CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-371s000

CHEMISTRY REVIEW(S)

Astepro™ 0.15%
(azelastine hydrochloride)
Nasal Spray

NDA 22-371

Summary of the Basis for the Recommended Action from Chemistry, Manufacturing, and Controls

Applicant: Meda Pharmaceuticals (formerly MedPointe Pharmaceuticals)
265 Davidson Avenue, Suite 300Piscataway, NJ 08854
Somerset, NJ 08873-4120

Indication: Treatment of seasonal allergic rhinitis or perennial allergic rhinitis

Presentation: The proposed drug product will be provided in a metered nasal spray (0.15%) that delivers 0.137 mL of solution containing 205.5 mcg of azelastine hydrochloride.
The marketed drug product is provided in a 34.5 mL, opaque, round, HDPE (b) (4) bottle containing either (b) (4) of solution with an HDPE base cup to provide support. The closure for both bottles is a (b) (4) Nasal Spray Pump which is screwed onto the top of the bottle. There is also a physician sample product in a 15 mL HDPE bottle containing (b) (4) of solution.

EER Status: Pending

Consults:

EA –	Categorical exclusion provided
Statistics –	N/A
Methods Validation –	Not required.
Microbiology –	N/A
Pharm/toxicology –	N/A

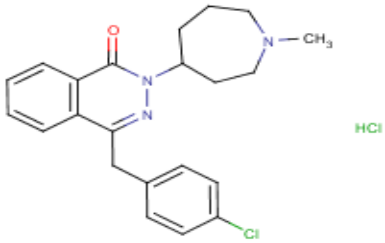
Original Submission: 01-August-2008
Re-submissions: N/A
Post-Approval CMC Agreements: None beyond the typical stability commitment.

Background:
This NDA is a 505 b2 submission referencing previously approved NDA (NDA #22-203). The drug product (Astepro) is an antihistamine formulated as a metered-spray aqueous solution for intranasal administration. Astepro Nasal Spray contains 0.15% w/v of the active ingredient, azelastine hydrochloride, which is a higher strength than the approved NDA 22-203 (strength 0.10%).

Astepro 0.15% Nasal Spray contains 0.15% (1.5 mg/mL) of the drug substance, azelastine hydrochloride. The formulation is an isotonic aqueous solution containing the following excipients: (b) (4) sorbitol, (b) (4) sucralose, (b) (4) hypromellose, (b) (4) sodium citrate, (b) (4) edetate disodium, (b) (4) benzalkonium chloride (b) (4) and purified water (pH 6.4). **The excipient concentrations match those used in the Astepro 0.10% formulation except for sorbitol** (b) (4)

Drug Substance:
The drug substance, azelastine hydrochloride (see structure below), 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. The drug substance is manufactured by Degussa AG GmbH, Radebeul, Germany, the holder of DMF #15440. The drug substance DMF was reviewed recently for Meda Pharmaceutical's NDA 21-127, Optivar Ophthalmic Solution (0.05% azelastine hydrochloride) and found adequate. All manufacturing and testing facilities remain the same as those used for the current azelastine hydrochloride Nasal Spray products. All drug substance information is referenced to Meda Pharmaceutical's three approved azelastine hydrochloride NDAs. There are no changes to the drug substance and the drug substance specifications are unchanged.

Chemical name, structural formula, molecular formula and molecular weight



Chemical name: (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-~ 1H-azepin-4-yl)-, monohydrochloride
Molecular formula: $C_{22}H_{24}Cl_2N_3O$
Molecular weight: 418.37g/mole

Conclusion: Drug substance is acceptable.

Drug Product:
The drug product is manufactured by Meda Pharmaceuticals in Decatur, IL, which is the same manufacturer for the previous NDA 22-203 using essentially the same manufacturing process. (b) (4)

(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 identical to those for the approved Astepro 0.1% Nasal Spray product except that provisions for a new 17 mL fill package presentation have been added.

