CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206544Orig1s000

CHEMISTRY REVIEW(S)

NDA 206-544

Morphine Sulfate Extended-Release Tablet

Inspirion Delivery Technologies, LLC

Xiaobin Shen, Ph.D.
for
Division of Anesthesia, Analgesia and Addiction Drug Products

(This review includes Dr. Yong Wang's evaluation of the drug product process related contents located on pages 30 – 53 and 63 - 95)

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Chemistry Review Data Sheet

1. NDA 206-544

2. REVIEW #: 1

3. REVIEW DATE: 16-Jul-2015

4. REVIEWER: Xiaobin Shen & Yong Wang, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	NA

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original submission	21-Nov-2014
Amendment 0002	29-Apr-2015
Amendment 0003	15-May-2015
Amendment 0005	23-Jun-2015

Other amendments dated older than the last listed do not have CMC related information for review.

7. NAME & ADDRESS OF APPLICANT:

Name:	Inspirion Delivery Technologies, LLC
Address:	612 Corporate Way, Suite 10, Valley Cottage, NY 10989-2027
Representative (Agent):	Stefan Aigner, MD; CEO
Telephone:	845-589-0277

Fax: Not provided

Email: stefan.aigner@inspirionrx.com

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Morphine Sulfate
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 5
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 21 CFR 314.54 Section 505(b)(2), in reference to RLD MS CONTIN® (NDA 019-516)

10. PHARMACOL. CATEGORY: Opioid agonist

11. DOSAGE FORM: Tablet, extended-release

12. STRENGTH/POTENCY: 15, 30, 60, and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

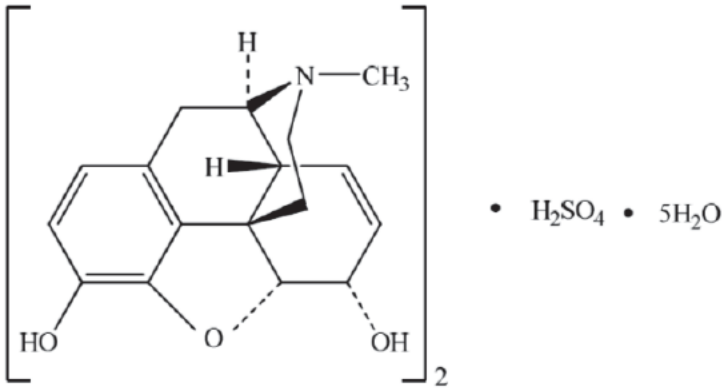
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical name: 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate

United States Adopted Name (USAN): Morphine Sulfate
Compendial name: Morphine Sulfate
Chemical structure:



Molecular Formula: $C_{17}H_{19}NO_2 \cdot H_2SO_4 \cdot 5H_2O$
Molecular Weight: 758.83 g/mol

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETE	COMMENTS
6967	II	Noramco	Morphine sulfate drug substance	1	Adequate	30-Jun-2015	
(b) (4)	IV	(b) (4)	(b) (4)	4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

(b) (4)		(b) (4)				
			4			
	III		4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	115822	Meeting minutes filed on 5/12/2014

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	03-Feb-2015	Dr. Juandria Williams
Pharm/Tox	Pending	17-Jul-2015	Dr. Carlic Huynh
Biopharm	Acceptable	13-Jul-2015	Dr. Tien Mien Chen
Methods Validation	Not needed	05-Jun-2015	Dr. Xiaobin Shen
EA	Adequate	05-Jun-2015	Dr. Xiaobin Shen
Microbiology	Approval	14-Jul-2015	Dr. Erika Pfeiler

The Chemistry Review for NDA 206-544

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, the NDA is recommended for approval.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

NA.

II. Summary of Chemistry Assessments

A. Description of the Drug Substance and Drug Product

Morphine sulfate is an opioid agonist. It exists as a white (b) (4) crystalline powder. (b) (4)

The morphine sulfate drug substance is manufactured by Noramco in Wilmington, DE per DMF 6967. The DMF has been last reviewed by this reviewer on 30-Jun-2015 and deemed adequate. The drug substance manufacturer site EES status is acceptable.

Specifications for morphine sulfate drug substance include both USP and ICH requirements. Collectively they include appearance, identification, assay, acidity, chloride, ammonium salts, impurities, limit of foreign alkaloids, residue on ignition, residual solvents, and particle size distribution. The drug substance is packaged in (b) (4). The drug substance stability data was referenced to DMF 6967, which is adequate to support its use in the NDA.

The drug product is available as 15, 30, 60 and 100 mg strength tablets packaged with a (b) (4) packet in 100-cc round (b) (4) HDPE bottle (b) (4) and closed with child-resistant closure. The tablet excipients include hypromellose, xanthan gum, microcrystalline cellulose, sodium alginate, alginic acid, mannitol, colloidal silicon dioxide, magnesium stearate, two ethyl acrylate and methyl methacrylate copolymer dispersions (b) (4), lactose monohydrate, polysorbate 80, (b) (4). All excipients are of compendial or equivalent grades. The drug product is manufactured by Cerovene Inc. at Valley Cottage, New York. The drug product manufacturing and testing sites all have acceptable EES status.

