

2 QUESTION BASED REVIEW

2.1 General Attributes

2.1.1 What are the general attributes of _____ M?

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_____ ⁴ (azelastine hydrochloride) Nasal Spray 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. Its chemical name is (±)-1-(2H)-phthalazinone,4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-, monohydrochloride. The structural formula is presented in Figure 1 below.

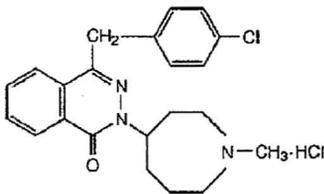


Figure 1. Structural formula of Azelastine Hydrochloride

Molecular formula: C₂₂H₂₄ClN₃O·HCl

Molecular weight: 418.37

Solubility: Sparingly soluble in water, methanol, and propylene glycol and slightly soluble in ethanol, octanol, and glycerine.

Melting Point: 225 °C

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FORMULATION

_____ ⁴ Nasal Spray contains 0.1% azelastine hydrochloride in an isotonic aqueous solution containing sorbitol, sucralose, hypromellose, sodium citrate, edetate disodium, benzalkonium chloride (125 mcg/mL) and purified water (pH 6.4).

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). The 30-mL bottle delivers 200 metered sprays.

INDICATIONS (as per proposed label)

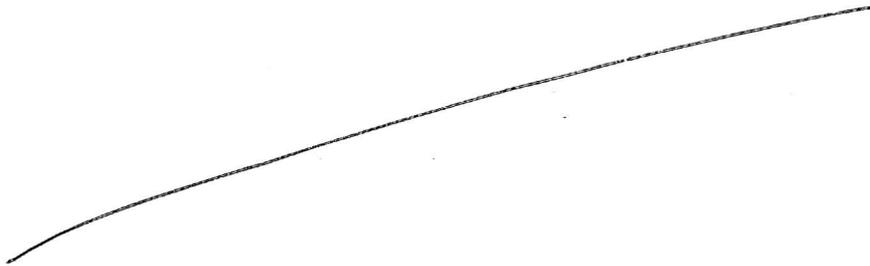
Seasonal Allergic Rhinitis

Indicated for the treatment of the symptoms of seasonal allergic rhinitis such as rhinorrhea, congestion, sneezing and itching in adults _____

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Vasomotor Rhinitis

DOSAGE AND ADMINISTRATION (as per proposed label)



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2.2 General Clinical Pharmacology

2.2.1 What is known about the pharmacokinetics of _____ M?

The sponsor evaluated single-dose pharmacokinetics of azelastine in an open-label, single-center, randomized, parallel group relative bioavailability study in which 18 healthy male subjects ages 18-50 years were treated with one of three intranasal formulations (2 sprays per nostril) of azelastine hydrochloride: (1) commercial formulation of 0.1% Astelin® (total dose: 548 mcg), (2) proposed new formulation of 0.1% _____ M (total dose: 548 mcg) and (3) higher strength formulation of 0.15% _____ M (total dose: 822 mcg).

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The pharmacokinetic results of azelastine and its major active metabolite, desmethylazelastine from 0.1% _____ M and 0.15% _____ M are presented below in Table 2. Azelastine was found to be absorbed into the systemic circulation with a median T_{max} of 3 hours following single dose intranasal administration. The mean (SD) terminal half-life values of azelastine and desmethylazelastine were calculated to be 22 (7.5) hrs and 52 (21) hrs, respectively.

Table 2. Mean \pm SD (n =18) plasma pharmacokinetic parameters of azelastine and desmethylazelastine following intranasal administration of 0.1% (dose: 548 mcg) and 0.15% (dose: 822 mcg).