The proposed marketed drug product is provided in a 34.5 mL, opaque, round, HDPE (b) (4) bottle containing either (b) (4) of solution with an HDPE base cup to provide support. There is also a physician sample product in a 15 mL HDPE bottle containing (b) (4) of solution. The closure for both bottles is a (b) (4) Nasal Spray Pump, which is screwed onto the top of the bottle.

The exact same pump unit and bottle are currently used for the approved Astepro 0.1% and other Astelin Nasal Spray related products. The spray pump unit consists of the pump fitted with a blue safety clip and blue plastic dust cover. After priming, the attached spray pump unit delivers 0.137 mL of solution containing 205.5 micrograms (mcg) of azelastine hydrochloride in a fine mist when actuated (equivalent to 187 mcg of azelastine base). Drug product spray specifications include spray content uniformity, pump delivery volume, spray pattern and droplet size distribution. The spray specifications are identical to those for the approved Astepro 0.1% Nasal Spray product.

The drug product has been shown to provide at least 22 sprays/bottle (b) (4) 106 sprays/bottle (b) (4) and 200 sprays/bottle (b) (4)

The drug product is stored at controlled room temperature 20 – 25°C (68 – 77°F). Based on 12 months of real-time data (18 months for one batch), which demonstrated little if any degradation, an expiry of 24 months is acceptable for the 17 and 30 mL-fill drug product.

Conclusion: Drug product is satisfactory.

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

Overall Conclusion: From a CMC perspective, the application is recommended for approval pending an acceptable recommendation from the Office of Compliance regarding cGMP inspection. Currently, the recommendation is PENDING.

Ali Al-Hakim, Ph.D.
Branch Chief, Branch II
DPA I/ONDQA

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/s/

Ali Al-Hakim

3/11/2009 02:32:19 PM

CHEMIST

NDA 22-371

Astepro 0.15%
(azelastine hydrochloride)
Nasal Spray

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

Table of Contents

Chemistry Review Data Sheet

1. NDA 22-371

2. REVIEW #1

3. REVIEW DATE: March 11, 2009

4. REVIEWER: Martin Haber, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	8/1/08
Amendment	12/19/08
Amendment	1/12/09

7. NAME & ADDRESS OF APPLICANT:

Name:	Meda Pharmaceuticals (formerly 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: Astepro 0.15% (proposed)
b) Non-Proprietary Name (USAN): azelastine hydrochloride
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:

10. PHARMACOL. CATEGORY: Antihistamine

11. DOSAGE FORM: Nasal Spray

12. STRENGTH/POTENCY: Solution (0.15% w/v formulation) for nasal spray, each spray delivers 137 µL of an aqueous solution containing 205.5 mcg of azelastine hydrochloride.

13. ROUTE OF ADMINISTRATION: Intranasal

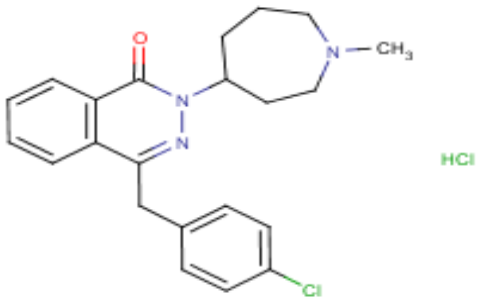
14. Rx/OTC DISPENSED: __X_Rx ___OTC

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:

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	$C_{22}H_{24}Cl_2N_3O$
Molecular weight	418.37
Structure	

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	Degussa AG	Azelastine HCl drug substance	3	Adequate	6/21/07	Dr. S. Zimmerman
	III	(b) (4)		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			7			Review not required.

