CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

201517Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	201517	*Submission Date(s)*	March 1, 2010
Brand Name		Morphine Sulfate Oral Solution	
Generic Name		Morphine Sulfate Oral Solution	
Reviewer		Sheetal Agarwal, Ph.D.	
Team Leader		Suresh Doddapaneni, Ph.D.	
OCP Division		Division of Clinical Pharmacology-2	
OND Division		Division of Anesthesia and Analgesia	
Sponsor		Lannett Company, Inc.	
Submission Type; Code		505 (b) (2)	S
Formulation; Strength(s)		Morphine Sulfate Oral Solution, 20 mg/mL	
Indication		Relief of moderate to severe acute and chronic pain where an opioid analgesic is appropriate	
Proposed Dosing Regimen		Morphine Sulfate Oral Solution: 10 to 20 mg every 4 h as needed.	

TABLE OF CONTENTS

TABLE OF FIGURES AND TABLES

1. EXECUTIVE SUMMARY

1.1 Recommendation

From the viewpoint of the Office of Clinical Pharmacology, original NDA 201517 for Morphine Sulfate Oral Solution, 20mg/mL submitted on March 1, 2010 is acceptable provided that the Agency and the sponsor come to a mutual agreement regarding the language in the package insert.

1.2 Phase 4 Commitments

From the Clinical Pharmacology perspective, no phase 4 commitment is applicable to this NDA.

1.3 Summary of Important Clinical Pharmacology Findings

This NDA for an unapproved, marketed Morphine Sulfate Oral Solution, 20 mg / mL was submitted by Lannett Holdings Inc., as a 505 (b) (2) application referring to the previous findings of safety and efficacy of Morphine Sulfate 20mg/5mLsolution approved on March 17, 2008 (NDA 22195; Roxane Laboratories). The Agency and the sponsor met for a pre-NDA meeting on July 1, 2009 at which time the only approved Morphine Sulfate Oral Solutions were 20mg/5mLsolution and 10mg/5mL solution under NDA 22195. Agreement was reached between the Agency and Lannett that a bioequivalence study comparing their product with Roxane's 20mg/5mL product would be the only study required for submission of the NDA. Subsequent to this pre-NDA meeting and just prior to this NDA submission, Roxane's 20mg/mL solution was approved on January 25, 2010. Therefore, to support approval of this NDA, the sponsor conducted a single Clinical Pharmacology study (**Study MRN-P9-644**) that tested bioequivalence (BE) of the Test product to the Reference under fasted conditions and also evaluated the effect of a high fat, high calorie breakfast on the exposure of the Test product in this study. Per the prior agreement between the Agency and the Sponsor, no other new clinical or clinical pharmacology information was submitted. For all other Clinical Pharmacology related aspects (pharmacokinetics in renal and hepatic impairment patients, elderly patients and drug-drug interactions etc., Lannett is relying on previous findings from Roxane's NDA 22195

Study MRN-P9-644 tested BE of 1 mL of Morphine Sulfate 20mg/mL (Test) to 5 mL of Morphine Sulfate 20mg/5mL(Reference) in 33 naltrexone blocked healthy male and female volunteers under fasting conditions. Naltrexone (opioid antagonist) was administered before morphine sulfate solution administration to block opioid effects in opioid-naïve healthy volunteers. In addition, the study also evaluated effect of a high fat, high calorie breakfast on the PK of 1 mL of Morphine Sulfate 20mg/mL solution. The Test was bioequivalent to the Reference in terms of both Cmax and AUC meeting the 90% confidence intervals limits of 80-125%. In the presence of food, Cmax of morphine was reduced by 25% while AUC was increased by 15%; these effects are not considered clinically significant. DSI inspection of this study was deemed not necessary in light of

the fact that at the time of NDA submission, a pharmaceutical equivalent of the reference was available and this product would have qualified for a biowaiver with appropriate justification. Overall, this NDA has adequate Clinical Pharmacology information and there are no significant Clinical Pharmacology issues that would preclude its approval.

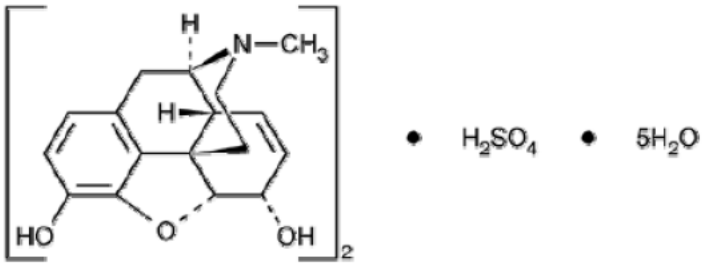
2. CLINICAL PHARMACOLOGY REVIEW

2.1 General Attributes/Background:

2.1.1 What are the highlights of the chemistry and physico-chemical properties of the drug substance and formulation of the drug product?

Drug Substance: Morphine sulfate: Soluble in water and freely soluble in hot water, one gram dissolves in 15.5 mL water at 25 ºC and 0.7 mL water at 80 ºC. It is slightly soluble in alcohol but more so in hot alcohol, 240 mL alcohol at 60 ºC and insoluble in chloroform and in ether. It has a pKa of 7.9. The structural formula is shown in Figure 1 below:

Figure 1: Structure of Morphine Sulfate
Molecular Formula: (C17H19NO3)2·H2SO4·5H2O; *Molecular Weight:* 758.83



Drug Product: Table 1 below shows the qualitative and quantitative composition of the final formulation for Morphine Sulfate Oral Solution.

