

**MEDA PHARMACEUTICALS AND CIPLA LTD.**

**V.**

**APOTEX**

**C.A. No. 14-cv-1453**



**Maureen Donovan, Ph.D.**

**DIRECT EXAMINATION DEMONSTRATIVES**

# Maureen Donovan, Ph.D. – Background and Education

## Curriculum Vitae

Maureen D. Donovan, Ph.D.

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**Education:** University of Minnesota College of Pharmacy  
Minneapolis, Minnesota  
Bachelor of Science in Pharmacy, 1983  
  
University of Michigan College of Pharmacy  
Horace H. Rackham School of Graduate Studies  
Ann Arbor, Michigan  
Ph.D. (Pharmaceutics), 1989

## PROFESSIONAL EXPERIENCE

**2013-present** Associate Dean for Undergraduate Programs  
College of Pharmacy  
University of Iowa  
Iowa City, IA

**2008-2013** Division Head  
Division of Pharmaceutics and Translational Therapeutics  
University of Iowa College of Pharmacy  
Iowa City, IA

**2008-present** Professor  
Division of Pharmaceutics and Translational Therapeutics  
University of Iowa College of Pharmacy  
Iowa City, IA

**1996-2008** Associate Professor  
University of Iowa College of Pharmacy  
Division of Pharmaceutics  
Iowa City, IA

**1989-1996** Assistant Professor  
University of Iowa College of Pharmacy  
Division of Pharmaceutics  
Iowa City, IA

**1991** Visiting Scholar  
SmithKline Beecham Pharmaceuticals  
King of Prussia, PA

**1986-88** Staff Pharmacist  
Clark Professional Pharmacy  
Ypsilanti, MI

**Education:** University of Minnesota College of Pharmacy  
Minneapolis, Minnesota  
Bachelor of Science in Pharmacy, 1983

University of Michigan College of Pharmacy  
Horace H. Rackham School of Graduate Studies  
Ann Arbor, Michigan  
Ph.D. (Pharmaceutics), 1989

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**2008-present** Professor  
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University of Iowa College of Pharmacy  
Iowa City, IA

# Summary of Opinions

- A POSA formulator co-formulating a fluticasone/azelastine nasal spray would have started working from the Flonase® and Astelin® products.
- The claimed combinations of fluticasone/azelastine in a nasal spray are obvious.

# Framework for Analysis

- Level of ordinary skill in the art.
- Assess the scope of the prior art.
- Assess any differences between the prior art and the claimed inventions.
- Were the claims obvious in light of any differences from the prior art?

# Person of Ordinary Skill in the Art: Formulation

- **The relevant art:** pharmaceutical formulations of topical agents.
- **Level of ordinary skill in the art:**
  - At least a bachelor's degree in chemistry, biology, chemical engineering or pharmaceutical science;
  - 3-5 years of experience in formulation development of nasal dosage forms, and the ability to operate independently on formulation activities.
  - Familiarity with pharmaceutical excipients and their uses.
  - Could have advanced degree, with fewer years of experience
- **Date of invention:** June 2002



# Scope of the Prior Art: Fluticasone Propionate (Flonase)

## Flonase Label (1998)

### PRODUCT INFORMATION

#### FLONASE®

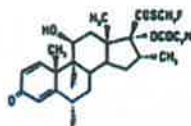
(fluticasone propionate)

Nasal Spray, 50 mcg

SHAKE GENTLY  
BEFORE USE.

For Intranasal Use Only.

**DESCRIPTION:** Fluticasone propionate, the active ingredient of FLONASE Nasal Spray, is a synthetic corticosteroid with the chemical name of 8-fluoromethyl 6a,8a-difluoro-11β-hydroxy-16a-methyl-3-oxo-17a-propionyloxandrost-1,4-diene-17β-carboxylate and the following chemical structure:



Fluticasone propionate is a white to off-white powder with a molecular weight of 500.6. It is practically insoluble in water, freely soluble in dimethyl sulfoxide and dimethylformamide, and slightly soluble in methanol and 95% ethanol.

FLONASE Nasal Spray 50 mcg is an aqueous suspension of micronized fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.

It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mcg of formulation through the nasal adapter. Each bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be constant and the unit should be discarded.

**CLINICAL PHARMACOLOGY:** Fluticasone propionate is a synthetic, trifluorinated corticosteroid with anti-inflammatory activity. In vitro dose response studies on a cloned human glucocorticoid receptor system involving binding and gene expression afforded 50% responses at 1.25 and 0.17 nM concentrations, respectively. Fluticasone propionate was threefold to fivefold more potent than dexamethasone in these assays. Data from the McKendrick vasoconstrictor assay in man also support its potent glucocorticoid activity.

In preclinical studies, fluticasone propionate revealed progesterone-like activity similar to the natural hormone. However, the clinical significance of these findings in relation to the low plasma levels (see Pharmacokinetics) is not known.

APOTEX\_AZPL 0060186



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	
<b>Particle Size</b>	"microfine" (< 10 microns)	
<b>Vehicle</b>	Water	
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	
<b>Surfactants</b>	Polysorbate 80	
<b>Thickening Agents</b>	Microcrystalline cellulose / Carboxymethyl cellulose sodium ("MCC / CMC") (Avicel)	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	

# Scope of the Prior Art:

## Tonicity

### The Art, Science, and Technology of Pharmaceutical Compounding

Lloyd V. Allen, Jr., PhD  
Professor and Chair  
Department of Medicine  
and Pharmaceutics  
College of Pharmacy  
University of Oklahoma  
Oklahoma City, Oklahoma



American Pharmaceutical Association  
Washington, D.C.

Allen: The Art, Science and Technology of Pharmaceutical Compounding (1998)

#### Tonicity Adjustment

The preferred agents for adjusting the tonicity of nasal solutions are sodium chloride and dextrose. Severely hypertonic solutions should be avoided. Nasal fluid has an isotonicity value similar to a 0.9% sodium chloride solution. If the isotonicity is beyond the proper range, the nasal ciliary movement may slow or even stop. Tonicity values ranging from 0.6% to 1.8% sodium chloride equivalency are generally acceptable. If the solution of the active drug is hypotonic, it may be necessary to add a substance to attain the proper tonicity range. Sodium chloride, boric acid, and dextrose are commonly used for this purpose. A tonicity of 300 mOsm/L is ideal, although a range of 200 to 600 mOsm/L is acceptable.