[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	20-114	Astelin Nasal Spray (azelastine HCl)
NDA	21-127	Optivar Ophthalmic Solution (azelastine HCl)
NDA	22-203	Astepro 0.1% Nasal Spray (azelastine HCl)
IND	69,785	Azelastine HCl
IND	32,704	Azelastine HCl

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Pending	9/28/07 (last acceptable date)	S. Ferguson
Methods Validation	Not required		
EA	Acceptable		Exclusion requested and approved
Microbiology	Not required		
Labeling/Office of Safety Evaluation	Pending		

The Chemistry Review for NDA 22-371

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommending Approval, pending an acceptable Establishment Evaluation Report (EER) for manufacturing sites.

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)

The drug product is an antihistamine formulated as a metered-spray aqueous solution for intranasal administration. Astepro 0.15% Nasal Spray (NDA 22-371, this NDA) is a higher strength (0.15% w/v active) formulation very similar to a recently approved 0.10% strength formulation, Astepro 0.1% Nasal Spray (NDA 22-203) from the same sponsor.

The recently approved NDA 22-203 (Astepro 0.1% Nasal Spray) contains in turn a revised sweetened formulation of an old approved Astelin Nasal Spray product (NDA 20-114, also 0.1% w/v active), marketed in the US since 1996 and currently owned by the same sponsor. The major formulation changes required for the sweetened product were the addition of sucralose and sorbitol excipients.

Astepro 0.15% Nasal Spray contains 0.15% (1.5 mg/mL) azelastine hydrochloride, the drug substance, in an isotonic aqueous solution containing the following excipients: (b) (4) sorbitol, (b) (4) sucralose, (b) (4) hypromellose, (b) (4) sodium citrate, (b) (4) edetate disodium, (b) (4) benzalkonium chloride (b) (4) and purified water (pH 6.4). The excipient concentrations exactly match those used in the Astepro 0.10% formulation except for the sorbitol concentration (b) (4) .

The drug product is manufactured by Meda Pharmaceuticals in Decatur, IL, the same manufacturer as for the previous NDA 22-203 and using essentially the same process. (b) (4)

(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 identical to those for the approved Astepro 0.1% Nasal Spray product except that provisions for a new 17 mL fill package have been added.

The marketed drug product is provided in a 34.5 mL, opaque, round, HDPE (b) (4) bottle containing either (b) (4) of solution with an HDPE base cup to provide support. There is also a physician sample product in a 15 mL HDPE bottle containing (b) (4) of solution. The closure for both bottles is a (b) (4) Nasal Spray Pump manufactured by (b) (4), which is screwed onto the top of the bottle during drug product manufacture.

The exact same pump unit and bottle are currently used for both the approved Astepro 0.1% Nasal Spray and Astelin Nasal Spray products. The spray pump unit consists of the pump fitted with a blue safety clip and blue plastic dust cover. After priming, the attached spray pump unit delivers when actuated 0.137 mL of solution containing for the 0.15% formulation 205.5 micrograms (mcg) of azelastine hydrochloride in a fine mist (equivalent to 187 mcg of azelastine base). Drug product spray specifications include spray content uniformity, pump delivery volume, spray pattern and droplet size distribution. The spray specifications are identical to those for the approved Astepro 0.1% Nasal Spray product. The drug product has been shown to provide at least 22 sprays/bottle (b) (4) 106 sprays/bottle (b) (4) and 200 sprays/bottle (b) (4)

The drug product is stored at controlled room temperature 20 – 25°C (68 – 77°F). Based on 12 months of real-time data (18 months for one batch) demonstrating no change in assay and little if any degradation, an expiry of 24 months is acceptable for the 17 and 30 mL-fill trade packages.

The drug substance, azelastine hydrochloride, is a histamine H1-receptor antagonist (antihistamine). 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 three previously approved azelastine hydrochloride NDA's, from the current NDA sponsor, Meda Pharmaceutical, as supplemented:

NDA 22-203 for Astepro® 0.1% Nasal Spray, 0.10% azelastine hydrochloride solution, submitted 9/17/07 and approved 10/15/08

NDA 21-127 for Optivar® Ophthalmic Solution, 0.05% azelastine hydrochloride, submitted 8/3/99 and approved 5/22/00
NDA 20-114 for Astelin® Nasal Spray, 0.10% azelastine hydrochloride solution, submitted 3/31/91 and approved 11/1/96

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 Degussa AG GmbH, Radebeul, Germany, the holder of DMF #15440. The drug substance DMF was re-reviewed recently for a supplement to Meda Pharmaceutical's NDA 21-127, Optivar Ophthalmic Solution (0.05% azelastine hydrochloride) and found adequate.