Table 1: Composition of 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			
Sodium Benzoate, NF			
Sorbitol USP			
Glycerin, USP			
Citric Acid Anhydrous, USP			
Edetate Disodium Dihydrate, USP			
Purified Water, USP			

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Mechanism of Action: Morphine is a pure opioid agonist relatively selective for the mu receptor. It is mainly used as analgesic to control moderate to severe pain.

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

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Dosage: 10 to 20 mg every 4 h as needed.

Route of Administration: Oral.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

To support approval of this NDA, the sponsor conducted a single Clinical Pharmacology study (**Study MRN-P9-644**) that tested bioequivalence (BE) of the Test product to the Reference under fasted conditions and evaluated effect of a high fat, high calorie breakfast on the exposure of the Test product. No new studies related to any other aspect of Clinical/Clinical Pharmacology has been submitted by the sponsor as per the agreement reached at the pre-NDA meeting (see meeting minutes dated July 27, 2009 for additional details). The Sponsor is relying on Agency's previous findings of safety and efficacy of the Reference for all other clinical pharmacology aspects.

Title of the Study: Study No. MRN-P9-644: Single Dose Crossover Comparative Bioavailability Study of Two Oral Solutions of Morphine 20mg/mL vs 20mg/5mLIn Healthy Male and Female Volunteers Following the Administration of a 20 mg Dose / Fasting and Fed States

Study Design: Single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover study in healthy male and female volunteers. Naltrexone (opioid antagonist) was administered before morphine sulfate solution administration to avoid unpleasant, opioid effects in opioid-naïve healthy volunteers. It is known that naltrexone does not interfere with the PK of opioids.

2.2.2 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, morphine and its known active metabolite (morphine-6-glucuronide) were measured in plasma and analyzed.

2.2.3 What are the PK characteristics of the drug and its major metabolite?

2.2.3.1 What are the single dose and multiple dose PK parameters?

Single dose PK of morphine and morphine-6-glucuronide (M6G; both the major and active metabolite) was characterized in the pivotal BE study MRN-P9-644 and PK parameters obtained are shown in Table 2 below. The mean PK parameters for both morphine and M6G are listed in Table 5. The mean Cmax values for morphine and M6G were 18.784 ng/mL and 88.00 ng/mL respectively. The median Tmax values for morphine and M6G were 0.58 h and 1.33 h respectively.

Table 2: PK Parameters of Morphine and M6G After Single Dose Administration (1 mL of Morphine Sulfate Solution 20 mg/mL)

	Cmax (ng/mL)	Tmax (h)	AUCt (ng.h/mL)	AUCinf	Thalf	Kel
Morphine	19 $\pm$ 7	0.58 (0.25-4)	53 $\pm$ 19	60 $\pm$ 23	6 $\pm$ 2	0.14 $\pm$ 0.05
M6G	88 $\pm$ 21	1.33 (0.75-4)	3441±83	394 ± 81	5 $\pm$ 2	0.16 $\pm$ 0.07

2.3 Intrinsic Factors

2.3.1 What is the pediatric plan?

Since the number of pediatric patients requiring 100mg/5mL morphine sulfate medication is small and because necessary studies are impossible or highly impractical, pediatric study requirements will be waived. This is in line with action taken with a similar morphine sulfate solution product (Morphine Sulfate Oral Solution 100mg/5mL, NDA 22-195 for Roxane).

2.4 General Biopharmaceutics

2.4.1 What is the relative bioavailability of the proposed to-be-marketed formulation to the Reference?

Study MRN-P9-644 evaluated BE of proposed-to-be-marketed formulation (Test) to Reference. The study was a single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover design in 36 healthy male and female subjects. The study demonstrated that the Test Formulation is bioequivalent to the Reference Formulation with respect to both the Cmax and AUCt values for the parent moiety, morphine as well as the major/active metabolite morphine-6-glucuronide, under fasting conditions. In addition, similar incidence of adverse events was observed in both Test and Reference groups (61% in Test, fasted vs. 55% in Reference, fasted). However, since naltrexone blockade was provided to the volunteers, meaningful safety information is not expected from this study.

The following treatments were to be administered under fasting or fed conditions:
Test : 20 mg Morphine sulfate concentrate (1 x 1 mL of 20mg/mL oral solution)
Reference: 20 mg Morphine sulfate (1 x 5 mL of 20mg/5mLoral solution)

Plasma was sampled for 15 h after each dose and washout period between treatments was 7 days. To provide blockade of the pharmacological effects of morphine, a single 50 mg dose of naltrexone (1 x 50 mg tablet) was to be administered approximately 1 hour prior to morphine administration.

BE analysis and PK parameters obtained under fasted conditions are discussed in this section. PK parameters obtained under fed conditions are discussed in Section 2.5.3 (food effect).