PK parameters	Azelastine		Desmethylazelastine	
	(548 mcg)	(822 mcg)	(548 mcg)	(822 mcg)
AUC _{0-t} (pg.hr/mL)	4917 \pm 1394	8941 \pm 3749	1634 \pm 603	2780 \pm 857
AUC _{0-inf} (pg.hr/mL)	5122 \pm 1546	9312 \pm 3950	2131 \pm 609	3824 \pm 1184
AUC _{0-inf} /D [pg.hr/mL/(μ g/kg)]	704 \pm 207	804 \pm 375	292 \pm 72	328 \pm 108
C _{max} (pg/mL)	200 \pm 67	409 \pm 160	23 \pm 11	38 \pm 15
C _{max} /D [pg/mL/(μ g/kg)]	27 \pm 7.9	35 \pm 14	3.1 \pm 1.3	3.3 \pm 1.3
T _{max} (hr)*	3.0 (0.5 – 4.0)	4.0 (0.25-6.0)	24 (12 – 96)	24 (24-48)
T _{1/2} (hr)	22 \pm 7.5	25 \pm 8.7	52 \pm 21	57 \pm 23
V _z /F (L/kg)	50 \pm 36	52 \pm 21	272 \pm 140	266 \pm 110
CL/F (mL/min/kg)	26 \pm 9.5	26 \pm 15	61 \pm 16	57 \pm 23

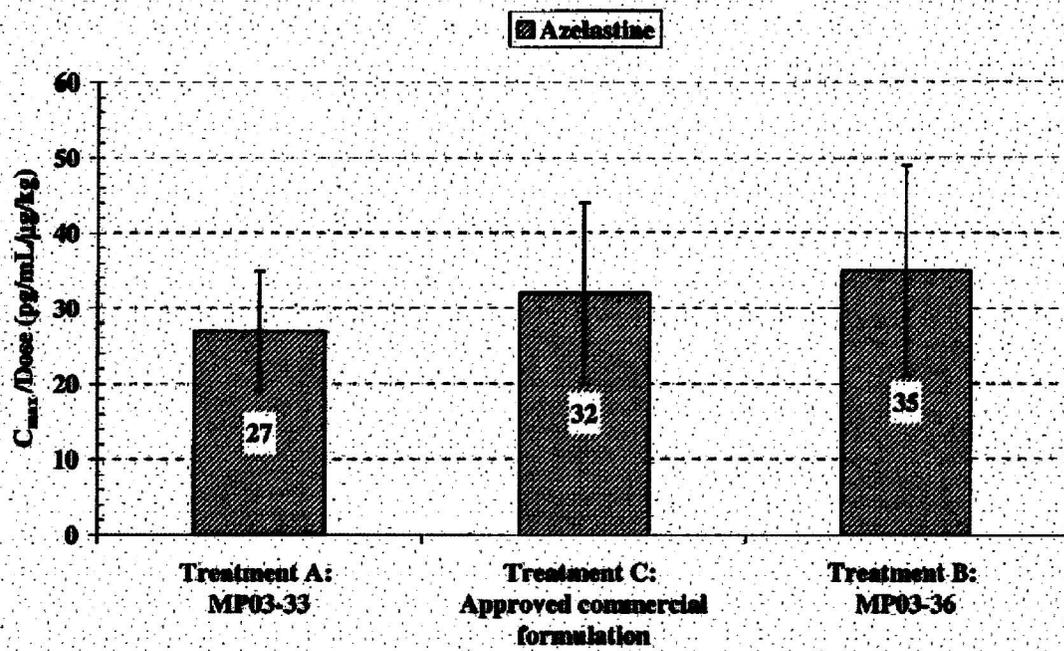
* median (range)

Dose-proportionality:

As shown in Table 2 above and also illustrated in Figures 2-5, the dose and body weight normalized mean C_{max} and AUC_{0-inf} values of azelastine and desmethylazelastine were slightly higher for the 0.15% compared to 0.1%. Therefore, exhibits a slightly greater than dose proportional pharmacokinetics across the dose range of 548 mcg and 822 mcg.