All manufacturing and testing facilities remain the same as those used for the current azelastine hydrochloride Nasal Spray products. The cGMP inspection status of all manufacturing and testing facilities was last found acceptable on 9/28/07 for NDA 22-203. The drug substance manufacturing site in Germany was found acceptable as of 9/8/08. The drug product manufacturing site in Decatur, IL is still under evaluation pending re-inspection.

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

Astepro 0.15% Nasal Spray is a topical antihistamine indicated for seasonal allergic rhinitis or perennial 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 205.5 mcg of azelastine hydrochloride (equivalent to 187 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 (b) (4) is supplied for 22, 106 and 200 actuations, respectively. The in-use antimicrobial effectiveness of the preservative has been demonstrated.

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

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/s/

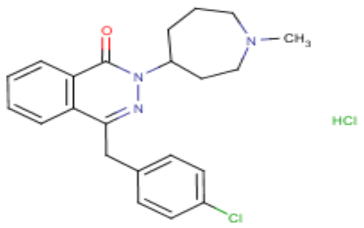
Martin Haber
3/11/2009 12:01:31 PM
CHEMIST

Ali Al-Hakim
3/11/2009 12:15:41 PM
CHEMIST

OND Division of Pulmonary and Allergy Products

NDA: 22-371
Applicant: MedPoint Pharmaceuticals
Stamp Date: 1-Aug-2008
PDUFA Date: 1-Jun-2009
Proposed Proprietary Name: Astelin-S
Established Name: azelastine hydrochloride nasal spray
Dosage form and strength: Nasal Spray (each spray delivers 137 microliters of formulation containing 205.5 mcg of azelastine hydrochloride). After priming, each metered spray delivers a mean volume of 0.137 mL containing 205.5 mcg of azelastine hydrochloride (equivalent to 187.6 mcg of azelastine base)
Route of Administration: Intranasal
Indications: Indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years and older
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 10-Sept-2008 (NDA accessible on 15-Aug-2007)
Chemistry filing memo in DFS: by 12-Sept-2008 (after filing meeting)
Filing decision "Day 60": **30-Sept-2008** (tentative; to be set by Clinical Division)
Filing Date "Day 74": 14-Oct-2008 (tentative; to be set by Clinical Division)
Chemistry Review (DR/IR) letter: by 1-Jan-2009
Mid-cycle meeting "Month 5": 1-Jan-2009 (to be set by Clinical Division)
Final Chemistry Review "Month 8" in DFS: by 1-Apr-2009
PDUFA: 1-Jun-2009

Related Documents
INDs pertaining to this are: 69,785 and 32,704
NDAs pertaining to this are: 20-114 (azelastine hydrochloride nasal spray) and NDA 21-127 Optivar (azelastine hydrochloride ophthalmic solution); NDA 22-371 (azelastine hydrochloride nasal spray 0.1%w/v)

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	$C_{22}H_{24}ClN_3O$
Molecular weight	418.37
Structure	

CONSULTS/ CMC RELATED REVIEWS	COMMENT
Clinical Pharm (BA/BE) - Dissolution	No Applicable
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	Not necessary
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 a Quality Overall Summary. This NDA is filed as a 505(b) 1 application.
- This NDA is essentially the same as the approved NDA 20-114 (Astelin Nasal Spray) with the exception of the sweet excipients (sucrose and sorbitol) and higher strength (0.15% vs. the approved 0.10%).
- The applicant claims that the drug substance is very bitter in taste and hence initially reformulated the drug product in NDA 22-203 to include sorbitol, sodium citrate, and sucralose to mask the taste. As a result, some of the excipients from the current approved formulation are deleted (b) (4) . Due to lack of efficacy issues, the applicant has reformulated the drug product in NDA 22-203 to increase the strength to 0.15% strength and resubmitted the application which is the subject of this review.

