

**OND Division of Pulmonary and Allergy Products**

**NDA: 22-203**

**Applicant: MedPoint Pharmaceuticals**

**Stamp Date: 30-Jul-2007**

**PDUFA Date: 30-May-2008**

**Proposed Proprietary Name: \_\_\_\_\_**

**Established Name: azelastine hydrochloride nasal spray**

**Dosage form and strength: Nasal Spray (each spray delivers 137 microliters of formulation containing 137 mcg of azelastine hydrochloride)**

**Route of Administration: Intranasal**

**Indications: treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, congestion, sneezing and itching in adults**

**PAL: Prasad Peri, Ph.D. Branch 2/DPA I/ONDQA**

**Fileability recommendation: Acceptable for filing**

**Review team recommendation: Primary reviewer: Martin Haber, Ph.D.**

**Time goals:**

**Initial Quality Assessment in DFS: by 07-Sept-2007 (NDA accessible on 15-Aug-2007)**

**Chemistry filing memo in DFS: by 07-Sept-2007**

**Filing decision "Day 60": 28-Sept-2007 (tentative; to be set by Clinical Division)**

**Filing Date "Day 74": 14-Sep-2007 (tentative; to be set by Clinical Division)**

**Chemistry Review (DR/IR) letter: by \_\_\_\_\_**

**Mid-cycle meeting "Month 5": 30-Nov-2007 (to be set by Clinical Division)**

**Final Chemistry Review "Month 8" in DFS: by 29-Feb-2007**

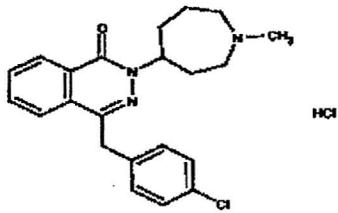
**Related Documents**

**INDs pertaining to this are: 69,785 and 32,704**

**NDA's pertaining to this are: 20-114 (azelastine hydrochloride nasal spray) and NDA 21-127 Optivar (azelastine hydrochloride ophthalmic solution)**

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USAN/INN/JAN	Azelastine hydrochloride
Chemical Name	(±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride
CAS #	79307-93-0
Molecular Formula	C <sub>22</sub> H <sub>24</sub> ClN <sub>3</sub> O
Molecular weight	418.37
Structure	

ONDQA PAL's Initial Quality Assessment  
Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Clinical Pharm (BA/BE) - Dissolution	To be decided if necessary by the reviewer
CDRH	Not Applicable
EA	To be assessed by Primary Reviewer
EES	The drug substance site (Germany) has an acceptable status however, it is not clear who does the stability testing of the drug substance. The drug product manufacturing sites are entered into EES on Sept. 5, 2007. No contact names and phone numbers are provided. They have been requested.
DMETS/DDMAC	Consensus is pending.
Methods Validation	To be sent when appropriate
Microbiology	Consult for antimicrobial assessment to be requested.
Pharm/Tox	Depends to stability data for leachables and impurities.
Biometrics	To be decided by the reviewer

**Summary:**

- This is a standard (10 months) electronic NDA in paper format with electronic labeling provided in SPL format. There is no Quality Overall Summary. This NDA is filed as a 505(b) 1 application.
- This NDA is essentially the same as the approved NDA with the exception of the sweet excipients.
- The applicant claims that the drug substance is very bitter in taste and hence has reformulated the drug product to include sorbitol, sodium citraté, and sucralose to mask the taste. As a result some of the excipients from the current approved formulation are deleted (sodium chloride, citric acid and dibasic sodium phosphate).

**Drug Substance**

- Note that the applicant claims that there are no changes in the specifications to the currently approved drug substance.
- The drug substance is a white to beige white powder with the following attributes tested in the specifications: Description, ID (HPLC, UV, chloride), Melting point, Color of Solution, Clarity, Water Content, Residue on Ignition, Heavy Metals, Sulfate content, Arsenic Content, Optical Rotation, pH, Impurities

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\_\_\_\_\_ . The drug substance is stated to be made by \_\_\_\_\_ on the certificates of analysis.

- The drug substance information is referenced to the current approved NDA 20-114 submitted March 31, 1991 and approved in Nov 1996. There are several supplements approved for the NDA that are drug substance manufacturing related however, it appears that the approved specifications and analytical methods are located in Sept. 30, 1996 amendment to NDA 20-114.
- Final release testing is done by MedPoint Decatur, Illinois facility, with the exception of residual solvents which is accepted based on CoA.
- Note that the structures of known impurities are provided in a table in the NDA. There are a couple of impurities that are \_\_\_\_\_ which are reported at very low levels. Since the drug substance specifications were approved in 1991, these impurities need to be re-evaluated to current standards and if necessary a pharm-tox consult may be sent.
- The lots of API and drug product used for clinical trial and registration are reported in the table on the next page.