Morphine Test fasted vs. Reference fasted: Thirty (30) subjects were included in the statistical analysis. The mean Cmax values were 18.784 ng/mL and 19.849 ng/mL respectively for the Test and Reference formulations. The Test to Reference Cmax ratio of geometric LSmeans was 93.53% (90% CI: 82.36 to 106.21%). The mean AUCt values were 52.683 ng·h/mL and 55.288 ng·h/mL respectively for the Test and Reference formulations. The Test to Reference AUCt ratio of geometric LSmeans was 91.37% (90% CI: 83.93 to 99.46%). The median Tmax was 0.58 h for both the Test and Reference formulations. These results demonstrate that Test is bioequivalent to the Reference with respect to the parent moiety, morphine (Tables 3 and 4 and Figure 2).

Table 3: PK Parameters for Morphine (Test fast vs Reference fast comparison)

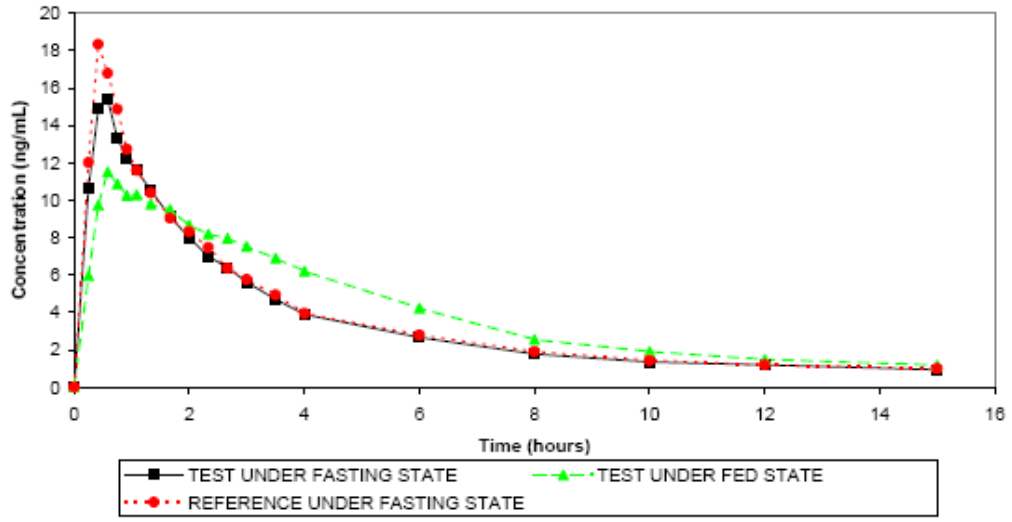
PARAMETER	TEST (FAST)		REFERENCE (FAST)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	18.784	38.9	19.849	43.0
ln (C_{max})	2.8381	17.0	2.8872	16.4
T_{max} (hours) *	0.58	94.3	0.58	54.1
AUC_T (ng·h/mL)	52.683	35.3	55.288	33.1
ln (AUC_T)	3.8907	10.9	3.9604	8.3
AUC_∞ (ng·h/mL)	59.904	38.3	61.730	31.3
ln (AUC_∞)	4.0158	10.5	4.0756	7.7

Table 4: BE Analysis for Morphine (Test fast vs Reference fast comparison)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (FAST)	REFERENCE (FAST)		LOWER	UPPER
C_{max}	30.4	17.020	18.198	93.53	82.36	106.21
AUC_T	20.0	48.423	52.999	91.37	83.93	99.46
AUC_∞	20.3	55.073	59.363	92.77	85.10	101.13

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Figure 2: Plasma Profiles of Morphine (Test Fasted and Fed and Reference Fasted)



Morphine-6-glucuronide (M6G) Test fasted vs. Reference fasted: Thirty (30) subjects were included in the statistical analysis. The mean Cmax values were 88.00 ng/mL and 86.85 ng/mL respectively for the Test and Reference formulations. The Test to Reference Cmax ratio of geometric LSmeans was 98.14% (90% CI: 88.28 to 109.10%). The mean AUCt were respectively 344.21 ng·h/mL and 348.09 ng·h/mL for the Test and Reference formulation. The Test to Reference AUCt ratio of geometric LSmeans was 94.20% (90%CI: 85.46 to 103.82%). The median Tmax was 1.33 h for both the Test and Reference formulations. These results demonstrate that Test is BE to Reference with respect to M6G (Tables 5 and 6).

Table 5: PK Parameters for M6G (Test fast vs Reference fast comparison)

PARAMETER	TEST (FAST)		REFERENCE (FAST)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	88.00	23.3	86.85	23.4
ln (C_{max})	4.4273	9.0	4.4361	5.5
T_{max} (hours) §	1.33	45.5	1.33	29.8
AUC_T (ng·h/mL)	344.21	24.1	348.09	16.3
ln (AUC_T)	5.7855	7.4	5.8397	2.8
AUC_∞ (ng·h/mL)	394.26	20.6	379.97	18.7
ln (AUC_∞)	5.9582	3.2	5.9231	3.2

Table 6: BE Analysis for M6G (Test fast vs Reference fast comparison)

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (FAST)	REFERENCE (FAST)		LOWER	UPPER
C_{max}	25.2	82.63	84.20	98.14	88.28	109.10
AUC_T	23.1	320.01	339.73	94.20	85.46	103.82
AUC_∞	11.0	382.10	368.02	103.83	98.99	108.90

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

2.4.2 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The pivotal BE Study MRN-P9-644 tested for effect of a high fat, high calorie diet on the PK of 20 mg Morphine sulfate concentrate (1 x 1 mL of 20mg/mL oral solution) (study design and treatments discussed in Section 2.5.1). Overall, food did not have a clinically significant effect on the exposure of morphine.