Table 2.3.P.2.2-1 Comparison of Formulation Components and Their Functions

Component	Azelastine Hydrochloride 0.15% w/v (NDA 22-371)	Azelastine Hydrochloride 0.1% w/v (NDA 22-203)	Astelin® Nasal Spray 0.1% w/v (NDA 20-114)	Component Function
Azelastine Hydrochloride	0.15	0.10	0.10	Active ingredient
Hypromellose, USP, (b) (4)	(b) (4)			
Sucralose, NF				
Sorbitol Solution, USP, (b) (4) (b) (4)				
Edetate Disodium, USP				
Sodium Citrate, USP, (b) (4) (b) (4)				
Benzalkonium Chloride Solution, NF, 50%				
Purified Water, USP				

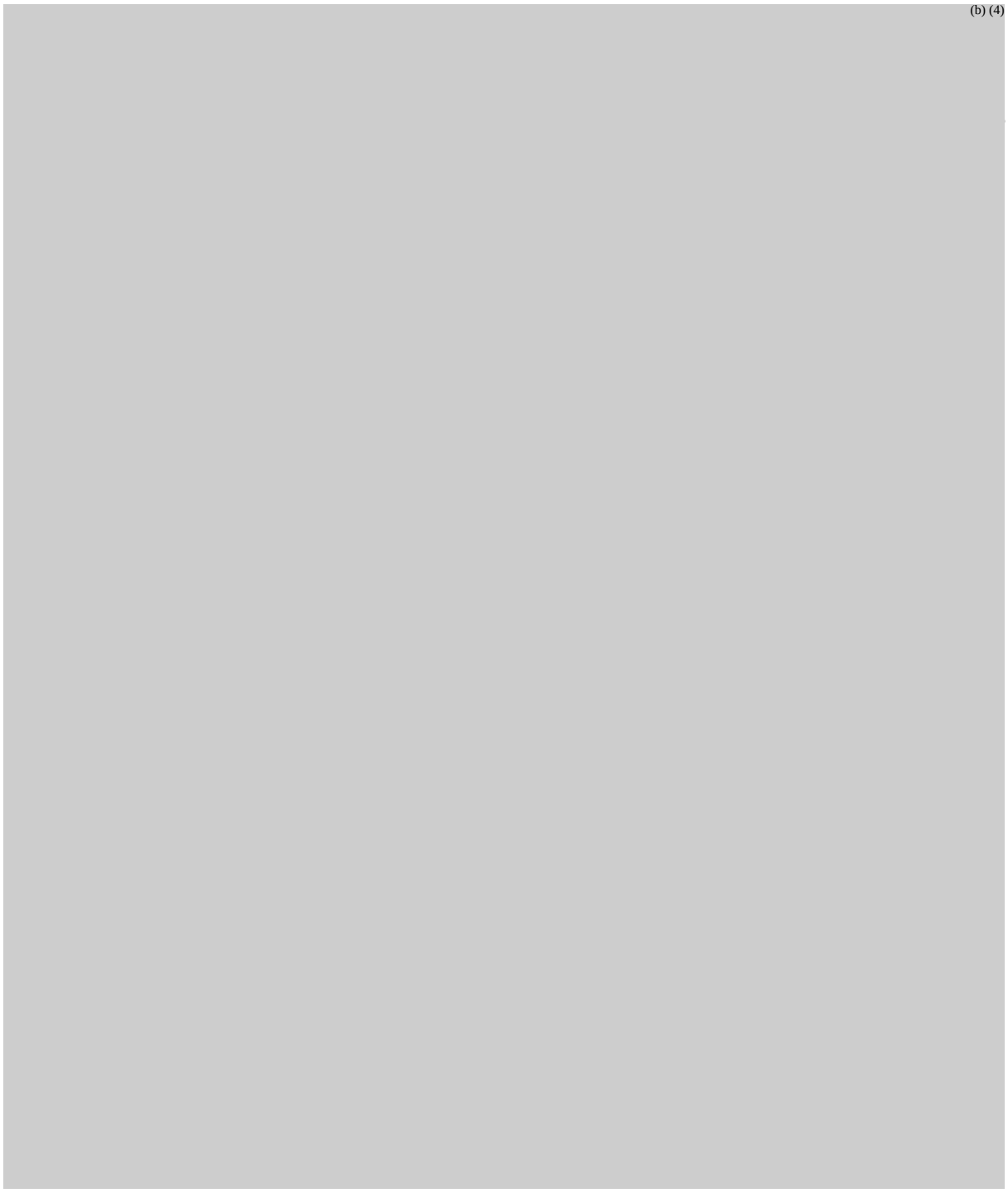
Drug Substance

- 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 (Melting Point, UV, IR, Proof of Chloride), Color of Solution, Clarity, Water Content, (b) (4), Optical Rotation, pH, Impurities (b) (4), Unknown (Single), Total Impurities), Assay, Residual Solvents (b) (4) and Microbiological Purity. The drug substance is stated to be made by Viatris GmbH on the certificates of analysis. It appears that there are some minor differences between the specifications for this NDA and that for NDA 22-203. It appears that the applicant references NDA 21-127 for the drug substance analytical methods and their validation data.
- 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 related to the drug substance manufacturing process, however, it appears that the approved specifications and analytical methods are located in Sept. 30, 1996 amendment to NDA 20-114.
- The drug substance azelastine hydrochloride is used in the currently marketed Astelin Nasal Spray (NDA 20-114) and in the currently marketed Optivar Ophthalmic Solution (NDA 21-127). Specific reference is made to the applicant's approved NDA 21-127 for Optivar, as supplemented.