MedPoint API Lot #	Vendor API Lot #	Used in Drug Product Lot #	Batch type	Batch Size
2047	4A15016A	03-033-03c	Registration/Clinical	/
2238	4A15017A	03-033-04s	Registration	/
2505	4A15017A	03-033-05s	Registration	/
1291	3D16003A	03-033-02c	Clinical	/

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**Drug Product**

- Proposed commercial batch scale is [redacted]. All excipients are USP or NF grade.

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- The formulation is shown in the table below.

Ingredient	Concentration in Currently Approved Astelin® Nasal Spray (% w/v)	Concentration in Investigational Improved Formulation Astelin® (% w/v)	Function of Component
Azelastine Hydrochloride	0.100	0.100	Active Ingredient
Hypromellose, USP,			
Benzalkonium Chloride NF,			
Edetate Disodium, USP			
JSP			
Sorbitol USP,			
Sodium Citrate, USP,			
Sucralose, NF			
Purified Water, USP			

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- Note that placebo formulations were also manufactured that were used in tox studies. (page 99)
- Note that the fill volume is targeted at [redacted] mL for trade bottles and 4.5 mL for the sample bottles. The bottles are capped with a closure that will be replaced with the nasal spray pump. The target closure removal torque is [redacted] inch-pounds, similar to the current commercial product.

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**Container closure system**

Trade bottle: [redacted] mL white round, HDPE V bottom manufactured by [redacted]  
 Sample Bottle: [redacted] mL white round [redacted] bottomed manufactured by [redacted]  
 Closure: [redacted] multidose metered nasal spray pump manufactured by [redacted]

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- Controls for incoming bottles for visible defects, dimensions, material identification, and extractables are proposed and for incoming nasal spray pumps controls for visible defects, dimensions, leakage,

priming, material identification, pump delivery, spray pattern, droplet size distribution, nitrosamine extractable, elastomer extractables, and plastic extractables are proposed.

**CRITICAL ISSUES**

- **Pharmaceutical development**  
Formulation development has been reported and the selection of each excipient has been justified.
- **Dose Dumping.** Not applicable.
- **Microbial Testing:**  
Note that there is a report on preservative effectiveness testing (Report PPD07-04R, page 110, volume 2). This should be sent to the micro team for their assessment.
- **In-process controls:**

\_\_\_\_\_

\_\_\_\_\_

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5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

ONDQA PAL's Initial Quality Assessment  
 Prasad Peri, Ph.D., Division of Pre-Marketing Assessment 1, Branch 2

DMF	TYPE	HOLDER	ITEM REFERENCED	COMMENTS
	II			Review dated 21-Jun-2007 states this is adequate as an alternate source of _____ y. No major review required.
	III			Last review for _____ in 22-Jun-2006. Same materials as approved DP. No major review required.
	III			Updates to DMF need to be reviewed. Same materials as approved DP. No major review required.
	III			Same materials as approved DP. No major review required.
	III			Same materials as approved DP. No review required.
	III			Same materials as approved DP. No review required.
	III			Same materials as approved DP. No review required. _____ data to be reviewed in DP
	III			DMF to be evaluated for updates in methods.

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• Note that \_\_\_\_\_ part numbers \_\_\_\_\_ and \_\_\_\_\_ are identical \_\_\_\_\_ using identical materials.

**CHEMISTRY NDA FILEABILITY CHECKLIST**

**IS THE CMC SECTION OF APPLICATION FILEABLE?    Yes**

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<b>Parameter</b>	<b>Yes</b>	<b>No</b>	<b>Comment</b>
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?		X	Most facilities were found to be acceptable as of this date. Some are pending evaluation.
5	Is a statement provided that all facilities are ready for GMP inspection?		X	To be provided, however all sites sent for EES.
6	Has an environmental assessment report or categorical exclusion been provided?		X	Vol. 1 not accessible. Evaluated by reviewer
7	Does the section contain controls for the drug substance?		X	Reference to DMFs and NDA
8	Does the section contain controls for the drug product?	X		
9	Have stability data and analysis been provided to support the requested expiration date?	X		
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulations section been provided?	X		
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?		X	Justification for not having microbial limits have been provided

**Draft CMC Comments for 74 day Letter**

- 1. Provide stability data for leachables in the drug product. While every effort will be made to review the stability updates, their review will depend on the timeliness of submission, extent of submitted data, and available resources. Therefore, and as per GRMP timelines we may not be able to review any amendments to stability data late in the review cycle.**
- 2. Provide samples of the drug product in your proposed commercial packaging configuration.**
- 3. Provide draft mockups (100 % size) of the proposed carton, container labels.**

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**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
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/s/  
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Prasad Peri  
9/10/2007 03:55:26 PM  
CHEMIST  
IQA for Azelastine Nasal Spray sweetened formulation