The drug product specifications include appearance, identification, assay, content uniformity, dissolution, degradation products, (b) (4) (b) (4) and (b) (4). The drug product primary stability studies were conducted on 3 production scale batches for each strength. 12 to 24 months of stability data is provided for the products stored under long term (25°C/60% RH) storage conditions and 6 months of stability data is provided for products stored under accelerated conditions (40°C/75% RH). For the tested quality attributes, except the degradant (b) (4) over time, all others remained relatively unchanged when analytical variations are considered. The (b) (4) in the 15 mg product strengths, it reached a maximum of (b) (4)% after 12 months. Nevertheless, the projected (b) (4) level clearly supports a product expiry of 24 months. Overall, the provided stability data supports the applicant's proposed 24 month product expiry.

B. Description of How the Drug Product is Intended to be Used

The product is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment where alternative options are inadequate.

The dosing regimen should take into account the patient's prior analgesic treatment experience and risk factors for addiction, abuse and misuse. Dosing should be initiated with the 15 mg tablets every (b) (4) 12 hours and adjusted if the patient is opioid tolerant.

C. Basis for Approvability or Not-Approval Recommendation

The NDA submission and amendments provided acceptable information on the chemistry, manufacturing, and controls of the morphine sulfate tablet extended release tablet. The product is recommended for approval based on the following:

- The drug substance and product specifications provide adequate controls;
- The drug product excipients are of USP/NF or equivalent grade;
- The drug product container closure systems are acceptable for pharmaceutical use.
- Both drug substance and drug product are stable in the studied stability period and support the currently proposed expiry of 24 months for the drug product.

D. Risk Assessment

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking***	**Risk Mitigation approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
API Stability	Formulation Raw materials Process parameters Scale and	Low	Consistent control of raw materials; Development of	No risk to be concerned with. The API has been manufactured for	None

	Equipment		a set of robust process parameters that work reliably at the commercial scale and with all equipment	many years and demonstrated to have good stability.	
Assay, Stability (DP)	Formulation Raw materials Process parameters Scale and Equipment	Low	Development of a robust formulation; Consistent control of raw materials (excipients); Development of a set of robust process parameters that work reliably at the commercial scale and with all equipment	No risk to be concerned with. The assay is controlled through in process quality control and release testing. The drug product is also very stable.	None
Process DP	(b) (4)	Medium	(b) (4)	The processes used are typical.	None
Dissolution	Formulation Scale/equipment Extended release Alcohol dose dumping	High	The formulation is typical for the abuse deterrent extended release product. The batch scale and equipment are standard and pose no risk to dissolution. The mitigation approach for extended release and alcohol dose dumping include manufacturing drug product with good quality and avoid co-administration of alcohol with this drug product.	To closely monitor the DP to meet the approved dissolution specifications. To evaluate the post-marketing safety report.	Continuously monitoring the manufacture of the DP for good quality

III. Administrative

A. Reviewer's Signature

Yong Wang -A
Digitally signed by Yong Wang -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Yong Wang -A, 0.9.2342.19200300.100.1.1=2000618723
Date: 2015.07.16 15:47:50 -04'00'

Yong Wang, Ph.D.
Review Chemist, Branch VI, OPF
(For drug product process review)

Xiaobin Shen -S
Digitally signed by Xiaobin Shen -S
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Date: 2015.07.16 15:43:12 -04'00'

Xiaobin Shen, Ph.D.
Review Chemist, Branch IV, ONDP
(For remaining review)

B. Endorsement Block

Ubrani V. Venkataram -S
Digitally signed by Ubrani V. Venkataram -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300067833, cn=Ubrani V. Venkataram -S
Date: 2015.07.16 16:06:03 -04'00'

Ubrani V. Venkataram, Ph.D.
Chief, Branch VI, OPF
(For drug product process review)

Julia C. Pinto -A
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Julia C. Pinto -A, 0.9.2342.19200300.100.1.1=1300366849
Date: 2015.07.17 11:41:02 -04'00'

Julia Pinto, Ph.D.
Chief, Branch IV, ONDP
(For remaining review)

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Evaluation: Adequate. The labels have all required information from CMC perspective.

Package Insert

Refer to details of the package insert in Section 1.14.1.3 of the eCTD. The relevant edits and comments will be communicated to the applicant together with labeling comments from other review disciplines.

The SPL is provided with the required details.

Evaluation: Acceptable. The package insert's Sections 3, 11 and 16 have the information elements required per CFR 201.57.

B. Environmental Assessment Or Claim Of Categorical Exclusion

The applicant requested categorical exclusion in accordance with 21 CFR25.31(a). There is no extraordinary circumstances exist.

Evaluation: Adequate. Categorical exclusion is granted.

III. EES Report

The overall establishment evaluation status is acceptable.

Project	Project: Application Type	Project: Application Number	Project: Submission Type	Project: Submission Number	Task: Status	Task: Progress Status	Desc	Task: Assigned To	Task: Planned Completion Date	Project: Target Action Date	Facility Inspection - Overall Application Recommendation	Facility Inspection - Overall Application Re-evaluation Date
Status: Complete (1)												
Facility Inspection - Overall Application Re-evaluation Date: Oct, 2015 (1)												
NDA 206544-Orig1-New - User Fee - Form 3674/NDA - Coversheet(1)	NDA	206544	Original	1	Complete	Late		Juandria Williams	2/3/15		Approve	10/18/15