DEFENDANT'S  
EXHIBIT  
DTX-078

APOTEX\_AZFL 0132304



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	
<b>Particle Size</b>	"microfine" (< 10 microns)	
<b>Vehicle</b>	Water	
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	
<b>Surfactants</b>	Polysorbate 80	
<b>Thickening Agents</b>	MCC / CMC	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	

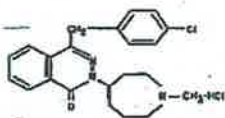
# Scope of the Prior Art: Azelastine HCl (Astelin)

## Astelin Label (2000)

**ASTELIN®**  
(azelastine hydrochloride)  
Nasal Spray, 137 mcg  
IN-023S3-14  
For Intranasal Use Only

### DESCRIPTION

Astelin® (azelastine hydrochloride) Nasal Spray, 137 micrograms (mcg), is an antihistamine formulated as a metered-spray solution for intranasal administration. Azelastine hydrochloride occurs as a white, almost odorless, crystalline powder with a bitter taste. It has a molecular weight of 418.37. It is sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine. It has a melting point of about 225°C and the pH of a saturated solution is between 5.0 and 5.4. Its chemical name is (+)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. Its molecular formula is  $C_{27}H_{31}ClN_5O \cdot HCl$  with the following chemical structure:



Astelin® Nasal Spray contains 0.1% azelastine hydrochloride in an aqueous solution at pH 6.8 ± 0.3. It also contains benzalkonium chloride (125 mcg/mL), edetate disodium, hydroxypropyl methyl cellulose, citric acid, dibasic sodium phosphate, sodium chloride, and purified water.

After priming, each metered spray delivers a 0.137 mL mean volume containing 137 mcg of azelastine hydrochloride (equivalent to 125 mcg of azelastine base). Each bottle can deliver 100 metered sprays.

### CLINICAL PHARMACOLOGY

Azelastine hydrochloride, a phthalazinone derivative, exhibits histamine  $H_1$ -receptor antagonist activity in isolated tissues, animal models, and humans. Astelin® Nasal Spray is administered as a racemic mixture with no difference in pharmacologic activity noted between the enantiomers in *in vitro* studies. The major



APOTEX\_AZFL 0059086

DTX-022.0006

# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	<b>Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)</b>
<b>Particle Size</b>	"microfine" (< 10 microns)	
<b>Vehicle</b>	Water	
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	
<b>Surfactants</b>	Polysorbate 80	
<b>Thickening Agents</b>	MCC / CMC	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	

# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	<b>Dissolved in solution</b>
<b>Vehicle</b>	Water	<b>Water</b>
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	
<b>Surfactants</b>	Polysorbate 80	
<b>Thickening Agents</b>	MCC / CMC	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution
<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	<b>(1) Benzalkonium chloride (0.0125% w/w);</b> <b>(2) EDTA disodium</b>
<b>Surfactants</b>	Polysorbate 80	
<b>Thickening Agents</b>	MCC / CMC	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	

# Scope of the Prior Art: Preservative Concentration 0.002% to 0.05%

## Astelin Patent (1992)

### United States Patent [19]

US005164194A  
Patent Number: 5,164,194  
Date of Patent: Nov. 17, 1992

#### HEITCHE

[54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Heitche, Dietzenbach, Fed. Rep. of Germany

[73] Assignor: Asta Pharm AG, Fed. Rep. of Germany

[21] Appl. No.: 051,644

[22] Filed: Jul. 12, 1990

[63] Continued from Ser. No. 268,772, Nov. 9, 1988, abandoned.

[30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany ..... 3738681

[51] Int. Cl. A61K 9/14; A61K 31/35

[52] U.S. Cl. 424/45; 424/464; 514/421; 514/212

[58] Field of Search 424/45; 424/464; 424/421; 424/45; 514/212; 222/394; 141/24; 239/302; 248/108

[56] References Cited

U.S. PATENT DOCUMENTS

158,564 1/1975 Barner 141/24

2,119,643 6/1978 Mendel 222/394

2,136,940 11/1978 Ehrlich 222/394

2,457,024 12/1948 Arp 248/108  
2,955,308 8/1961 Ashkenz 239/302  
3,813,384 5/1974 Vogelang 544/133  
4,764,387 11/1987 Sagel et al. 514/212  
4,765,369 9/1988 Thomas et al. 248/108

#### FOREIGN PATENT DOCUMENTS

2164058 7/1972 Fed. Rep. of Germany ..... 544/133  
3330773 3/1966 Fed. Rep. of Germany ..... 514/212  
1377231 1/1972 United Kingdom

#### OTHER PUBLICATIONS

Negwer, Organic-Chemicals, Drugs and Their Synonyms, vol. 14, (1987) p. 1145.

European Search Report.

Org.-Chem. drugs and their synonyms, vol. III, No. 6496 (1987).

Arzneimittel. Fortschritte 1972-1985, pp. 936 and 939 (1977).

Primary Examiner—Thurston K. Page

Assistant Examiner—Neil S. Levy

Attorney, Agent, or Firm—Cushman, Darby & Cushman

#### ABSTRACT

A medicament for nasal use or for use in the eye which contains as active ingredient azelastine or a physiologically acceptable salt.

12 Claims, No Drawings



APOTEX\_AZFL 001

DTX

The solutions or formulations preferably contain preservatives and stabilizers. These include, for example: ethylene diamine tetra-acetic acid (edetic acid) and their alkali salts (for example dialkali salts such as disodium salt, calcium salt, calcium-sodium salt), lower alkyl p-hydroxybenzoates, chlorohexidine (for example in the form of the acetate or gluconate), phenyl mercury borate. Furthermore, it is possible, for example, to use sodium-(2- ethylmercurithio)-benzoate generally known as "thimerosal" which may be present in an amount of 0.001 to 0.05, preferably from 0.005 to 0.02, for example 0.01% (weight/volume in liquid formulations, otherwise weight/weight). Other suitable preservatives are: pharmaceutically useful quaternary ammonium compounds, for example cetylpyridinium chloride, tetradecyltrimethyl ammonium bromide, generally known as "cetrimide", benzyldimethyl-[2-[2-[p-(1,1,3,3-tetramethyl- butyl)]phenoxy]ethoxy]-ammonium chloride, generally known as "benzethonium chloride" and myristyl-picolinium chloride. Each of these compounds may be used in a concentration of 0.002 to 0.05, for example 0.02% (weight/volume in liquid formulations, otherwise weight/weight).

# Scope of The Prior Art

	Flonase®	Astelin®
Active Ingredient	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
Particle Size	"microfine" (< 10 microns)	Dissolved in solution
Vehicle	Water	Water
Preservatives	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium <b>Astelin patent: other preservatives; concentrations at 0.002% to 0.05%</b>
Surfactants	Polysorbate 80	
Thickening Agents	MCC / CMC	
Tonicity Adjuster	Dextrose	
pH	5 to 7	



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
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<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	<b>None needed</b>
<b>Thickening Agents</b>	MCC / CMC	
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution
<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	None needed
<b>Thickening Agents</b>	MCC / CMC	<b>HPMC</b>
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	

# Scope of the Prior Art CMC Is Compatible With Azelastine HCl

## United States Patent [19] Hettche

US005164194A  
[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING  
MEDICAMENTS  
[75] Inventor: Maimon Hettche, Dietzenbach, Fed.  
Rep. of Germany  
[73] Assignee: Astra Pharm AG, Fed. Rep. of  
Germany  
[21] Appl. No.: 851,664  
[22] Filed: Jul. 12, 1990

2,457,034 12/1948 Ard ..... 244/108  
2,995,308 8/1961 Ashkreuz ..... 239/302  
2,812,384 5/1974 Vogelmeier ..... 546/133  
4,704,347 11/1987 Engel et al ..... 514/212  
4,760,369 9/1988 Thomas et al ..... 514/234.5

### FOREIGN PATENT DOCUMENTS

2164038 7/1972 Fed. Rep. of Germany ..... 546/133  
3530793 3/1986 Fed. Rep. of Germany ..... 514/212  
1377231 1/1972 United Kingdom .....