Morphine fasted vs. fed: The mean Cmax values were 14.10 ng/mL and 18.79 ng/mL for the Test (fed) and Test (fast) formulation, respectively. The Test (fed) to Test (fast) Cmax ratio of geometric LSmeans and corresponding 90% confidence interval was 78.37% (90% CI: 69.27 to 88.66%) indicating that Cmax of morphine is lower in presence of food (~25%). The mean AUCt were respectively 62.10 ng·h/mL and 52.68 ng·h/mL for the Test (fed) and Test (fast) formulation indicating that exposure of morphine is higher in presence of food (~15%). The Test (fed) and Test (fast) AUCt ratio of geometric LSmeans and corresponding 90% confidence interval was 122.99% (90% CI: 113.28 to 133.53%). The median Tmax was 0.75 and 0.58 h for the Test (fed) and

Test (fast) formulations, respectively. These results demonstrate that food did not have a clinically significant effect on the PK of morphine. (Tables 7 and 8).

Table 7: PK Parameters for Morphine (Test fed vs Test fast comparison) N 33

PARAMETER	TEST (FED)		TEST (FAST)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	14.083	36.3	18.784	38.9
ln (C_{max})	2.5839	13.7	2.8381	17.0
T_{max} (hours) *	0.75	70.5	0.58	94.3
AUC_T (ng·h/mL)	62.097	30.7	52.683	35.3
ln (AUC_T)	4.0861	7.2	3.8907	10.9
AUC_∞ (ng·h/mL)	69.287	29.6	59.904	38.3
ln (AUC_∞)	4.1994	6.6	4.0158	10.5

Table 8: Comparison of Results for Food Effect – Morphine (Test fed vs Test fast comparison)

PARAMETER	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST (FED)	TEST (FAST)		LOWER	UPPER
C_{max}	13.338	17.020	78.37	69.27	88.66
AUC_T	59.556	48.423	122.99	113.28	133.53
AUC_∞	66.858	55.073	121.40	111.67	131.98

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

2.5 Analytical Section

2.5.1 How the active moieties are identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Both morphine and its active metabolite M6G were identified and measured in the plasma.

2.5.2 Which metabolites have been selected for analysis and why?

Morphine has 2 major metabolites: morphine-3-glucuronide (M3G) and morphine-6-glucuronide. M3G is not known to have pharmacological activity. M6G is known to bind potently, in vitro, to opioid receptors. Therefore only M6G was detected and measured in plasma.

2.5.3 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation?

Validated HPLC methods using MS/MS detection was employed in determining sample concentrations of morphine (MRN-V6-230 (R3),) and M6G (MRD-V9-713) in human plasma. The following tables 9 and 10 outline the important parameters of the validation methods:

Table 9: Bioanalytical Method Validation – Morphine

Analyte	Morphine
Internal standard (IS)	(b) (4)
Method description	Solid phase extraction; HPLC with MS/MS detection
Limit of quantitation	0.250 ng/mL
Average recovery of drug (%)	87.9%
Average recovery of IS (%)	93.7%
Standard curve concentrations (ng/mL)	0.250 ng/mL, 0.500 ng/mL, 1.500 ng/mL, 4.000 ng/mL, 7.500 ng/mL, 12.000 ng/mL, 20.000 ng/mL, 25.000 ng/mL, 30.000 ng/mL
QC concentrations (ng/mL)	0.250 ng/mL, 0.750 ng/mL, 5.000 ng/mL, 22.500 ng/mL
QC Intraday precision range (%)	1.6% - 6.7%
QC Intraday accuracy range (%)	102.5% - 107.6%
QC Interday precision range (%)	2.7% - 9.6%
QC Interday accuracy range (%)	97.7% - 106.0%
Bench-top stability (hrs)	23.2 hours at a temperature of 22°C nominal 23.2 hours at a temperature of 22°C nominal in the presence of Morphine-6-Glucuronide and Morphine-3-Glucuronide
Stock stability (days)	100 days for Morphine at a temperature of 4°C nominal in ACN:H_2O 50:50% v/v at a concentration of 100.00 µg/mL 10 days for Morphine at a temperature of 4°C nominal in ACN:H_2O 50:50% v/v at a concentration of 25.00 ng/mL 11 days for (b) (4) at a temperature of 4°C nominal in ACN:H_2O 50:50% v/v at a concentration of 100.00 µg/mL 59 days for Morphine-6-Glucuronide at a temperature of 4°C nominal in MeOH:H_2O 50:50% v/v at a concentration of 100.00 µg/mL
Processed stability (hrs)	67.8 hours at a temperature of 22°C nominal 60.7 hours at a temperature of 22°C nominal in the presence of Morphine-6- Glucuronide and Morphine-3-Glucuronide
Freeze-thaw stability (cycles)	6 cycles 3 cycles in the presence of Morphine-6- Glucuronide and Morphine-3-Glucuronide
Long-term storage stability (days)	491 days at a temperature of -20°C nominal 3 days at a temperature of -20°C nominal in the presence of Morphine-6- Glucuronide and Morphine-3-Glucuronide