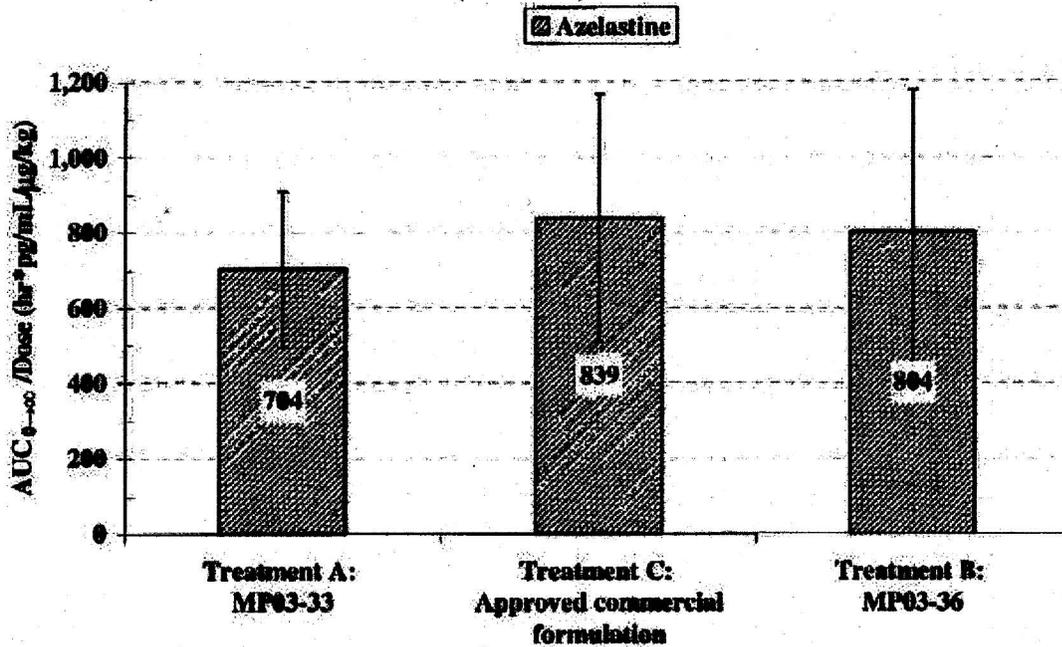
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Figure 2. Dose and weight normalized plasma C_{max} [pg/mL/(μ g/kg)] of Azelastine following administration of 0.1% μ M (MP03-33), 0.1% Astelin® (approved commercial) and 0.15% μ M (MP03-36)



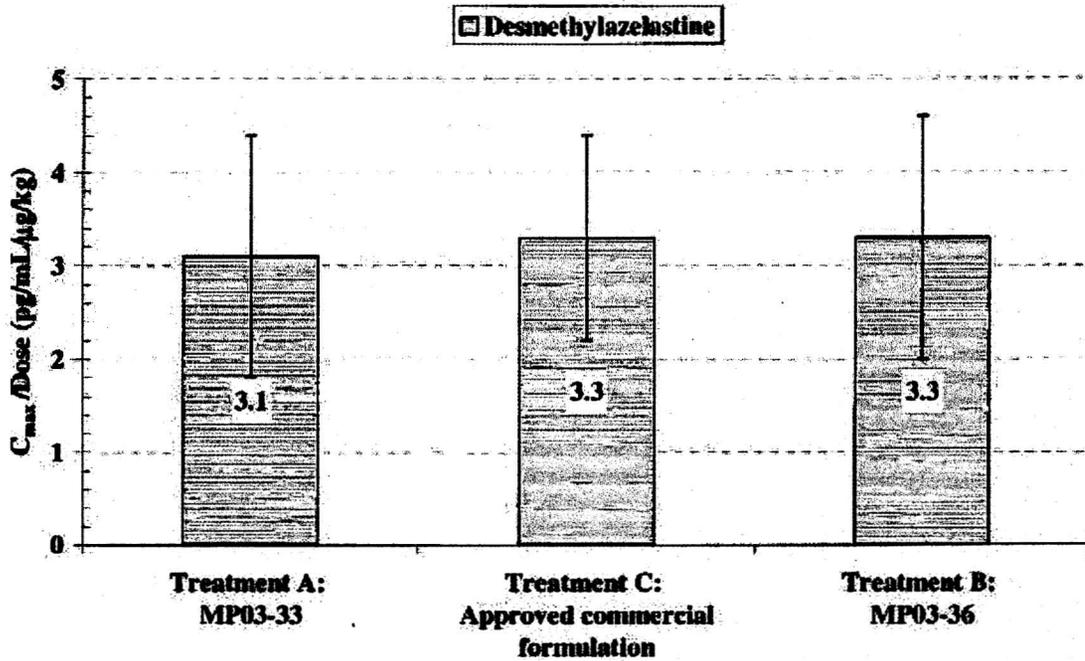
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Figure 3. Dose and weight normalized plasma $AUC_{0-\infty}$ [hr*pg/mL/(μ g/kg)] of Azelastine following administration of 0.1% μ M (MP03-33), 0.1% Astelin® (approved commercial) and 0.15% μ M (MP03-36)