### OTHER PUBLICATIONS

Negwer, Organic-Chemicals, Drugs and Their Syn-  
onyms, vol. II, (1987) p. 1145.  
European Search Report.  
Org.-Chem. drugs and their synonyms, vol. III. No.  
6496 (1987).  
Arzneimittel. Fortschritte 1972-1985, pp. 936 and 939  
(1977).

Primary Examiner—Thurman K. Page  
Assistant Examiner—Neil S. Levy  
Attorney, Agent, or Firm—Cushman, Darby & Cushman

[57] ABSTRACT  
A medicament for nasal use or for use in the eye which  
contains as active ingredient azelastine or a physiologi-  
cally acceptable salt.

12 Claims, No Drawings

### Related U.S. Application Data

[63] Continuation of Ser. No. 258,772, Nov. 9, 1988, aban-  
doned.

### Foreign Application Priority Data

Nov. 11, 1987 (DE) Fed. Rep. of Germany ..... 3778481

[51] Int. Cl. A61K 9/14; A61K 31/35

[52] U.S. Cl. 424/45; 424/46; 424/48; 424/49; 424/50; 424/51; 424/52; 424/53; 424/54; 424/55; 424/56; 424/57; 424/58; 424/59; 424/60; 424/61; 424/62; 424/63; 424/64; 424/65; 424/66; 424/67; 424/68; 424/69; 424/70; 424/71; 424/72; 424/73; 424/74; 424/75; 424/76; 424/77; 424/78; 424/79; 424/80; 424/81; 424/82; 424/83; 424/84; 424/85; 424/86; 424/87; 424/88; 424/89; 424/90; 424/91; 424/92; 424/93; 424/94; 424/95; 424/96; 424/97; 424/98; 424/99; 424/100

### References Cited

U.S. PATENT DOCUMENTS  
158,564 1/1875 Barber ..... 141/24  
2,119,443 8/1938 Hendl ..... 222/994  
2,136,940 11/1938 Ebbrecht ..... 222/994

## Astelin Patent (1992)

Moreover, it is possible to add thickening agents to the solutions to prevent the solution from flowing out of the nose too quickly and to give the solution a viscosity of about 1.5 to 3, preferably 2 mPa.s. Such thickening agents may, for example, be: cellulose derivatives (for example cellulose ether) in which the cellulose-hydroxy groups are partially etherified with lower unsaturated aliphatic alcohols and/or lower unsaturated aliphatic oxyalcohols (for example methyl cellulose, carboxy-methyl cellulose, hydroxypropylmethylcellulose), gelatin, polyvinylpyrrolidone, tragacanth, ethoxose (water soluble binding and thickening agents on the basis of ethyl cellulose), alginic acid, polyvinyl alcohol, poly-acrylic acid, pectin and equivalent agents. Should these substances contain acid groups, the corresponding physiologically acceptable salts may also be used.

DTX-016

APOTEX\_AZFL 0004360

DTX-016.0001

# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution
<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	None needed
<b>Thickening Agents</b>	MCC / CMC	HPMC <b>Astelin patent: others, including CMC</b>
<b>Tonicity Adjuster</b>	Dextrose	
<b>pH</b>	5 to 7	



# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
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<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	None needed
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC
<b>Tonicity Adjuster</b>	Dextrose	NaCl
<b>pH</b>	5 to 7	



# Scope of the Prior Art Tonicity Adjusters

## United States Patent [19] Hettche



US005164194A  
[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

### [54] AZELASTINE CONTAINING MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed.  
Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of  
Germany

[21] Appl. No.: 391,644

[22] Filed: Jul. 12, 1990

### Related U.S. Application Data

[63] Continuation of Ser. No. 268,772, Nov. 9, 1988, aban-  
doned.

### [30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany ..... 3726401

[51] Int. Cl. .... A61K 9/14; A61K 31/35

[52] U.S. Cl. .... 424/489; 424/431;

424/45; 424/454; 424/422; 514/212

[58] Field of Search .... 424/43, 464, 422, 45,

424/489; 514/212; 222/354; 141/24; 239/202;

248/108

### [56] References Cited

#### U.S. PATENT DOCUMENTS

158,564 1/1875 Barrer ..... 141/24

2,119,843 6/1928 Mencl ..... 222/394

2,136,940 11/1928 Ehbrecht ..... 222/394

2,457,024 12/1948 Arp ..... 248/108

2,965,308 9/1961 Aulicewicz ..... 239/202

3,813,384 5/1974 Vogelsang ..... 544/123

4,704,347 1/1987 Engel et al. .... 514/212

4,769,369 9/1988 Thomas et al. .... 514/234.3

### FOREIGN PATENT DOCUMENTS

2164058 1/1972 Fed. Rep. of Germany ..... 546/133

3320793 3/1966 Fed. Rep. of Germany ..... 514/212

1377231 1/1972 United Kingdom .....

### OTHER PUBLICATIONS

Nagwer, Organic-Chemicals, Drugs and Their Syn-  
onyms, vol. 11, (1987) p. 1145.

European Search Report.

Org.-Ch.

1456 (1987)

## Astelin Patent (1992)

In the case of dosage forms containing water, it is optionally possible to use additional isotonization agents. Isotonization agents which may, for example, be used are: saccharose, glucose, glycerine, sorbitol, 1,2-propylene glycol, NaCl.