- Drug substance for this NDA (drug product registration batches) is manufactured at Degussa AG, Werk Radebeul, Germany. Note that this site is sold off to another company. Related documentation for the drug substance manufactured at the Radebeul site is now stored at the Evonik Degussa GmbH Wolfgang site. The Radebeul site has been sold to another company and azelastine hydrochloride is not currently being manufactured at the Radebeul facility. All future manufacture of azelastine hydrochloride drug substance will take place at the Evonik Degussa GmbH Wolfgang site. The applicant has a referenced drug master file (15440) for the CMC information of Azelastine at the Wolfgang site and this DMF was found acceptable in a review dated 21-Jun-2007 by Dr. Stuart Zimmermann. The Wolfgang site is approved for manufacture of the Azelastine Hydrochloride as per CMC supplements for NDA 20-114 and NDA 21-127. This site has an acceptable compliance status as of Sept. 8, 2008, as a result of this NDA.
- Final release testing is done by MedPoint Decatur, Illinois facility, with the exception of residual solvents which is accepted based on CoA.
- .
- The lots of API and drug product used for clinical trial and registration are reported in the table on the next page.

Table 2.3.S.4.4-1 Detailed Information of Drug Substance Lot Used in Manufacture of Drug Product

Supplier's Lot Number (Viatris)	Lot Number (Meda, Decatur)	Date of Manufacture	Used in Drug Product Lot	Used in Studies
0400001699	0000002238	Feb 2004	03-36-02c	Clinical
0400001699	0000003132	Feb 2004	03-36-03s	Registration
0400001702	0000003239	Jan 2004	03-36-06s	Registration
0400001703	0000003298	Jan 2004	03-36-07s	Registration

A representative certificate of analysis is also attached below.



- Justification of Drug substance specifications and stability information is referenced to NDA 21-127 and DMF 15440.

