CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-964

CHEMISTRY REVIEW(S)

MEMORANDUM

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

DATE: April 23, 2008

TO: Review #1 of NDA 21-964

FROM: Jane Chang
Review Chemist, ONDQA

SUBJECT: **Labeling Review**
NDA 21-964
Relistor (Methylnaltrexone Bromide) Subcutaneous Injection

SUMMARY

After completion of CMC Review #1, revised labeling information for package insert and immediate container and carton were provided by the applicant via emails and found to be acceptable. Additional recommendation for Drug Listing Data Elements in Structured Product Labeling was also conveyed to the applicant via email.

RECOMMENDATION

This NDA may be approved from a chemistry, manufacturing, and controls review perspective.

(See attached electronic signature page)

Jane L. Chang, Ph.D.
Review Chemist

Date

(See attached electronic signature page)

Moo-Jhong Rhee, Ph.D.
Branch Chief

Date

6 Page(s) Withheld

X Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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/s/

Jane Chang
4/23/2008 05:27:10 PM
CHEMIST

Moo-Jhong Rhee
4/23/2008 05:32:25 PM
CHEMIST
Chief, Branch III

Relistor
(Methylnaltrexone Bromide)
Injection

NDA 21-964

Division Director Review
Chemistry, Manufacturing, and Controls

Applicant: Progenics Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

Indication: Treatment of opioid-induced constipation in patients receiving palliative care

Presentation: **Relistor** Injection is supplied as a single strength, sterile, [redacted] 20 mg/mL solution of methylnaltrexone bromide. Each single-use, 3 mL glass vial contains 12 mg of methylnaltrexone bromide, 3.9 mg sodium chloride USP, 0.24 mg edetate calcium disodium USP, and 0.18 mg glycine hydrochloride in 0.6 mL of solution. One vial per carton or one vial per tray (packaged with syringe and swabs).

EER Status: Acceptable 5-JUL-2007

Consults: Microbiology – Approval 30-NOV-2007
EA – Categorical exclusion granted under 21 CFR §25.31(b)
Methods Validation – Revalidation by Agency not requested

Original Submission: 30-MAR-2007

Post-Approval Agreements: None

Drug Substance:

Methylnaltrexone bromide is a chiral derivative of naltrexone, the opiod receptor antagonist, and is a small, synthetic, New Molecular Entity (NME) with an empirical formula of $C_{21}H_{26}NO_4Br$ and a molecular weight of 436.36. Known chemically as (*R*)-N-(cyclopropylmethyl)noroxymorphone methobromide, it exists as a white to faint gray, [redacted] crystalline powder with a melting point of [redacted] Methylnaltrexone bromide is soluble in water ([redacted] ng/mL) and aqueous buffers (pH 1.0 to 12.0), has a pKa of 8.4, and is very slightly soluble in alcohols. Its partition coefficient (log P) in [redacted] is consistently produced by the commercial manufacturing process and is considered the [redacted] stable form of the drug substance.

The bulk drug substance is manufactured by Mallinckrodt, Inc., St. Louis, Missouri. The chemistry, manufacturing, and controls information for the drug substance is appropriately referenced, is described in Mallinckrodt's Type II DMF , has been reviewed, and is concluded to be adequate. A summary description of the manufacturing process was provided in the application.

The proposed regulatory methods are either compendial or were developed and validated for their intended purpose. The impurities and degradants have been investigated. The primary reference standard for drug substance, manufactured by the commercial process, and reference standards for specified impurities have been characterized by the proposed regulatory methods as well as by additional methods.

The stability data for three commercial batches support a month retest period for the bulk drug substance stored either inside an , bags contained in containers with lids at controlled room temperature, 25±2°C /60%RH.

Conclusion: Drug substance is acceptable.

Drug Product:

Relistor is supplied as a single-use, sterile solution of (allowing withdrawal of 0.6 mL) in a nominal 3 mL clear, Type I, glass vial sealed with a gray rubber stopper with plug and oversealed with an aluminum, flip-top cap.