APOTEX\_AZFL 0054360

DTX-016.0001

# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution
<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	None needed
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC
<b>Tonicity Adjuster</b>	Dextrose	NaCl <b>Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol</b>
<b>pH</b>	5 to 7	

# Scope of The Prior Art

	Flonase®	Astelin®
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution
<b>Vehicle</b>	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%
<b>Surfactants</b>	Polysorbate 80	None needed
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC
<b>Tonicity Adjuster</b>	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol
<b>pH</b>	5 to 7	<b>6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)</b>



# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)  Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	
<b>Vehicle</b>	Water	Water	
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w);  (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w);  (2) EDTA disodium  Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	
<b>Surfactants</b>	Polysorbate 80	None needed	
<b>Thickening Agents</b>	MCC / CMC	HPMC  Astelin patent: others, including CMC	
<b>Tonicity Adjuster</b>	Dextrose	NaCl  Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	



# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)  Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	<b>"microfine" (&lt; 10 microns)</b>
<b>Vehicle</b>	Water	Water	
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium  Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	
<b>Surfactants</b>	Polysorbate 80	None needed	
<b>Thickening Agents</b>	MCC / CMC	HPMC  Astelin patent: others, including CMC	
<b>Tonicity Adjuster</b>	Dextrose	NaCl  Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	

# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)  Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	<b>Water</b>
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium  Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	
<b>Surfactants</b>	Polysorbate 80	None needed	
<b>Thickening Agents</b>	MCC / CMC	HPMC  Astelin patent: others, including CMC	
<b>Tonicity Adjuster</b>	Dextrose	NaCl  Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	

# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	<b>(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)</b>
<b>Surfactants</b>	Polysorbate 80	None needed	
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC	
<b>Tonicity Adjuster</b>	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	



# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
<b>Surfactants</b>	Polysorbate 80	None needed	<b>Polysorbate 80</b>
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC	
<b>Tonicity Adjuster</b>	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	



# Scope of the Prior Art

## Thickening Agent Concentration: MCC/CMC

### Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

Edited by  
Ainley Wade and Paul J

American Pharmaceutical Association  
Washington

1994

DEFENDANT'S  
EXHIBIT  
DTX-062

#### Handbook of Pharmaceutical Excipients

Microcrystalline cellulose and carboxymethylcellulose sodium

*Synonyms:* Avicel RC-581; Avicel RC-591; Avicel CL-611; colloidal cellulose; dispersible cellulose.

*Appearance:* white colored, odorless and tasteless hygroscopic powder.

*Pharmacopelias:* Br, Jpn and USPNF.

*Acidity/alkalinity:*

pH = 6-8 for a 1.2% w/v aqueous dispersion.

*Comments:* mixtures of microcrystalline cellulose and carboxymethylcellulose sodium that are dispersible in water and produce thixotropic gels are suitable as suspending vehicles in pharmaceutical formulations. The amount of carboxymethylcellulose present can vary between 8.3-18.8% w/w depending upon the grade of material.

# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)  Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
<b>Surfactants</b>	Polysorbate 80	None needed	Polysorbate 80
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC	<b>MCC/CMC (Avicel) (1.2%), HPMC</b>
<b>Tonicity Adjuster</b>	Dextrose	NaCl  Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	

# Scope of the Prior Art

## Tonicity Adjusters

### Handbook of PHARMACEUTICAL EXCIPIENTS

Second Edition

*Edited by*  
Ainley Wade and Paul J Weller

American Pharmaceutical Association  
Washington

1994

The Pharmaceutical Press  
London

DEFENDANT'S  
EXHIBIT  
DTX-062

#### Handbook of Pharmaceutical Excipients

## Glycerin

Antimicrobial preservative; emollient; humectant; plasticizer; solvent; sweetening agent; tonicity agent.

Osmolarity: a 2.6% v/v aqueous solution is iso-osmotic with serum.



# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
<b>Surfactants</b>	Polysorbate 80	None needed	Polysorbate 80
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC	MCC/CMC (Avicel): 1.2% HPMC
<b>Tonicity Adjuster</b>	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	<b>Dextrose, NaCl, saccharose, sorbitol, 1,2-propylene glycol, glucose, glycerin (&lt;2.6%)</b>
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	



# Scope of the Prior Art:

## Compatible pH Range

### The Art, Science, and Technology of Pharmaceutical Compounding

Lloyd V. Allen, Jr., PhD  
Professor and Chair  
Department of Medicinal Chemistry  
and Pharmaceutics  
College of Pharmacy  
University of Oklahoma Health  
Oklahoma City, Oklahoma



American Pharmaceutical Association  
Washington, D.C.

Allen: The Art, Science and Technology of Pharmaceutical Compounding (1998)

#### pH and Buffering

Nasal preparations are ordinarily buffered at the pH of maximum stability for the drug(s) they contain. The buffers are included to minimize any change in pH that may occur during the storage life of the drug. This change in pH can affect the solubility and stability of drugs; consequently, it is important to minimize such fluctuations. The buffer system should be designed to maintain the pH throughout the expected shelf life of the product, but with a low buffer capacity. Generally, pH in the range of 4 to 8 is considered optimum. pH and buffer-phosphate buffer systems are usually compatible with most nasal medications.

DEFENDANT'S  
EXHIBIT  
DTX-078

APOTEX\_AZFL 0132304

# Scope of The Prior Art

	Flonase®	Astelin®	Obvious Combination Formulation
<b>Active Ingredient</b>	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray)	Azelastine HCl (0.1% (w/w or w/v), 0.137 mg per spray)	Fluticasone propionate (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) Azelastine HCl (0.1% (w/w) or (w/v), 0.137 mg per spray)
<b>Particle Size</b>	"microfine" (< 10 microns)	Dissolved in solution	"microfine" (< 10 microns)
<b>Vehicle</b>	Water	Water	Water
<b>Preservatives</b>	(1) Benzalkonium chloride (0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w)	(1) Benzalkonium chloride (0.0125% w/w); (2) EDTA disodium Astelin patent: other preservatives; concentrations at 0.002% to 0.05%	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
<b>Surfactants</b>	Polysorbate 80	None needed	Polysorbate 80
<b>Thickening Agents</b>	MCC / CMC	HPMC Astelin patent: others, including CMC	MCC/CMC (Avicel): 1.2% HPMC
<b>Tonicity Adjuster</b>	Dextrose	NaCl Astelin patent: saccharose, glucose, glycerin, sorbitol, 1,2-propylene glycol	Dextrose, NaCl, saccharose, sorbitol, 1,2-propylene glycol, glucose, glycerin (<2.6%)
<b>pH</b>	5 to 7	6.8 +/- 0.3 (6.5 to 7.1) (buffered with citric acid and dibasic sodium phosphate)	<b>4 to 8, adjusted as desired with pH adjusters</b>



# The Asserted Claims Are Obvious

## '428 Patent, Claim 11

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w)</b> , 0.137 mg per spray)
Vehicle	Water
Preservatives	<b>(1) Benzalkonium chloride (0.0125% or 0.02% w/w);</b> <b>(2) Phenyl ethyl alcohol (0.25% w/w)</b> <b>(3) EDTA disodium (0.002% – 0.05%)</b>
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin (&lt;2.6%)</b>
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

1. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

11. The method of claim 1, wherein the formulation comprises:  
0.1% (weight/weight) azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride;  
from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium;  
polysorbate 80;  
2.3% (weight/weight) of glycerine; and  
0.25% (weight/weight) of phenyl ethyl alcohol.

Claim  
Obvious?



