading to death). Submit a summary of analysis in two years of all available data (including DAWN and AERS) from the US market for this formulation of morphine sulfate oral solution and relevant information on drug diversion.

The medication guide-only REMS has been submitted and comments have been sent to the applicant. The REMS will need to be reviewed upon resubmission of the application.

12. Labeling

See Section 8, Safety. The labeling and medication guide has been reviewed by DRISK, DMEPA and DDMAC. Recommended changes to the package insert, medication guide and container and carton labels were forwarded to the applicant, however, final agreement has not yet been reached.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: Complete response

- Risk Benefit Assessment

While there is adequate evidence for efficacy and safety of Morphine Oral Solution for use in adults, the DMF deficiency for the drug substance and GMP deficiencies at Lannett Company, Inc. preclude approval until the manufacturing deficiencies can be resolved.

- Recommendation for Postmarketing Risk Management Activities

A medication guide-only REMS is required.

- Recommendation for other Postmarketing Study Commitments

None at this time.

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/s/

SHARON H HERTZ
12/10/2010