Each vial of **Relistor** contains 20 mg/mL methylnaltrexone bromide mg/mL sodium chloride USP, mg/mL edentate calcium disodium USP, and mg/mL glycine hydrochloride, adjusted to pH 3.0 to 5.0 with USP and USP, in Water for Injection USP. Glycine hydrochloride is manufactured under cGMP using

[redacted] USP. The formulation is [redacted] into vials by [redacted]

Specification of the drug product includes: appearance, clarity, identification by [redacted] HPLC and UV spectrophotometry, strength by [redacted] HPLC, degradants and impurities by [redacted] HPLC, volume in container, pH, particulate matter, edentate calcium disodium, sterility, and bacterial endotoxins. Reference standards for drug product impurities were developed for use in validating analytical methods. All test methods have been appropriately validated for their intended purpose.

Sufficient stability data for three commercial-scale batches of drug product support the requested expiry of 24 months when stored at room temperature, 68°-77°F (20°-25°C); excursions permitted to 15-30°C (59-86°F), and protected from light. Do not freeze.

Conclusion: Drug product is acceptable.

Additional Items:

The sponsor committed to [redacted]

All associated Drug Master Files (DMFs) are acceptable or the pertinent information has been adequately provided in the application.

The applicant submitted a methods validation package containing all relevant documentation (tests, methods, and acceptance criteria) for the control of the drug substance and the drug product.

Overall Conclusion:

From a CMC perspective, the application is recommended for **Approval,** pending agreement on product labeling.

Blair A. Fraser, Ph.D.
Director
DPA I/ONDQA

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/s/

Blair Fraser
2/5/2008 03:34:15 PM
CHEMIST

NDA 21-964

Relistor (Methylnaltrexone Bromide) Injection

Progenics Pharmaceuticals, Inc.

Jane L. Chang, Ph.D.

Review Chemist

Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment II
Branch III

For Division of Gastroenterology Products
(HFD-180)

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Chemistry Review Data Sheet

1. NDA 21-964

2. REVIEW #: 1

3. REVIEW DATE: 04-FEB-2008

4. REVIEWER: Jane L. Chang

5. PREVIOUS DOCUMENTS:

Documents	Document Date
11/1/2004 Pre-NDA CMC Meeting Minutes	30-NOV-2004
8/15/2005 Pre-NDA Meeting Minutes	13-SEP-2005
8/23/2006 Teleconference Meeting Minutes	22-SEP-2006

6. SUBMISSION(S) BEING REVIEWED:

Submissions Reviewed	Document Date
Original Submission	30-MAR-2007
Correspondence (C)	17-MAY-2007
Amendment (BC)	07-SEP-2007
Amendment (BC)	17-OCT-2007
Amendment (BC)	08-NOV -2007
Amendment (BC)	30-NOV-2007
Amendment (BI)	18-JAN-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Progenics Pharmaceuticals, Inc.
Address:	777 Old Saw Mill River Road
	Tarrytown, NY 10591
Representative:	Alexander W. Rochefort
Telephone:	914-784-1881

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Relistor
b) Non-Proprietary Name: Methylnaltrexone Bromide Injection
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):
   1) Chem. Type: 1
   2) Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: selective mu-opioid receptor antagonist

11. DOSAGE FORM: Injection

12. STRENGTH/POTENCY: 12 mg/0.6 mL (20 mg/mL)

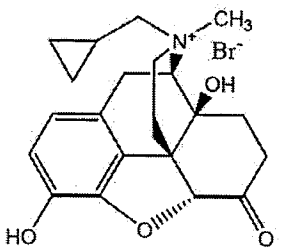
13. ROUTE OF ADMINISTRATION: Subcutaneous

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:



Methylnaltrexone bromide

(*R*)-N-(cyclopropylmethyl)noroxymorphone methobromide.
Molecular formula: $C_{21}H_{26}NO_4Br$ MW: 436.36 g/mol