# The Asserted Claims Are Obvious

## '428 Patent, Claim 10

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w)</b> , 0.137 mg per spray)
Vehicle	Water
Preservatives	<b>(1) Benzalkonium chloride (0.0125% or 0.02% w/w);</b> <b>(2) Phenyl ethyl alcohol (0.25% w/w)</b> <b>(3) EDTA disodium (0.002% – 0.05%)</b>
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin (&lt;2.6%)</b>
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

1. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

9. The method of claim 1, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.

10. The method of claim 9, wherein the formulation comprises:  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride;  
from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and  
from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

Claim Obvious?





# The Asserted Claims Are Obvious

## '428 Patent, Claim 13

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or <b>0.05 mg</b> , or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), <b>0.137 mg</b> per spray)
Vehicle	Water
Preservatives	(1) <b>Benzalkonium chloride</b> (0.0125% or 0.02% w/w); (2) <b>Phenyl ethyl alcohol</b> (0.25% w/w) (3) <b>EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel)</b> (1.2%), HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

1. A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

13. The method of claim 1, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

Claim  
Obvious?



# The Asserted Claims Are Obvious

## '428 Patent, Claim 15

**Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, the Handbook, and Allen**

<b>Active Ingredient</b>	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w))</b> , 0.137 mg per spray)
<b>Vehicle</b>	Water
<b>Preservatives</b>	(1) <b>Benzalkonium chloride</b> (0.0125% or 0.02% w/w); (2) <b>Phenyl ethyl alcohol</b> (0.25% w/w) (3) <b>EDTA disodium</b> (0.002% – 0.05%)
<b>Surfactants</b>	<b>Polysorbate 80</b>
<b>Thickening Agents</b>	<b>MCC/CMC (Avicel) (1.2%)</b> , HPMC
<b>Tonicity Adjuster</b>	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
<b>Particle Size</b>	"microfine" (< 10 microns)
<b>pH</b>	4 to 8, adjusted as desired with pH adjusters

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonation agents.

15. The method of claim 14, wherein the formulation has a pH of 4.5 to about 6.5.

**Claim Obvious?**





# The Asserted Claims Are Obvious

## '428 Patent, Claim 16

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w))</b> , 0.137 mg per spray)
Vehicle	<b>Water</b>
Preservatives	<b>(1) Benzalkonium chloride</b> (0.0125% or 0.02% w/w); <b>(2) Phenyl ethyl alcohol</b> (0.25% w/w) <b>(3) EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%)</b> , HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, glycerin (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

16. The method of claim 14, wherein the formulation is an aqueous suspension.

Claim  
Obvious?



# The Asserted Claims Are Obvious

## '428 Patent, Claim 23

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w)</b> , 0.137 mg per spray)
Vehicle	Water
Preservatives	<b>(1) Benzalkonium chloride (0.0125% or 0.02% w/w);</b> <b>(2) Phenyl ethyl alcohol (0.25% w/w)</b> <b>(3) EDTA disodium (0.002% – 0.05%)</b>
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin (&lt;2.6%)</b>
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

22. The method of claim 14, wherein the formulation comprises edetate disodium, benzalkonium chloride, microcrystalline cellulose, carboxymethyl cellulose sodium, polysorbate 80, glycerine, and phenyl ethyl alcohol.

23. The method of claim 22, wherein the formulation comprises:  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride;  
from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline cellulose and carboxymethyl cellulose sodium; and  
from 2.3% (weight/weight) to 2.6% (weight/weight) of glycerine.

Claim  
Obvious?





# The Asserted Claims Are Obvious

## '428 Patent, Claim 24

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w)</b> , 0.137 mg per spray)
Vehicle	Water
Preservatives	(1) <b>Benzalkonium chloride (0.0125% or 0.02% w/w)</b> ; (2) <b>Phenyl ethyl alcohol (0.25% w/w)</b> (3) <b>EDTA disodium (0.002% – 0.05%)</b>
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%)</b> , HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin (&lt;2.6%)</b>
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

24. The method of claim 14, wherein the formulation comprises:  
0.1% (weight/weight) azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
from 0.002% (weight/weight) to 0.02% (weight/weight) of benzalkonium chloride;  
from 0.65% (weight/weight) to 3% (weight/weight) of a combination of microcrystalline and carboxymethyl cellulose sodium;  
polysorbate 80;  
2.3% (weight/weight) of glycerine; and  
0.25% (weight/weight) of phenyl ethyl alcohol.

Claim  
Obvious?



# The Asserted Claims Are Obvious

## '428 Patent, Claim 26

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or <b>0.05 mg</b> , or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), <b>0.137 mg</b> per spray)
Vehicle	Water
Preservatives	(1) <b>Benzalkonium chloride</b> (0.0125% or 0.02% w/w); (2) <b>Phenyl ethyl alcohol</b> (0.25% w/w) (3) <b>EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%)</b> , HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

14. A method for minimizing symptoms of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) to 1% (weight/weight) of azelastine hydrochloride;  
from 0.0357% (weight/weight) to 1.5% (weight/weight) of fluticasone propionate;  
one or more preservatives;  
one or more thickening agents;  
one or more surfactants; and  
one or more isotonicization agents.

26. The method of claim 14, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

Claim  
Obvious?





# The Asserted Claims Are Obvious

## '428 Patent, Claim 29

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, the Handbook, and Allen

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or <b>0.05 mg</b> , or 0.05% (w/w), or <b>0.5 mg/mL</b> per spray) <b>Azelastine HCl</b> (0.1% (w/w), <b>0.137 mg</b> per spray)
Vehicle	<b>Water</b>
Preservatives	<b>(1) Benzalkonium chloride (0.0125% or 0.02% w/w);</b> <b>(2) Phenyl ethyl alcohol</b> (0.25% w/w) <b>(3) EDTA disodium (0.002% – 0.05%)</b>
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	<b>4 to 8, adjusted as desired with pH adjusters</b>

**28.** A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) % (weight/weight) of azelastine hydrochloride;  
from about 50 µg/mL to about 5 mg/mL of fluticasone propionate;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
glycerine;  
polysorbate; and  
a thickening agent;  
wherein the formulation has a pH of 4.5 to about 6.5; and  
wherein the formulation is an aqueous suspension.

**29.** The method of claim 28, wherein the formulation is contained in a nasal spray product; and wherein from 0.03 mg to 3 mg of azelastine hydrochloride and from 0.05 mg to 0.15 mg of fluticasone propionate is released per individual actuation of the nasal spray product.

Claim  
Obvious?