Table 10: Bioanalytical Method Validation- Morphine-6-Glucuronide

Analyte	Morphine-6-Glucuronide
Internal standard (IS)	(b) (4)
Method description	Protein precipitation extraction; HPLC with MS/MS detection
Limit of quantitation	2.50 ng/mL
Average recovery of drug (%)	81.4%
Average recovery of IS (%)	100.7%
Standard curve concentrations (ng/mL)	2.50 ng/mL, 5.00 ng/mL, 20.00 ng/mL, 50.00 ng/mL, 100.00 ng/mL, 150.00 ng/mL, 250.00 ng/mL, 300.00 ng/mL, 350.00 ng/mL
QC concentrations (ng/mL)	2.50 ng/mL, 7.50 ng/mL, 75.00 ng/mL, 275.00 ng/mL
QC Intraday precision range (%)	3.0%-4.5%
QC Intraday accuracy range (%)	99.5%-105.6%
QC Interday precision range (%)	2.6%-7.8%
QC Interday accuracy range (%)	99.7-%-102.3%
Bench-top stability (hrs)	25.6 hours at a temperature of 22°C nominal
Stock stability (days)	6 days for Morphine-6-Glucuronide at a temperature of -20°C nominal in MeOH:H_2O 50:50% v/v at a concentration of 100.00 µg/mL 7 days for Morphine-6-Glucuronide at a temperature of -20°C nominal in MeOH:H_2O 50:50% v/v at a concentration of 0.10 µg/mL 10 days for (b) (4) at a temperature of -20°C nominal in MeOH:H_2O 50:50% v/v at a concentration of 100.00 µg/mL 17 days for (b) (4) at a temperature of 4°C nominal in MeOH at a concentration of 50.00 ng/mL
Processed stability (hrs)	94.8 hours at a temperature of 4°C nominal
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	772 days at a temperature of -20°C nominal

3. LABELING RECOMMENDATIONS

Minor changes as suggested in Section 12 are outlined below. Double strike indicates suggested deletion and double underline indicates suggested addition.

- *Food Effects*

(b) (4)

Presence of food is not expected to significantly impact absorption of morphine from Morphine Sulfate Oral Solution. The concurrent intake of a high-fat, high-calorie meal enhanced the extent of absorption (about 16% increase in AUC), reduced the rate of absorption (about 25% decrease in Cmax), and delayed the Tmax (from 0.58 to 0.75 h) of morphine from the Morphine Sulfate Oral Solution.

(b) (4)

Steady-state levels with Morphine Sulfate Oral Solution are expected to be achieved within 48 hours.

21 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

4.2 Clinical Pharmacology and Biopharmaceutics Individual Study Review

A synopsis of the single pivotal BE study MRN-P9-644 conducted in support of this NDA application is presented below:

Title of Study:
Single Dose Crossover Comparative Bioavailability Study of Two Oral Solutions of Morphine 20 mg / mL vs 20 mg / 5 mL In Healthy Male and Female Volunteers Following the Administration of a 20 mg Dose / Fasting and Fed States

Protocol N°: MRN-P9-644

Qualified Investigator:
Eric Sicard, M.D., Clinical Investigator.

Study Center:
Algorithme Pharma Inc., 1200 Beaumont Ave., Mount-Royal, Quebec, Canada, H3P 3P1.

Publication (reference):
None

Time of Clinical Part:
2009/11/07 to 2009/12/14

Phase of Development:
Phase I

Objectives:
To evaluate and compare the relative bioavailability and therefore the bioequivalence of two different oral solutions of morphine after a single oral dose administration under fasting conditions. In addition, the influence of food was to be assessed for the Test formulation.

Methodology:
Single center, randomized, single dose, laboratory-blinded, 3-period, 6-sequence, crossover study.

Number of Subjects (Planned and Analyzed):
Planned for inclusion: 36
Included: 36
Drop-outs from entire study: 3
Analyzed and considered in the statistical analysis: 33

Diagnosis and Main Criteria of Inclusion:
Male and female volunteers, non- or ex-smokers, of at least 18 years of age but not older than 50 years with a body mass index (BMI) greater than or equal to 18.5 and below 30 kg/m^2. Subjects were in good health as determined by a medical history, physical examination (including vital signs), electrocardiogram (12-lead ECG), oxygen saturation of blood and the usual clinical laboratory tests (hematology, biochemistry, urinalysis) including negative HIV, Hepatitis B and Hepatitis C tests as well as negative screening of ethyl alcohol and drugs of abuse in urine and negative pregnancy test (for female subjects).