Chemistry Review Data Sheet

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II	Mallinckrodt	Naltrexone Methobromide	1	Adequate	1/18/2008	By J. Chang
	II			1	Adequate	11/29/2007	By J. Chang
				1	Adequate	1/16/2008	By J. Chang
*	II			1	Adequate	11/29/2007	By J. Chang
	III			4	N/A		
	III			1	Adequate	10/3/2007	By J. Chang
				1	Adequate	10/3/2007	By J. Chang
				3	Adequate	4/12/2007	By M. Sassaman
	V			7	N/A	N/A	See the 11/30/07 Microbiology Review by V. Pawar
	V			7	N/A	N/A	See the 11/30/07 Microbiology Review by V. Pawar

*DMF — was referenced in DMF — with letter of authorization dated 21-Oct-2007.
**DMF — was referenced in DMFs — with letter of authorization dated 21-Oct-2007 and 16-May-2003, respectively.

[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)

Chemistry Review Data Sheet

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	64,583	Methylnaltrexone
IND		
IND		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	7/5/2007	S. Ferguson
Pharm/Tox	N/A		
Biopharm	N/A		
Methods Validation	N/A, according to the current ONDC policy		
Office of Drug Safety	Acceptable for "Relistor" as the proprietary name.	8/2/2007	L. Wisniewski, K. Taylor, D. Toyer, C. Holquist
EA	Categorical exclusion (see this review)	10/03/2007	J. Chang
Microbiology	Approval	11/30/2007	V. Pawar

The Chemistry Review for NDA 21-964

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry, manufacturing, and controls review perspective, this NDA may be approved pending resolution of minor labeling issues.

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

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Product

Relistor (methylnaltrexone bromide) Injection, 20 mg/mL, consists of an aqueous solution of methylnaltrexone bromide in a clear, Type I glass vial, grey rubber stopper and aluminum overseal with a flip-off cap. The volume of drug product in the vial is n order to assure a volume of 0.6 mL for withdrawal.

The proposed commercial formulation consists of 20 mg/mL methylnaltrexone bromide mg/mL edetate calcium disodium (CaEDTA), mg/mL glycine hydrochloride and mg/mL sodium chloride in Water for Injection.

The product, which is stable at room temperature storage conditions, is filled in single-use vials for subcutaneous administration up to a 0.6 mL volume or 12 mg methylnaltrexone bromide per vial.

Commercial manufacture of the product will occur at This facility manufactured the full-scale site-specific primary stability batches. The commercial formulation is the same as the primary registration stability batches.

The proposed drug product specification includes tests for

Stability data were provided for up to 12 months at 25°C/60%RH and 30°C/75%RH, and up to six months at 40°C/75%RH on three production-scale primary stability batches of the drug product using the commercial container closure. Stability data show no loss in potency and no significant changes in impurities, appearance, and pH for packaged product. Vial orientation was not found to have an impact on product quality. Photostability of the drug product using ICH Option 2 light conditions was also studied for one of the three primary stability registration batches in both the exposed and packaged configurations. The results showed that the secondary opaque container protects the drug product from photodegradation.

Linear regression analyses of naltrexone methobromide content predict that it will be maintained within the limit for the proposed expiration period of 24 months. The applicant has committed to

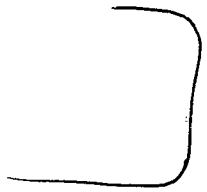
The stability data support the requested expiry of 24 months when stored at room temperature, 68-77°F (20-25°C); excursions permitted to 15-30°C (59-86°F), and protected from light. Do not freeze.

(2) Drug Substance

The active pharmaceutical ingredient, methylnaltrexone bromide (MNTX), is a new molecular entity. It is a derivative of the opioid receptor antagonist, naltrexone. Methylation of naltrexone base gives the desired *R*-configuration at the quaternary nitrogen center. The addition of a methyl group at the amine ring nitrogen forms a permanent positive charge and provides the compound with greater polarity and lower lipid solubility. These properties restrict the ability of MNTX to access the central nervous system in humans. Therefore, MNTX is designed to block undesired adverse effects of opioid pain medications, such as constipation, mediated predominately by the peripherally located opioid receptors, while sparing the desired centrally mediated analgesic effect. MNTX provides a specific treatment for opioid-induced constipation.