# The Asserted Claims Are Obvious

## '428 Patent, Claim 30

**Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, the Handbook, and Allen**

<b>Active Ingredient</b>	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or 0.05% (w/w), or <b>0.5 mg/mL</b> per spray) <b>Azelastine HCl (0.1% (w/w),</b> 0.137 mg per spray)
<b>Vehicle</b>	<b>Water</b>
<b>Preservatives</b>	(1) <b>Benzalkonium chloride (0.0125% or 0.02% w/w);</b> (2) <b>Phenyl ethyl alcohol (0.25% w/w)</b> (3) <b>EDTA disodium (0.002% – 0.05%)</b>
<b>Surfactants</b>	<b>Polysorbate 80</b>
<b>Thickening Agents</b>	<b>MCC/CMC (Avicel)</b> (1.2%), HPMC
<b>Tonicity Adjuster</b>	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
<b>Particle Size</b>	"microfine" (< 10 microns)
<b>pH</b>	<b>4 to 8, adjusted as desired with pH adjusters</b>

**28.** A method for the treatment of seasonal allergic rhinitis, comprising administration of a therapeutically effective amount of a nasal spray formulation comprising:  
from 0.001% (weight/weight) % (weight/weight) of azelastine hydrochloride;  
from about 50 µg/mL to about 5 mg/mL of fluticasone propionate;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of benzalkonium chloride;  
from 0.002% (weight/weight) to 0.05% (weight/weight) of edetate disodium;  
glycerine;  
polysorbate; and  
a thickening agent;  
wherein the formulation has a pH of 4.5 to about 6.5; and  
wherein the formulation is an aqueous suspension.

**30.** The method of claim 28, wherein the thickening agent comprises microcrystalline cellulose and carboxymethyl cellulose sodium.

**Claim Obvious?**



# The Asserted Claims Are Obvious

## '620 Patent, Claim 42

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), 0.137 mg per spray)
Vehicle	<b>Water</b>
Preservatives	<b>(1) Benzalkonium chloride</b> (0.0125% or 0.02% w/w); <b>(2) Phenyl ethyl alcohol</b> (0.25% w/w) <b>(3) EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

1. A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.

42. The pharmaceutical formulation of claim 1, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

Claim  
Obvious?





# The Asserted Claims Are Obvious

## '620 Patent, Claim 43

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), 0.137 mg per spray)
Vehicle	<b>Water</b>
Preservatives	<b>(1) Benzalkonium chloride</b> (0.0125% or 0.02% w/w); <b>(2) Phenyl ethyl alcohol</b> (0.25% w/w) <b>(3) EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%),</b> HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

24. A pharmaceutical formulation comprising azelastine hydrochloride; and, fluticasone propionate, wherein said formulation is in the dosage form of as a nasal spray, and wherein said formulation is used in the treatment of conditions for which administration of one or more anti-histamine and/or one or more steroid is indicated.

43. The pharmaceutical formulation of claim 24, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

Claim  
Obvious?





# The Asserted Claims Are Obvious

## '620 Patent, Claim 44

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), 0.137 mg per spray)
Vehicle	<b>Water</b>
Preservatives	<b>(1) Benzalkonium chloride</b> (0.0125% or 0.02% w/w); <b>(2) Phenyl ethyl alcohol</b> (0.25% w/w) <b>(3) EDTA disodium</b> (0.002% – 0.05%)
Surfactants	<b>Polysorbate 80</b>
Thickening Agents	<b>MCC/CMC (Avicel) (1.2%)</b> , HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, <b>glycerin</b> (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

25. A nasal spray formulation comprising (i) azelastine, or a pharmaceutically acceptable salt thereof, (ii) a pharmaceutically acceptable ester of fluticasone, and (iii) a pharmaceutically acceptable carrier or excipient therefor.

44. The pharmaceutical formulation of claim 25, further comprising edetate disodium, glycerine, a thickening agent comprising microcrystalline cellulose and sodium carboxy methyl cellulose, polysorbate 80, benzalkonium chloride, phenyl ethyl alcohol, and purified water.

Claim  
Obvious?



# The Asserted Claims Are Obvious

## '620 Patent, Claim 4

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

Active Ingredient	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or 0.05% (w/w), or 0.5 mg/mL per spray) <b>Azelastine HCl</b> (0.1% (w/w), 0.137 mg per spray)
Vehicle	Water
Preservatives	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)
Surfactants	Polysorbate 80
Thickening Agents	MCC/CMC (Avicel) (1.2%), HPMC
Tonicity Adjuster	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, glycerin (<2.6%)
Particle Size	"microfine" (< 10 microns)
pH	4 to 8, adjusted as desired with pH adjusters

1. A pharmaceutical formulation comprising:  
azelastine, or a pharmaceutically acceptable salt thereof,  
and  
a pharmaceutically acceptable ester of fluticasone,  
wherein said pharmaceutical formulation is in a dosage  
form suitable for nasal administration.

4. The pharmaceutical formulation of claim 1, wherein said  
formulation has a particle size of less than 10 µm.

Claim  
Obvious?










# The Asserted Claims Are Obvious

## '620 Patent, Claim 29

### Formulation Obvious Over: Flonase®, Astelin®, Astelin Patent, and the Handbook

<b>Active Ingredient</b>	<b>Fluticasone propionate</b> (50 mcg, or 0.05 mg, or <b>0.05% (w/w)</b> , or 0.5 mg/mL per spray) <b>Azelastine HCl (0.1% (w/w)</b> , 0.137 mg per spray)	1. A pharmaceutical formulation comprising: azelastine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable ester of fluticasone, wherein said pharmaceutical formulation is in a dosage form suitable for nasal administration.	Claim Obvious? 
<b>Vehicle</b>	Water		
<b>Preservatives</b>	(1) Benzalkonium chloride (0.0125% or 0.02% w/w); (2) Phenyl ethyl alcohol (0.25% w/w) (3) EDTA disodium (0.002% – 0.05%)	5. The pharmaceutical formulation of claim 1, wherein said formulation is an aqueous suspension comprising from 0.0005% (weight/weight) to 2% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	
<b>Surfactants</b>	Polysorbate 80	6. The pharmaceutical formulation according to claim 5, comprising from 0.001% (weight/weight) to 1% (weight/weight) of said azelastine, or said pharmaceutically acceptable salt thereof, and from 0.0357% (weight/weight) to 1.5% (weight/weight) of said pharmaceutically acceptable ester of fluticasone.	
<b>Thickening Agents</b>	MCC/CMC (Avicel) (1.2%), HPMC, gelatin, PVP, PVA	26. The pharmaceutical formulation of claim 6, comprising 0.1% (weight/weight) of azelastine hydrochloride, and from 0.0357% to 1.5% (weight/weight) of fluticasone propionate.	
<b>Tonicity Adjuster</b>	Dextrose, NaCl, saccharose, glucose, sorbitol, 1,2-propylene glycol, glycerin (<2.6%)	29. The pharmaceutical formulation of claim 26, wherein said dosage form suitable for nasal administration comprises a nasal spray.	
<b>Particle Size</b>	"microfine" (< 10 microns)		
<b>pH</b>	4 to 8, adjusted as desired with pH adjusters		



# Flonase®:

## A Suspension With Ingredients In Solution

### Flonase Label (1998)

**FLONASE Nasal Spray 50 mcg is an aqueous suspension of microfine fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.**

**It is necessary to prime the pump before first use or after a period of non-use (1 week or more). After initial priming (six actuations), each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation through the nasal adapter. Each bottle of FLONASE Nasal Spray provides 120 metered sprays. After 120 metered sprays, the amount of fluticasone propionate delivered per actuation may not be consistent and the unit should be discarded.**

APOTEX\_AZFL 0000100

# Textbooks Teach How To Make Nasal Suspensions

## The Art, Science and Technology of Pharmaceutical Compounding

### The Art, Science, and Technology of Pharmaceutical Compounding

Lloyd V. Allen, Jr., PhD  
Professor and Chair  
Department of Medicinal Chemistry  
and Pharmaceutics  
College of Pharmacy  
University of Oklahoma Health Sciences Center  
Oklahoma City, Oklahoma



American Pharmaceutical Association  
Washington, D.C.