Ali Al-Hakim  
9/10/2007 05:28:16 PM  
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 22203/000 Action Goal:  
 Stamp: 30-JUL-2007 District Goal: 31-MAR-2008  
 Regulatory Due: 30-MAY-2008 Brand Name: \_\_\_\_\_ NASAL SPRAY  
 Applicant: MEDA PHARMS Estab. Name: PRODUCT  
 265 DAVIDSON AVE STE 300 Generic Name: AZELASTINE HCL  
 SOMERSET, NJ 08873  
 Priority: 5S Dosage Form: (LIQUID FOR INHALATION)  
 Org Code: 570 Strength: 0.1% (137 MCG/SPRAY)

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Application Comment: THIS NDA ( \_\_\_\_\_ ) IS A SWEETENED FORMULATION OF THE CURRENTLY APPROVED NDA (20114). IT CONTAINS SUCRALOSE. AS PER THE APPLICANT THE DRUG SUBSTANCE AND DRUG PRODUCT MANUFACTURING SITES ARE THE SAME AS APPROVED IN A RELATED NDA FOR ASTELIN (20114) (on 05-SEP-2007 by P. PERI ( ) 301-796-1730)

FF Contacts: C. JACKSON 301-796-2300 , Project Manager  
 P. PERI 301-796-1730 , Review Chemist  
 A. AL HAKIM 301-796-1323 , Team Leader

Overall Recommendation: ACCEPTABLE on 20-DEC-2007 by H. KIEL (HFD-323) 301-796-3246  
 ACCEPTABLE on 28-SEP-2007 by S. FERGUSON (HFD-322) 301-796-3247

Establishment: CFN \_\_\_\_\_ FEI \_\_\_\_\_

DMF No: \_\_\_\_\_ AADA: \_\_\_\_\_

Responsibilities: \_\_\_\_\_

Pre le: CSN OAI Status: NONE

Estab. Comment: THIS SITE IS THE CONTRACT MANUFACTURER FOR THE \_\_\_\_\_ THIS IS THE SAME SITE AS THE APPROVED SITE IN NDA 20114. IT IS NOT CLEAR WHO DOES THE \_\_\_\_\_ NOT CONTACT

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INFORMATION IS PROVIDED SO FAR. THEY WILL BE ADDED WHEN AVAILABLE.

THEY HAVE BEEN REQUESTED. (on 05-SEP-2007 by P. PERI () 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-2007				PERIP
OC RECOMMENDATION	05-SEP-2007			ACCEPTABLE BASED ON PROFILE	ADAMSS

Establishment:      CFN      1419678                      FEI      1419678  
MEDPOINTE HEALTHCARE INC  
410 434 NORTH MORGAN ST  
DECATUR, IL 62525

DMF No:

AADA:

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Responsibilities: DRUG SUBSTANCE RELEASE TESTER  
 FINISHED DOSAGE MANUFACTURER  
 FINISHED DOSAGE PACKAGER  
 FINISHED DOSAGE RELEASE TESTER  
 FINISHED DOSAGE STABILITY TESTER

Profile: ADM OAI Status: NONE

Estab. Comment: THIS SITE IS RESPONSIBLE FOR THE RELEASE TESTING OF DRUG SUBSTANCE.  
 THIS SITE IS ALSO RESPONSIBLE FOR THE MANUFACTURE, PACKAGING,  
 ANALYTICAL AND STABILITY TESTING OF THE DRUG PRODUCT. (on 05-SEP-2007  
 by P. PERI ( ) 301-796-1730)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-2007				PERIP
SUBMITTED TO DO	12-SEP-2007	GMP			FERGUSONS
DO RECOMMENDATION	27-SEP-2007			ACCEPTABLE BASED ON FILE REVIEW	LJARRELL
INSPECTION CONDUCTED 8/9/07. PROFILES FOUND TO BE ACCEPTABLE.					
DO RECOMMENDATION	28-SEP-2007			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Profile: LIQ OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	05-SEP-2007				PERIP
SUBMITTED TO DO	05-SEP-2007	10D			KIEL
DO RECOMMENDATION	27-SEP-2007			ACCEPTABLE BASED ON FILE REVIEW	LJARRELL
EI CONDUCTED 8/9/07. PROFILES WERE FOUND TO BE ACCEPTABLE.					
OC RECOMMENDATION	28-SEP-2007			ACCEPTABLE DISTRICT RECOMMENDATION	FERGUSONS

Establishment: CFN FEI

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DMF No:

ADA:

Responsibilities:

Profile:

CTL

OAI Status:

NONE

Estab. Comment:

THIS IS ALTERNATE TESTING SITE FOR

TESTS ARE

(on 20-DEC-2007 by M.

HABER () 301-796-1675)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	20-DEC-2007				HABERM
OC RECOMMENDATION	20-DEC-2007			ACCEPTABLE	KIEL

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

BASED ON PROFILE

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