Commercial manufacture of methylnaltrexone bromide is conducted at Mallinckrodt Inc., St. Louis, Missouri. Details of the manufacturing process, control of materials, critical steps, process controls, and process validation are provided in Mallinckrodt's DMF# This DMF has been reviewed by this reviewer and found to be adequate to support the NDA.

The proposed MNTX drug substance specification includes



Real-time stability data (7 batches) ranged from 12 months to 36 months and six months accelerated data (6 batches) were provided at the nominal , MNTX batch size that is representative of the commercial process. Real-time and accelerated stability data are also available for up to nine months for three batches for the nominal 65 kg commercial process. All stability studies have been performed by Mallinckrodt using the proposed commercial container closure systems for all batch sizes. Stability data showed no significant changes.

The stability data support the proposed retest date of months for the bulk drug substance stored either inside an , at controlled room temperature, 25°C/60% RH.

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

The drug product is administered as a subcutaneous injection, no more frequently than one dose in a 24 hour period.

The recommended dose of Relistor Injection, 20 mg/mL, is 8 mg for patients weighing 38 to less than 62 kg (84 to less than 136 lb) or 12 mg for patients weighing 62 to 114 kg (136 to 251 lb). Patients whose weight falls outside of these ranges should be dosed at 0.15 mg/kg.

Patient Weight		Injection Volume	Dose
Pounds	Kilograms		
84 to less than 136	38 to less than 62	0.4 mL	8 mg
136 to 251	62 to 114	0.6 mL	12 mg

In patients with severe renal impairment (creatinine clearance less than 30 ml/min), reduce the dose of Relistor Injection by one-half.

The drug product is to be stored at controlled room temperature 20-25°C (68-77°F). When stored under the specified conditions, an expiration dating period of 24 months can be expected.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been submitted to ensure the drug product's identity, strength, quality, purity, potency, and stability as a subcutaneous product for its intended use. All manufacturing and testing facilities were found to be acceptable by the Office of Compliance. At the completion of this review, labeling review among all disciplines has not taken place. Therefore, from a CMC standpoint, this new drug application may be approved pending resolution of minor labeling issue.

III. Administrative

A. Reviewer's Signature: electronically signed in DFS

B. Endorsement Block: electronically signed in DFS

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/s/

Jane Chang
2/4/2008 04:48:21 PM
CHEMIST

Moo-Jhong Rhee
2/4/2008 04:56:42 PM
CHEMIST
Chief, Branch III

Initial Quality Assessment
Branch 3
Pre-Marketing Assessment Division 2

OND Division:	Division of Gastroenterology Products
NDA:	21-964
Applicant:	Progenics Pharmaceuticals
Stamp Date:	3/30/2007
Received by PAL:	4/16/2007
Review Date:	5/24/2007
PDUFA Date:	2/3/2007
Filing Meeting:	5/30/2006
Proposed Trademark:	To be established
Established Name:	methylnaltrexone bromide
Dosage Form:	lyophilized powder
Route of Administration:	subcutaneous
Indication:	opioid-induced constipation
PAL:	Marie Kowblansky, PhD

	YES	NO
ONDQA Fileability:	☒	
Comments for 74-Day Letter		☒

A. Summary

Methylnaltrexone Bromide Injection, 20 mg/mL has been developed as a subcutaneous injection product (to be taken no more than once daily) for the treatment of opioid-induced constipation. It is supplied in a clear 3 mL ~~glass~~ glass, single use vial, with gray ~~rubber~~ rubber stopper and aluminum overseal with flip-off-cap. The target fill volume is ~~al~~ al to allow for removal of 0.6 mL per dose. The recommended dose is on a patient weight basis, as indicated below

Patient Weight		Injection Volume	Dose
Pounds	Kilograms		
84 to less than 136	38 to less than 62	**0.4 mL**	8 mg
136 to 251	62 to 114	**0.6 mL**	12 mg

For patients whose weight falls outside these ranges, dosing at 0.15 mg/kg is recommended.