Test Product, Dose and Mode of Administration, Batch Number:
Name: Morphine sulfate concentrate
Dosage form/Route of administration: Concentrated solution / Oral
Regimen: Single dose of 20 mg (1 mL of 20 mg / mL)
Batch no.: 08801017

Reference Product, Dose and Mode of Administration, Batch Number:
Name: Morphine sulfate
Dosage form/Route of administration: Solution / Oral
Regimen: Single dose of 20 mg (5 mL of 20 mg / 5 mL)
Batch no.: 856828A

Concomitant Medication:
Name: Revia®
Dosage form/Route of administration: Tablet / Oral
Regimen: single dose of 1 x 50 mg given approximately 1 hour prior to morphine administration
Batch no.: 311768

Treatment Periods:
Period 1: 2009/11/08
Period 2: 2009/11/15
Period 3: 2009/11/22

Duration of Treatment:
In each study period, a single dose of the assigned morphine oral solution was administered in the morning to subjects immediately followed by about 235 mL of water at ambient temperature as follows:

Treatment 1: One single dose of the Test formulation (1 mL) was administered in the morning after a 10-hour overnight fast.

Treatment 2: One single dose of the Test formulation (1 mL) was administered in the morning after a 10-hour overnight fast, thirty (30) minutes after the start of a high-fat, high-calorie breakfast.

Treatment 3: One single dose of the Reference formulation (5 mL) was administered in the morning after a 10-hour overnight fast.

The morphine administrations were separated by a wash-out of at least 7 calendar days.

Blood Sampling Points:
The first blood sample was collected in the morning, prior to the naltrexone administration while the others were collected 0.25, 0.42, 0.58, 0.75, 0.92, 1.08, 1.33, 1.67, 2, 2.33, 2.67, 3, 3.5, 4, 6, 8, 10, 12, and 15 hours post morphine administration.

Criteria for Evaluation

Analytical Method:
Analytes: Morphine and morphine-6-glucoronide in human plasma
Method: HPLC with MS/MS detection
Assay range for morphine: 0.250 ng/mL to 30.000 ng/mL
Assay range for morphine-6-glucuronide: 2.50 ng/mL to 350.00 ng/mL

Safety:
Safety was evaluated through assessment of adverse events, standard laboratory evaluations and vital signs (including oxygen saturation of blood).

Mathematical Model and Statistical Methods of Pharmacokinetic Parameters

Main absorption and disposition parameters using a non-compartmental approach with a log-linear terminal phase assumption. Trapezoidal rule to estimate area under the curve, terminal phase estimation based on maximizing the coefficient of determination. The pharmacokinetic parameters of this trial were C_{max}, T_{max}, AUC_T, AUC_∞, $AUC_{T/\infty}$, K_{el} and $T_{½el}$.

Statistical analysis based on a parametric ANOVA model of the pharmacokinetic parameters; two-sided 90% confidence interval of the ratio of geometric means for the C_{max}, AUC_T and AUC_∞ based on ln-transformed data; T_{max} rank-transformed. Level of significance assessed at the two-sided 5% level.

ANOVA model:
- fixed factors: sequence, period, treatment, left-over interaction between the three factors
- random factor: subject (nested within sequence)

Criteria for Bioequivalence
Statistical inference of morphine based on a bioequivalence approach using the following standards:

- The ratio of geometric LSmeans with corresponding 90% confidence interval calculated from the exponential of the difference between the Treatment 1 (Test; fasting) and Treatment 3 (Reference; fasting) product for the ln-transformed parameters C_{max}, AUC_T and AUC_∞ were all to be within the 80 to 125% bioequivalence range.

- As a second outcome for this study, the ratio of geometric LSmean and corresponding 90% CI for the difference between Treatment 1 (Test; fasting) and Treatment 2 (Test; fed) of ln-transformed parameters C_{max}, AUC_T and AUC_∞ were to be used to assess the effect of food on the Test formulation.

The same criteria were to be applied for morphine-6-glucuronide and the results were to be presented as supportive evidence of comparable therapeutic outcome.

Safety:
Descriptive statistics.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:
A single center, randomized, single dose, laboratory-blinded, three-way, crossover comparative bioavailability study was conducted under fasting and fed conditions on thirthy-six (36) healthy male and female subjects. The rate and extent of absorption of morphine were measured and compared following a single 20 mg dose of Morphine sulfate concentrate solution (1 mL of 20 mg / mL) and Morphine sulfate solution (5 mL of 20 mg / 5 mL). The bioavailability of the two formulations of morphine was equivalent under fasting conditions.

Furthermore, the rate and extent of absorption of Morphine sulfate concentrate solution (1 mL of 20 mg / mL) test product was also measured following a single 20 mg dose under fed state. The comparative bioavailability of the test product under fasting and fed state was however not equivalent.

The results from measured data based on thirty-six (36) subjects are summarized in the subsequent summary tables.

Safety Results:
Thirty-one (31) of the thirty-six (36) subjects experienced a total of one hundred and twenty-three (123) adverse events during the study. Forty-two (42) adverse events (11 different types) were reported after the single dose administration of the Test product under fasting conditions (Treatment 1), forty-four (44) adverse events (13 different types) were reported after the single dose administration of the Test product under fed conditions (Treatment 2) and thirty-seven (37) adverse events (16 different types) were reported after the single dose administration of the Reference product under fasting conditions (Treatment 3). Four (4) adverse events judged to be possibly related to the investigational products (arthralgia, erection increased, influenza like illness and tachypnoea) were unexpected. No serious adverse events (SAEs) were recorded in this study.