DEFENDANT'S  
EXHIBIT  
DTX-078

APOTEX A

### Preparation

The methods used to formulate the four dosage forms of nasal preparations are similar. The box below lists the steps to be followed when preparing nasal solutions, suspensions, ointments, and gels.

#### Preparation of Nasal Products (cont.)

##### Suspensions (Method 1)

1. Accurately weigh or measure each ingredient.
2. Dissolve/mix the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
3. Add sufficient sterile water for injection to volume and mix well.
4. Take a sample of the suspension and determine the pH and other quality control factors.
5. Package in a suitable container for autoclaving.
6. Autoclave, cool, and label.
7. If a large number of suspensions are to be prepared, select a random sample to be assayed and checked for sterility.


##### Suspensions (Method 2)

1. Accurately weigh or measure each ingredient.
2. Sterilize each ingredient using a suitable method.
3. Dissolve/mix the ingredients in about three fourths of the quantity of sterile water for injection and mix well.
4. Add sufficient sterile water for injection to volume and mix well.
5. Take a sample of the suspension and determine the pH and other quality control factors.
6. Package and label.
7. If a large number of suspensions are to be prepared, select a random sample to be assayed and checked for sterility.



# Cramer: Example III

## Azelastine HCl / Steroid Nasal Spray


 Europäisches Patentamt  
 European Patent Office  
 Office européen des brevets

(11) EP 0 780 127 A1

(12) EUROPEAN PATENT APPLICATION

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 (22) Date of filing: 05.12.1996

(51) Int Cl. A61K 31/57, A61K 31/58, A61K 31/56, A61K 31/495, A61K 31/445, A61K 31/55 // (A61K31/56, 31:495), (A61K31/56, 31:445), (A61K31/56, 31:55), (A61K31/57, 31:495), (A61K31/57, 31:445), (A61K31/57, 31:55), (A61K31/58, 31:495), (A61K31/58, 31:445)

(84) Designated Contracting States: AT BE CH DE DK ES FI FR GB GR IE IT LI LU NL PT SE  
 (30) Priority: 19.12.1995 US 574791  
 (71) Applicant: THE PROCTER & GAMBLE COMPANY, Cincinnati, Ohio 45202 (US)  
 (72) Inventor: Cramer, Ronald Dean, Cincinnati, Ohio 45216 (US)  
 (74) Representative: Woolf, Victoria, Procter & Gamble Pharmaceuticals Patent Department, Lovett House, Lovett Road, Staines, Middlesex TW18 3JZ (GB)

(54) A nasal spray containing a steroid and an antihistamine  
 (57) The present invention relates to novel nasal spray compositions comprising a safe and effective amount of a glucocorticosteroid and an antihistamine having antiallergic properties.

EP 0 780 127 A1

### Cramer

#### Example III

The intranasally administered pharmaceutical composition of the present invention is prepared by combining the following components utilizing conventional mixing techniques similar to that described in Example I.

Component	Wgt %
triamcinolone acetonide	0.050
azelastine HCl	0.070
polysorbate 80	0.050
glycerin	2.000
hydroxypropyl methyl cellulose	1.000
sodium chloride	0.900
ethylenediamine tetraacetic acid	0.050
benzalkonium chloride	0.020
distilled water	q.s. to vol.

Administration of approximately 0.4 grams of the composition is used for topical nasal application to provide relief from allergy or allergy-like symptoms. Additionally, substantially similar results are also obtained using, in whole or in part, equivalent amounts of other glucocorticoid agents such as fluticasone, mometasone, budesonide, pharmaceutically acceptable salts thereof and mixtures thereof. Furthermore, the above described compositions may also contain a decongestant such as pseudoephedrine, phenylpropanolamine, phenylephrine, tetrahydrozoline, naphazoline, oxymetazoline, tramazoline, 5-(2-imidazolylamino)benzimidazoles, optically active racemates thereof, pharmaceutically acceptable salts thereof and mixtures thereof. Those skilled in the art will quickly realize other suitable ingredients, diluents and dosage forms (or readily ascertain such using routine experimentation) which may further be incorporated into the above compositions without departing from the scope and spirit of the present invention.



# Testing of Cramer's Example III: Ms. Malhotra's Declaration

## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Amar Lulla, *et al.*

Serial No.: 12/508,393

Filed: July 23, 2009

For: COMBINATION OF AZELASTINE AND  
STEROIDS

### DECLARATION OF GEENA MALHOTRA

Commissioner for Patents  
P.O. Box. 1450  
Alexandria, VA 22313-1450

Sir:

1. I, Geena Malhotra, hereby declare and state
2. I am currently employed by Cipla Ltd. referenced U.S. Pat. App. No. 12/508,393 (the Development.
3. I hold the degree of B. Pharm. from SNTD accurately listing my scientific credentials and was A.
4. I am a co-inventor of the invention claimed
5. I have been informed that the U.S. Patent C Publication No. 0780127A1 by Ronald Cramer application, and specifically that the U.S. Patent O closest prior art example.

9. From the observations set forth in paragraph 8, it is conclusive that the formulation described in Example 3 of *Cramer* is inoperable and unacceptable as a pharmaceutical formulation in a dosage form suitable for nasal administration for at least the following reasons:

- (A) Unacceptable settling and difficulty in resuspending – homogeneity of the active material in product is not expected to be maintained due to caking seen at the bottom of vial of the formulation;
- (B) Unacceptable jet rather than desired spray mist – after actuation of the nasal pump, the product comes out as jet (a stream of liquid forcefully shooting forth from the orifice) and not a spray (a mist of fine liquid particles), and due to which the drug is not expected to be suitably deposited on nasal mucosa; and
- (C) Unacceptable osmolality – It is widely known and accepted that nasal sprays are preferably isotonic (as is acknowledged by *Cramer* at page 3, lines 8 and 49) rather than hypertonic.<sup>1</sup> Accordingly, the undesirable hyperosmotic (i.e., 554 mOsm/kg), hypertonic character of the product is expected to give rise to irritation of the nasal mucosa.

