

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-203

CHEMISTRY REVIEW(S)

b(4)

_____, TM
(azelastine hydrochloride)
Nasal Spray

NDA 22-203

**Summary Basis of Recommendation
Chemistry, Manufacturing, and Controls**

Applicant: MedPointe Pharmaceuticals
265 Davidson Avenue,
Suite 300 Somerset, NJ 08873-4120

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Indication: _____ Nasal Spray is a topical antihistamine indicated for seasonal allergic rhinitis

Presentation: The proposed drug product will be provided in a _____ mL, opaque, round, HDPE V-bottom bottle containing _____ mL of solution with an HDPE base cup to provide support. There is also a physician sample product in a _____ bottle containing 4.5 mL of solution. The closure for both is a _____ Nasal Spray Pump.
The attached spray pump delivers 0.137 mL of solution containing 0.137 micrograms (mcg) of azelastine hydrochloride as a fine mist when actuated.

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EER Status: Acceptable 20-DEC-2007

Consults: EA – Categorical exclusion granted under 21 CFR 25.31(b)
Methods Validation – Not requested

Original Submission: 30-JUL-2007

Post-Approval Agreements: N/A

Background

The drug product, _____ Nasal Spray, is an antihistamine formulated as a metered-spray aqueous solution for intranasal administration. This is a new sweetened formulation of the approved Astelin Nasal Spray product (NDA 20-114 approved in 1996) with the major changes being the addition of two inactive excipients, sucralose and sorbitol.

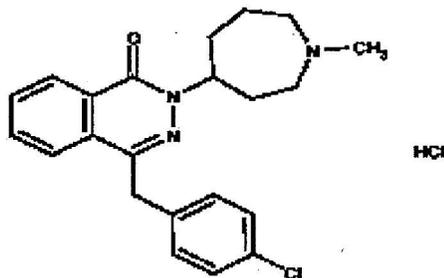
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Drug Substance

The drug substance, azelastine hydrochloride, is a histamine H1-receptor antagonist (structure is shown below). It is a stable white, crystalline

powder with an extremely bitter taste. It contains one chiral center and is made as the racemate. All drug substance information is referenced to MedPointe Pharmaceutical's approved NDA 20-114 for Astelin Nasal Spray. There are no changes to the drug substance.

The drug substance is manufactured by _____, Inc.,
_____ DMF # _____. The drug substance DMF was reviewed very recently for NDA 21-127, Optivar Ophthalmic Solution (0.05% azelastine hydrochloride) and found adequate.



Chemical Name: (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride
USAN Name: Azelastine hydrochloride
Molecular Formula: C₂₂H₂₄Cl₂N₃O
Molecular Weight: 418.37

All manufacturing and testing facilities remain the same as those used for the current Astelin Nasal Spray product. The cGMP inspection status of all manufacturing and testing facilities was found acceptable on 12/20/07.

Conclusion: Drug substance information is acceptable.

Drug Product

The drug product is manufactured by MedPointe Pharmaceuticals in Decatur, IL. The manufacturing process consists of _____

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The drug product contains 0.1% (w/w) azelastine hydrochloride, the drug substance, in an isotonic aqueous solution containing the following excipients: _____% sorbitol, _____% Sucralose, _____% hypromellose, _____% sodium citrate, _____% edetate disodium, 0.125% benzalkonium chloride (as a _____), and purified water (pH 6.4).

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The drug product specifications for the solution include description, active ingredient identification, assay and impurities by HPLC, pH, identification

of sucralose, assay of benzalkonium chloride, particulate matter, microbial limits and density.

The attached spray pump delivers 0.137 mL of solution containing 0.137 micrograms (mcg) of azelastine hydrochloride as a fine mist when actuated. Drug product spray specifications include spray content uniformity, pump delivery volume, spray pattern and droplet size distribution.

The exact same pump unit and bottle are currently used for the approved Astelin Nasal Spray product. The spray pump unit consists of the pump fitted with a blue safety clip and blue plastic dust cover. The drug product is stored at controlled room temperature 20 – 25°C (68 – 77°F). Based on 12 months of real-time data demonstrating very little if any degradation, an expiry of 24 months is acceptable for the 30 mL-fill package.

The metered-spray product is for intranasal use only. After priming the pump, each metered spray delivers 0.137 mL of solution containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg azelastine base).

Conclusion: Drug Product information is acceptable

Recommendation

The application is recommended for approval from the CMC point of view.