Conclusion:
The study can be considered to have been conducted with a good tolerance of the subjects to the study drugs.

The results presented herein show that the criteria used to assess bioequivalence between the Test and Reference formulations under fasting state were all fulfilled. The Test to Reference ratio of geometric LSmeans and corresponding 90% confidence interval for the C_{max}, AUC_T and AUC_∞ were all within the acceptance range of 80 to 125%.

Therefore, the Test formulation (Morphine sulfate concentrate 20 mg / mL solution, Cody Laboratories Inc., USA for Lannett Company Inc., USA) is judged to be bioequivalent to the Reference formulation (Morphine sulfate 20 mg / 5 mL solution, Boehringer Ingelheim Roxane Laboratories Inc., USA) under fasting conditions.

The effect of food on the pharmacokinetic of the Test product was assessed as a second outcome for this study. The results from the ratio of geometric LSmean and corresponding 90% confidence interval for the difference between Treatment 2 (Test; fed) and Treatment 1 (Test; fasting) of ln-transformed parameters C_{max}, AUC_T and AUC_∞ show the presence of a significant food effect. It can be concluded that food reduces the rate of absorption of morphine and increases its extent of absorption.

Morphine (Test fast vs Reference fast comparison)

PARAMETER	TEST (FAST)		REFERENCE (FAST)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	18.784	38.9	19.849	43.0
ln (C_{max})	2.8381	17.0	2.8872	16.4
T_{max} (hours) *	0.58	94.3	0.58	54.1
AUC_T (ng·h/mL)	52.683	35.3	55.288	33.1
ln (AUC_T)	3.8907	10.9	3.9604	8.3
AUC_∞ (ng·h/mL)	59.904	38.3	61.730	31.3
ln (AUC_∞)	4.0158	10.5	4.0756	7.7
$AUC_{T/\infty}$ (%)	88.53	8.0	89.32	6.6
K_{el} ($hours^{-1}$)	0.1445	36.7	0.1480	34.7
$T_{½el}$ (hours)	5.57	40.9	5.37	40.6

* median is presented

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (FAST)	REFERENCE (FAST)		LOWER	UPPER
C_{max}	30.4	17.020	18.198	93.53	82.36	106.21
AUC_T	20.0	48.423	52.999	91.37	83.93	99.46
AUC_∞	20.3	55.073	59.363	92.77	85.10	101.13

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Morphine (Test fed vs Test fast comparison)

PARAMETER	TEST (FED)		TEST (FAST)	
	MEAN	C.V. (%)	MEAN	C.V. (%)
C_{max} (ng/mL)	14.083	36.3	18.784	38.9
ln (C_{max})	2.5839	13.7	2.8381	17.0
T_{max} (hours) *	0.75	70.5	0.58	94.3
AUC_T (ng·h/mL)	62.097	30.7	52.683	35.3
ln (AUC_T)	4.0861	7.2	3.8907	10.9
AUC_∞ (ng·h/mL)	69.287	29.6	59.904	38.3
ln (AUC_∞)	4.1994	6.6	4.0158	10.5
$AUC_{T/\infty}$ (%)	89.56	7.5	88.53	8.0
K_{el} ($hours^{-1}$)	0.1597	28.3	0.1445	36.7
$T_{½el}$ (hours)	4.76	34.4	5.57	40.9

* median is presented

PARAMETER	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
	TEST (FED)	TEST (FAST)		LOWER	UPPER
C_{max}	13.338	17.020	78.37	69.27	88.66
AUC_T	59.556	48.423	122.99	113.28	133.53
AUC_∞	66.858	55.073	121.40	111.67	131.98