Drug Product

- Drug Product is a solution formulation that delivers 137 microlitres of formulation containing 202.5 mcg of azelastine hydrochloride.
- Proposed commercial batch scale is (b) (4). All excipients are USP or NF grade.
- Formulation development to reduce the bitter taste of the active was evaluated with several sweeteners resulting in the selection of sucralose which is 600 times sweeter than sucrose. Most others when

tested (saccharine, acesulfame K, thaumatin, prosweet, etc.) resulted in precipitation. The (b) (4) was changed to sorbitol due to its compatibility with other agents and for its effectiveness in (b) (4). It also contributes as a (b) (4). The pH chosen was ~6.4 since the solubility of azelastine hydrochloride is lower above pH 7.1. The concentration of benzalkonium chloride in the improved formulation was evaluated at (b) (4) of theoretical concentration and found to meet the requirements of USP 29 <51>. Note however that a (b) (4) overage of benzalkonium chloride is used in the drug product as is done in the current approved formulation.

- The formulation is shown in the table below.

Table 2.3.P.1-1 Formulation Components and Composition of the Drug Product

Component	Quality Standard or Grade	Function	Composition	
			mg/mL	% w/v
Azelastine Hydrochloride	House	Active ingredient	1.5	0.15
Hypromellose, Type (b) (4)	USP	(b) (4)		
Sucralose	NF			
Sorbitol[1]	USP			
Edetate Disodium	USP			
Sodium Citrate, (b) (4)	USP			
Benzalkonium Chloride[2]	NF			
Purified Water	USP			

[1] Sorbitol is added as a (b) (4) Solution, USP
[2] Benzalkonium Chloride is added as a (b) (4) Solution, NF

(b) (4)

- Note that placebo formulations were also manufactured and were used in tox studies for the previous NDA and for leachables in the current NDA (page 75 of QOS).
- Note that the fill volume is targeted at (b) (4) (200 sprays/bottle) and (b) (4) (106 sprays/bottle) for trade bottles where as the target is 4.5 mL (22 sprays/bottle) for the physician sample bottle. The bottles are capped with a closure that will be replaced with the nasal spray pump. (b) (4)

- **Container closure system**
- The formulation is packaged into a 34.5 mL HDPE bottle and capped with a white and blue plastic nasal spray pump.

  Trade bottle: 34.5 mL white round, HDPE (b) (4) manufactured by (b) (4)
  Sample Bottle: 15 mL white round HDPE (b) (4) manufactured by (b) (4)
  Closure: (b) (4).

(b) (4)

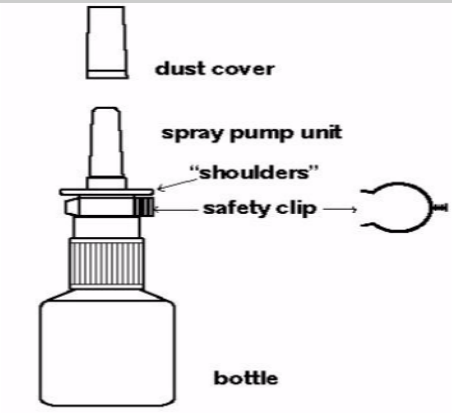


Figure 1

- (b) (4)

(b) (4)

- Drug product specifications include Description, ID by TLC and HPLC, Assay, Degradation Products, pH, Density, Assay for Benzalkonium chloride, Weight Loss, Spray Content Uniformity, Particulate, Matter, Net Content, Pump Delivery, Spray Pattern, and Droplet Size Distribution. For stability conditions, only Description, Assay for Azelastine HCl and Benzalkonium chloride, Degradation products, pH, Weight Loss, and Spray Content Uniformity. Preliminary results for osmolality are provided but are not specified in the specifications.