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/s/

Ali Al-Hakim
4/4/2008 12:40:13 PM
CHEMIST

NDA 22-203

Nasal Spray

b(4)

MedPointe Pharmaceuticals

**Martin Haber, Ph.D.
Office of New Drug Quality Assessment
Division of Pre-Marketing Assessment I**

**For
Division of Pulmonary and Allergy Products**

Chemistry Review Data Sheet

1. NDA 22-203
2. REVIEW #1
3. REVIEW DATE: March 27, 2008
4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

NA

Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original

Document Date

9/17/07

7. NAME & ADDRESS OF APPLICANT:

Name:	MedPointe Pharmaceuticals
Address:	265 Davidson Avenue, Suite 300
Representative:	Somerset, NJ 08873-4120
Telephone:	732-564-2200

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: _____
- b) Non-Proprietary Name (USAN): azelastine hydrochloride

Chemistry Review Data Sheet

c) Code Name/# (ONDC only):

d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: New Formulation, Type 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: NA

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: Each spray delivers 137 μ L of an aqueous solution formulation containing 137 mcg of azelastine hydrochloride

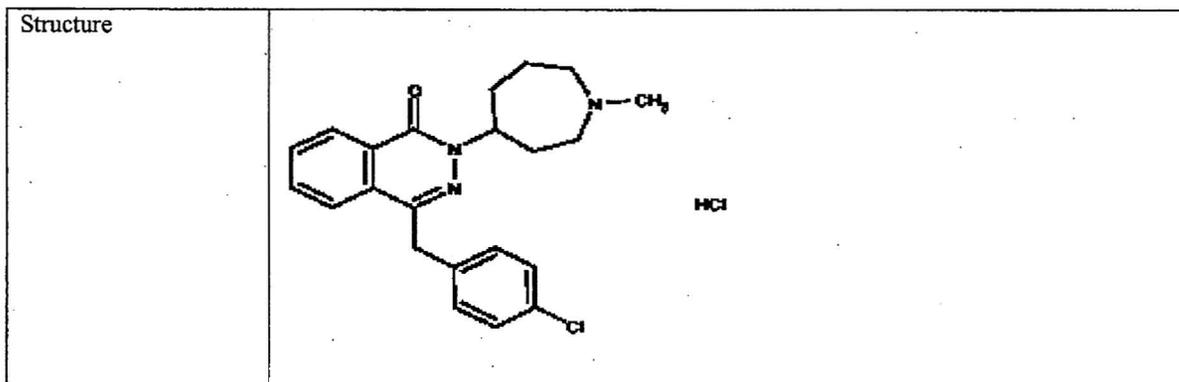
13. ROUTE OF ADMINISTRATION: Intranasal

14. Rx/OTC DISPENSED: Rx OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): SPOTS product – Form Completed Not a SPOTS product

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

USAN/INN/JAN	Azelastine hydrochloride
Chemical Name	(\pm)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride
CAS #	79307-93-0
Molecular Formula	C ₂₂ H ₂₄ Cl ₂ N ₃ O
Molecular weight	418.37

Chemistry Review Data Sheet



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
	II	[Redacted]		3	Adequate	6/21/07	Dr. S. C. Lin
	III			3	Adequate	6/22/06	Same materials as approved DP.
	III			3	Adequate		Same materials as approved DP.
	III			3	Adequate		Same materials as approved DP.
	III			3	Adequate		Same materials as approved DP. No review required.
	III			3	Adequate		Same materials as approved DP. No review required.
	III			3	Adequate		Same materials as approved DP. No review required.
	III			3	Adequate		Same materials as approved DP. No review required.

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Chemistry Review Data Sheet

		Clip					
—	III	_____	7				Review not required. b(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
NDA	20114	Astelin Nasal Spray (azelastine HCl)
NDA	21127	Optivar Ophthalmic Solution (azelastine HCl)
IND	69785	
IND	32704	

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not required		
EES	Acceptable	9/28/07	S. Ferguson
Pharm/Tox	Acceptable		
Biopharm	Acceptable		
Methods Validation	Not required		
EA	Acceptable		Exclusion requested and approved
Microbiology	Not required		

19. ORDER OF REVIEW (OGD Only) NA

The application submission(s) covered by this review was taken in the date order of receipt. ___ Yes
___ No If no, explain reason(s) below:

The Chemistry Review for NDA 22-203

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

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 Product(s) and Drug Substance(s)