* units are ng/mL for C_{max} and ng·h/mL for AUC_T and AUC_∞

Figure 1. Linear Profile of the Mean - Morphine

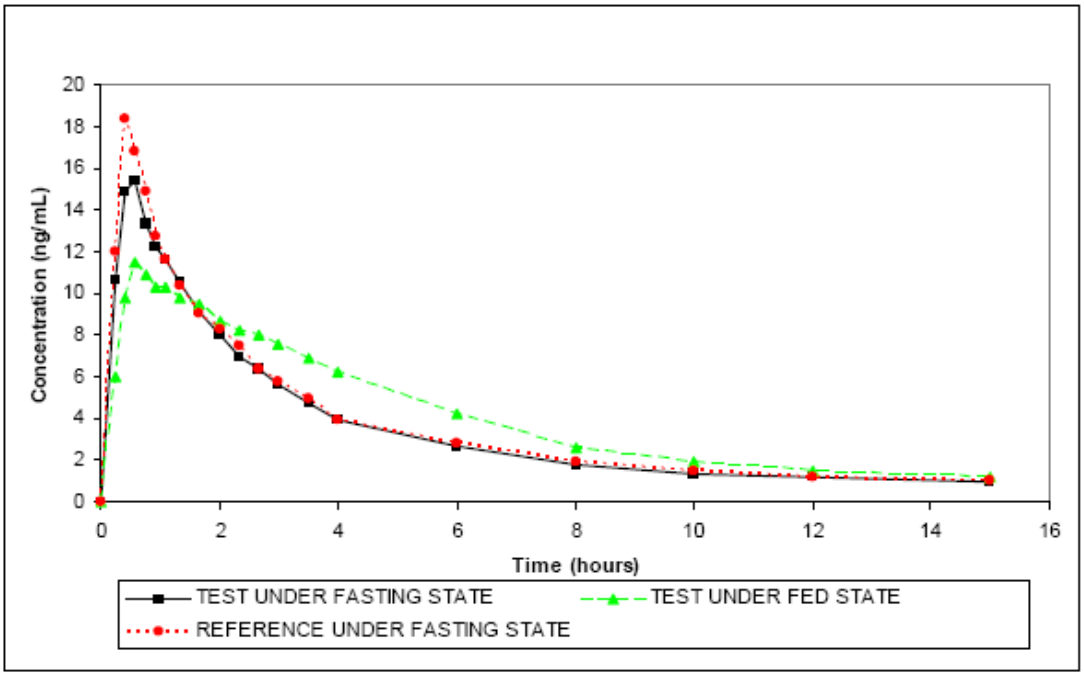
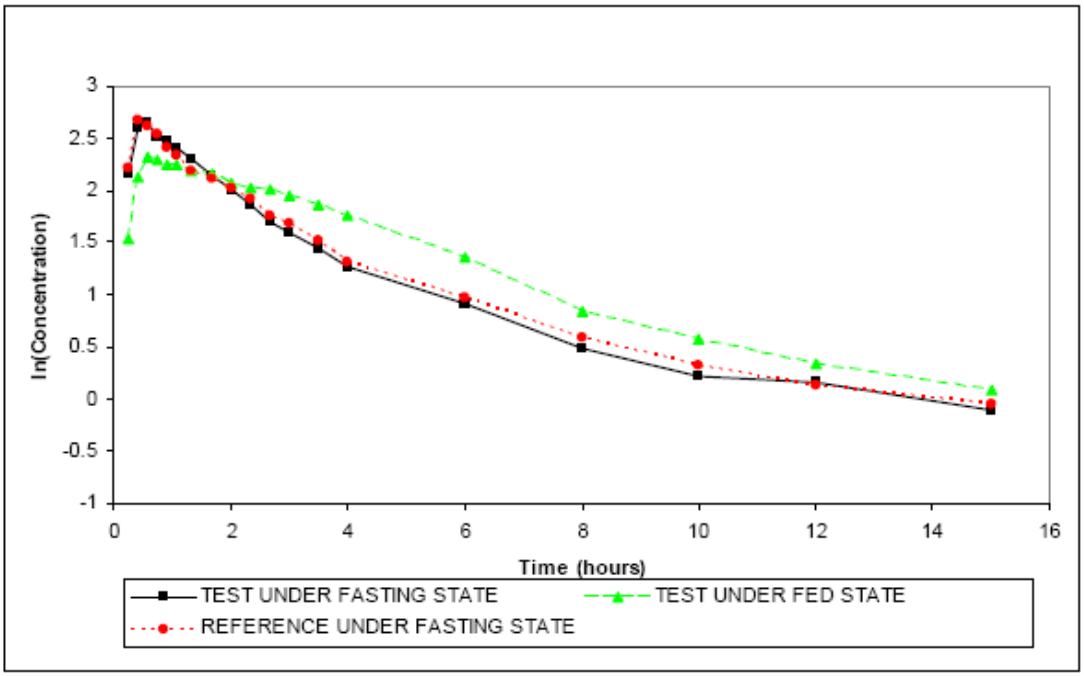


Figure 2. Logarithmic Profile of the Mean - Morphine



4.3 OCPB filing/review form (2-3 pages)

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**201517**	**Brand Name**	**Morphine Sulfate Oral Solution 20mg/mL**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	
Medical Division	**DAAP**	**Drug Class**	**Opioid Analgesic**
OCP Reviewer	**Sheetal Agarwal**	**Indication(s)**	**Mild to moderate pain**
OCP Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Solution**
Pharmacometrics Reviewer		**Dosing Regimen**	
Date of Submission		**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Lannett Company Inc**
Medical Division Due Date		**Priority Classification**	**S**
PDUFA Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE		3	3	**Pivotal BE study and bioanalytical studies for morphine and M6G**
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies	**X**			
HPK Summary				
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	1		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non fasting single dose:				
fasting / non fasting multiple dose:				
Drug-drug interaction studies -				
In vivo effects on primary drug:				
In vivo effects of primary drug:				
In vitro:				
Subpopulation studies -				
ethnicity:				
gender:				

pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:	**X**	**1**		
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan	**x**	**1**		**Seeking waiver**
Literature References				
Total Number of Studies	**3**			
		2	**2**	

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?			X	Reference
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?	X			
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?			X	505 (b)(2)
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			

Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	505 (b)(2)
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			X	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			X	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?	X			
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?			X	
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

SHEETAL AGARWAL

Reviewing Clinical Pharmacologist Date

SURESH DODDAPANENI

Team Leader/Supervisor Date

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

/s/

SHEETAL S AGARWAL
10/25/2010

SURESH DODDAPANENI
10/25/2010