(b) (4)

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 was a report on preservative effectiveness testing for the previous NDA (Report PPD07-04R, page 110, volume 2). Based on this report, the applicant claims that the preservative is effective at concentrations as low as (b) (4) of label claim. Hence the applicant has proposed a specification limit of NLT (b) (4) labeled claim in the specification. The applicant claims that the report is equally applicable here as well.
- **In-process controls:**
  Proposed critical steps and in process controls are (b) (4)

In-process tests for the bulk solution include testing of description, ID by HPLC, Assay, Impurities/Degradation products, Benzalkonium Chloride Assay, Density, and pH.

- (b) (4)
- **Excipients from Animal Origin.** None proposed.
- **OVIs in the drug Product.** Not applicable.
- **Manufacturing differences between pilot and commercial scales** (b) (4) Note that the clinical batches used only a 30 mL fill where the proposed commercial presentation also includes a 17 mL and 4 mL fill presentations. The 4 mL fill uses a smaller bottle (15 mL). The reviewer should evaluate if there are any stability differences between the 30 mL fill, 17 mL fill and 4 mL fill presentations. Note that the 17 mL and 4 mL presentations have a larger headspace compared to the 30 mL fill used in the clinical batch.
- **GMP status of the drug substance/drug product manufacturing sites.**
  All sites have been inspected earlier. EES has been sent for all sites and is pending at the current time. The drug substance manufacturing site in Germany was found acceptable as of 8-Sept-2008. The drug product site in Decatur, IL is still under evaluation.
- **Safety of imprinting inks**
  Although the sponsor claims no leachables, there are several extractables that will need to be evaluated in this NDA. The sponsor has not proposed acceptance criteria for leachables.
- **Dissolution of the drug product**
  Not applicable
- **Degradation products in the drug product:**
  See list in the figure. The (b) (4) impurities are specified at (b) (4) which is approved in the approved product.
- **Sensitivity of product to moisture and light.** This is an aq. solution packaged in HDPE bottles**.**
- **Weight Loss:** For the trade package and sample presentations weight loss acceptance criteria was unchanged (proposed limit of (b) (4) for trade and (b) (4) for sample). The currently approved limit for Astelin is (b) (4).
- **Shelf life** of the drug product proposed is 24 months for trade and (b) (4) for sample. Adequate justification for the proposed shelf life is proposed with the exception of leachables data which most likely will be similar to the previous approved product.
- **Bulk Drug Product Stability Packaging Data and Protocol**
  A bulk solution hold time of (b) (4) was proposed for the previous NDA 22-203, however it is not clear from the QOS if this is the case here. The reviewer should check to see if this is the case here. No reprocessing is proposed.
- **Comparability Protocol:** None proposed.
- **Stability:** Based on the stability data provided, the applicant recommend that the drug product should be stored upright at controlled room temperature 20-25°C (68-77°F). The product is not light sensitive when stored in the opaque HDPE container with pump closure. The product should be protected from freezing. The first three consecutive commercial batches will be placed on stability.

9 Page(s) has been Withheld in Full immediately following this page as B4 (CCI/TS)

- **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.

	Parameter	Yes	No	Comment
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		
5	Is a statement provided that all facilities are ready for GMP inspection?		X	To be provided, however all sites sent for EES and found acceptable based on profile.
6	Has an environmental assessment report or categorical exclusion been provided?	X		To be 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	Described in the development report
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		Antimicrobial Effectiveness Testing provided and will be evaluated
16	Is a production batch record provided	X		

Draft CMC Comments for 74 day Letter

1. **Provide results from in vitro dose proportionality (e.g., spray content uniformity, spray weight, spray volume etc.) studies between the two strengths (0.10% and 0.15% azelastine hydrochloride nasal spray) of the drug product.**

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.**

4. **Provide a statement to the NDA to indicate that all sites are ready for inspection at the time of the NDA submission.**

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

/s/

Prasad Peri
9/12/2008 04:59:39 PM
CHEMIST

Ali Al-Hakim
9/15/2008 09:53:04 AM
CHEMIST