Nasal Spray is an antihistamine formulated as a metered-spray aqueous solution for intranasal administration. Nasal Spray (NDA 22-203) is a new, sweetened formulation of the approved Astelin Nasal Spray product (NDA 20-114) with the major changes being the addition of sucralose and sorbitol. Astelin Nasal Spray has been marketed in the US since 1996. The drug product contains 0.1% (or 1 mg/mL) azelastine hydrochloride, the drug substance, in an isotonic aqueous solution containing the following excipients: % sorbitol, % sucralose, % hypromellose, % sodium citrate, % edetate disodium, 0.125% benzalkonium chloride (as a), and purified water (pH 6.4).

b(4)

The drug product is manufactured by MedPointe Pharmaceuticals in Decatur, IL. The manufacturing process consists of

b(4)

The drug product release specifications for the solution include description, active ingredient identification, assay and impurities by HPLC, pH, identification of Sucralose, assay of benzalkonium chloride, particulate matter, microbial limits and density. Specifications are almost identical to those for the approved Astelin Nasal Spray product.

The marketed drug product is provided in a mL, opaque, round, HDPE V-bottom bottle containing mL of solution with an HDPE base cup to provide

b(4)

Executive Summary Section

support. There is also a physician sample product in a _____, bottle containing 4.5 mL of solution. The closure for both is a _____ Nasal Spray Pump manufactured by _____, that is screwed onto the top of the bottle during drug product manufacture. b(4)

The exact same pump unit and bottle are currently used for the approved Astelin Nasal Spray product. The spray pump unit consists of the pump fitted with a blue safety clip and blue plastic dust cover. The attached spray pump unit delivers 0.137 mL of solution containing 137 micrograms (mcg) of azelastine hydrochloride as a fine mist when actuated. Drug product spray specifications include spray content uniformity, pump delivery volume, spray pattern and droplet size distribution. The spray specifications are almost identical to those for the approved Astelin Nasal Spray product.

The drug product is stored at controlled room temperature 20 – 25°C (68 – 77°F). Based on 12 months of real-time data demonstrating very little if any degradation, an expiry of 24 months is acceptable for the 30 mL-fill package.

Testing was carried out to evaluate the potential for contaminants leaching from the container/closure system into placebo solution. No identified semi-volatile compounds (mainly antioxidants), polynuclear aromatic hydrocarbons (PAH's), non-PAH's (mainly plasticizers), or N-nitrosamines were detected. Trace levels of a _____, were measured in solution at all time points. The concentration of sodium in bulk solution was _____ ppm consistent with the expected value from the excipients in the placebo formulation. b(4)

The drug substance, azelastine hydrochloride, is a histamine H1-receptor antagonist. It is a stable white, crystalline powder with an extremely bitter taste. It contains one chiral center and is made as the racemate. All drug substance information is referenced to MedPointe Pharmaceutical's approved NDA 20-114 for Astelin Nasal Spray. There are no changes to the drug substance and no drug substance review was required for this NDA. The drug substance specifications are unchanged. The drug substance is manufactured by _____, the holder of DMF _____. The drug substance DMF was reviewed very recently for NDA 21-127, Optivar Ophthalmic Solution (0.05% azelastine hydrochloride) and found adequate. b(4)

All manufacturing and testing facilities remain the same as those used for the current Astelin Nasal Spray product. The cGMP inspection status of all manufacturing and testing facilities was found acceptable on 9/28/07.

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

Executive Summary Section

Nasal Spray is a topical antihistamine indicated for seasonal allergic rhinitis. The metered-spray product is for intranasal use only. After priming the pump, each metered spray delivers 0.137 mL of solution containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg azelastine base). The pump should be primed before initial use by six actuations or less until a fine mist appears and re-primed after storage unused for 3 or more days by two sprays or less. The recommended dosage is: one to two sprays per nostril twice daily. Tail-off testing has shown that sufficient solution (— mL) is supplied for 200 actuations. The in-use antimicrobial effectiveness of the preservative has been demonstrated.

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C. Basis for Approvability or Not-Approval Recommendation

The chemistry, manufacturing and control information provided in the NDA for the new formulation of the drug product is adequate. There are no chemistry deficiencies.

III. Administrative

A. Reviewer's Signature

See DFS

B. Endorsement Block

See DFS

C. CC Block

See DFS

42 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

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/s/

Martin Haber
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CHEMIST

Ali Al-Hakim
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