Drug Substance

The active component in this product is methyl naltrexone (MNTX), a quaternary salt with bromide counterion

For complete information regarding the synthesis and characterization of this

new molecular entity, reference is made to Mallinckrodt's Type II DMF # which will need to be reviewed.

Characterization

The specification

Limits for individual identified impurities (related compounds) are set at or lower, in accord with ICH guidance, and for individual unidentified impurities at also in accord with ICH. For however, the proposed limit of exceeds the ICH qualification limit, but the applicant indicates that this limit is acceptable based on qualification in non-clinical studies.

At the pre-NDA meeting dated November 1, 2004, FDA discussed with Progenics that FDA is setting a qualification threshold for Agreement was reached that no more that 250 acceptable as an interim specification, but should eventually be In the present submission, an acceptance criterion of is included in the drug substance specification, with a commit to lower the specification to NMT by May, 2007. At the time of this review no revision of this acceptance criterion has yet been received from the sponsor.

Drug Product

The proposed commercial formulation contains 20 mg/mL methylnaltrexone bromide, edetate calcium disodium (CaEDTA), glycine hydrochloride, and sodium chloride in water for injection:

Table P.1.2.1: Composition of Methylnaltrexone Bromide Injection, 20 mg/mL

Component	Grade	Quantity/ 0.6 mL	Concentration (mg/mL)	Function
Methylnaltrexone Bromide	In-house Standard	12 mg[a]		Active
Sodium Chloride	USP/Ph.Eur.	3.9 mg		
Edetate Calcium Disodium	USP	0.24 mg		
Glycine Hydrochloride	In-house	0.18 mg		
Hydrochloric Acid	NF/Ph.Eur.			
Sodium Hydroxide	NF/Ph.Eur.			
Water for Injection	USP/Ph.Eur.			

a. Input based on 100% potency. This amount will be adjusted based upon actual assay of the drug substance.

All excipients conform to USP/NF requirements, with the exception of glycine hydrochloride, which will conform to an in-house specification.

It should be noted that no clinical trials were conducted with the commercial formulation proposed above. Clinical trials, including Phase III trials, were conducted with a different formulation, one that contained only saline [redacted] Since the saline formulation required refrigeration, [redacted] The [redacted] consequently, the proposed commercial product requires only room temperature storage. According to the applicant, both these components, in combination, are required to stabilize the product. Data comparing the bioequivalence of the commercial formulation with the one used in phase 3 clinical trials have been submitted and will need to be evaluated by the Biopharm reviewer.

The relatively uncomplicated manufacturing process involves [redacted]

The specification [redacted]

Product Stability: Up to six months of stability data at 25°C/60%RH, 30°C/75%RH, and 40°C/75%RH are provided for three production-scale batches of the proposed commercial product. Additional data (total of nine months) will be provided during the review period, with a proposal for an [redacted]-month expiry. In view of the very limited data that have been submitted, it is premature to comment on the proposed expiry at the present time.

Inspection requests for the facilities involved in the manufacture of the drug substance and drug product have been entered into EES. (See appended list.)

Environmental assessment: Progenics Pharmaceuticals appropriately requests categorical exclusion from preparing an environmental assessment on the basis that the estimated concentration of methyl naltrexone at the point of entry into the aquatic environment will be below 1 part per billion.

B. Critical issues for review

[redacted]

--Since glycine hydrochloride will conform to an in-house specification, the adequacy of the specification needs to be carefully evaluated

-- The manufacturing process

-- The pH acceptance criterion that is part of the specification for the drug product allows a range of ——— for pH. However, data submitted by the applicant indicate that the optimum pH range for product stability is ——— The appropriateness of the proposed range should be evaluated.

C. Comments for 74-Day Letter -- *None*

Marie Kowblansky, PhD
Pharmaceutical Assessment Lead

5/25/2007
Date

Moo-Jhong Rhee, PhD
Branch Chief

5/25/2007
Date

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/s/

Marie Kowblansky
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CHEMIST

Moo-Jhong Rhee
6/5/2007 02:25:24 PM
CHEMIST
Chief, Branch III