# Meda Combined Astelin® and Flonase®

## Astelin – Flonase Combination Product: Feasibility Assessment Plan.

### Background

**Table 1: Formulations comparison**

Product	Flonase
Active Compound	Fluticasone propionate
Active concentration per spray	50 microgram
Polymers	Micro-crystalline cellulose and carboxymethyl-cellulose sodium,
Sweetener, Osmolarity	Dextrose
Preservative	0.02% benzyalkonium chloride & 0.25% phenylethyl alcohol
Surfactant	Polysorbate 80
Chelating agent	
Buffer	
Water	q.s.
pH	5-7
Appearance	Suspension

### Plan A:

1. Filter or centrifuge Flonase product and determine Hydrochloride in the filtrate or centrifugate.
2. If Azelastine Hydrochloride is sufficiently soluble t Azelastine Hydrochloride powder to the Flonase su
3. If Azelastine Hydrochloride is not sufficiently solut process so that Azelastine Hydrochloride is comple
4. Identify suitable spray pump head for existing Aste spray pattern and droplet size distribution of Flonase
5. Determine accelerated stability of the product store glass bottle and commercial Astelin container clov

DEFENDANT'S  
EXHIBIT  
DTX-202

HIGHLY CONFIDENTIAL-  
SUBJECT TO STIPULATED PROTECTIVE ORDER

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**Table 1: Formulations comparison**

Product	Flonase	Astelin Improved Taste
Active Compound	Fluticasone propionate	Azelastine Hydrochloride
Active concentration per spray	50 microgram	137 microgram
Polymers	Micro-crystalline cellulose and carboxymethyl-cellulose sodium,	Hydroxypropyl methylcellulose
Sweetener, Osmolarity	Dextrose	Sucralose NF Sorbitol
Preservative	0.02% benzyalkonium chloride & 0.25% phenylethyl alcohol	0.025% benzyalkonium chloride
Surfactant	Polysorbate 80	
Chelating agent		EDTA
Buffer		Sodium Citrate, dihydrate
Water	q.s.	q.s.
pH	5-7	6.0-6.9
Appearance	Suspension	Clear, colorless liquid

# Meda Combined Astelin® and Flonase®

## Astelin – Flonase Combination Product: Feasibility Assessment Plan.

### Background

Table 1: Formulations comparison

Product	Flonase	Astelin
Active Compound		
Active concentration		
spray		
Polymers		
Sweetener, Osmolarity		
Preservative		
Surfactant		
Chelating agent		
Buffer		
Water		
pH		
Appearance		

### Plan A:

1. Filter or centrifuge Flonase product and determine the solubility of Azelastine Hydrochloride in the filtrate or centrifugate.
2. If Azelastine Hydrochloride is sufficiently soluble then add required amount of Azelastine Hydrochloride powder to the Flonase suspension.
3. If Azelastine Hydrochloride is not sufficiently soluble, modify the formulation or process so that Azelastine Hydrochloride is completely in solution.
4. Identify suitable spray pump head for existing Astelin bottle to attain similar spray pattern and droplet size distribution of Flonase spray.
5. Determine accelerated stability of the product stored in the Flonase amber colored glass bottle and commercial Astelin container closure system.

### Plan A:

1. Filter or centrifuge Flonase product and determine the solubility of Azelastine Hydrochloride in the filtrate or centrifugate.
2. If Azelastine Hydrochloride is sufficiently soluble then add required amount of Azelastine Hydrochloride powder to the Flonase suspension.
3. If Azelastine Hydrochloride is not sufficiently soluble, modify the formulation or process so that Azelastine Hydrochloride is completely in solution.
4. Identify suitable spray pump head for existing Astelin bottle to attain similar spray pattern and droplet size distribution of Flonase spray.
5. Determine accelerated stability of the product stored in the Flonase amber colored glass bottle and commercial Astelin container closure system.

DEFENDANT'S  
EXHIBIT  
DTX-202

HIGHLY CONFIDENTIAL-  
SUBJECT TO STIPULATED PROTECTIVE ORDER

MEDA\_APTX01645706

DTX-202 0001



# Astelin Patent: Covers Azelastine/Fluticasone Combination Products

United States Patent [19]  
Hettche

[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING  
MEDICAMENTS

[75] Inventor: Helmut Hettche, Dietzenbach, Fed.  
Rep. of Germany

[73] Assignee: Asta Pharma AG, Fed. Rep. of  
Germany

[21] Appl. No.: 851,644

[22] Filed: Jul. 12, 1990

Related U.S. Application Data

[63] Continuation of Ser. No. 248,772, Nov. 9, 1988, aban-  
doned.

[30] Foreign Application Priority Data

Nov. 13, 1987 [DE] Fed. Rep. of Germany ..... 3738681

[51] Int. Cl. A61K 9/14; A61K 31/35

[52] U.S. Cl. 424/402; 424/423

[58] Field of

42-

[56]

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US005164194A

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2,991,308 8/1961 Ashkenazi ..... 239/302  
3,813,384 5/1974 Vogelung ..... 546/133  
4,704,287 11/1987 Engel et al. .... 516/212  
4,769,349 9/1988 Thomas et al. .... 516/234.3

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1377231 1/1972 United Kingdom

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**Astelin Patent (1992)**

United States Patent [19]  
Hettche

US005164194A  
[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

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# Astelin Patent: Covers Azelastine/Fluticasone Combination Products

United States Patent [19]  
Hettche

US005164194A  
[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

[54] AZELASTINE CONTAINING MEDICAMENTS  
[75] Inventor: Helmut Hettche, Dietzenbach, Fed. Rep. of Germany  
[73] Assignee: Asta Pharma AG, Fed. Rep. of Germany  
[21] Appl. No.: 851,644  
[22] Filed: Jul. 12, 1990

Related U.S. Application Data  
[65] Continuation of Ser. No. 368,772, Nov. 9, 1988, abandoned.

Foreign Application Priority Data  
[30] Nov. 15, 1987 [DE] Fed. Rep. of Germany ..... 3750881

[51] Int. Cl. A61K 9/14; A61K 31/55  
[52] U.S. Cl. 424/482; 424/431

[58] Field of Invention

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Arzneimittel, Fortschritte 1972-1985, pp. 936 and 939 (1977).

**Astelin Patent (1992)**

United States Patent [19]  
Hettche

US005164194A  
[11] Patent Number: 5,164,194  
[45] Date of Patent: Nov. 17, 1992

1. A method for the treatment of irritation or disorders of the nose and eye which comprises applying directly to nasal tissues or to the conjunctival sac of the eyes a medicament which contains a member selected from the group consisting of azelastine and its physiologically acceptable salts.

DTX-018.0001