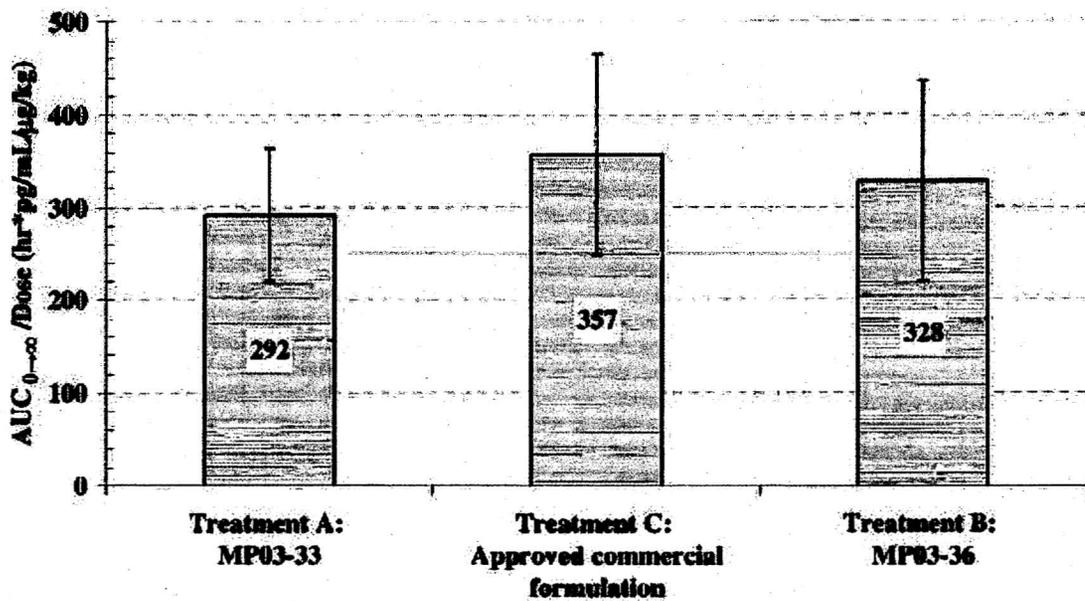
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Figure 4. Dose and weight normalized C_{max} [pg/mL/(μ g/kg)] of Desmethylazelastine following administration of 0.1% MP03-33 , 0.1% Astelin® (approved commercial) and 0.15% MP03-36



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Figure 5. Dose and weight normalized $AUC_{0-\infty}$ [hr*pg/mL/(μ g/kg)] of Desmethylazelastine following administration of 0.1% MP03-33 , 0.1% Astelin® (approved commercial) and 0.15% MP03-36



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2.3 General Biopharmaceutics

2.3.1. What was the relative bioavailability of the new azelastine hydrochloride nasal spray formulation (——— M) when compared to the currently marketed nasal spray formulation (Astelin®)?

A relative bioavailability study (MP429), as described in section 2.2.1 above, was conducted with two primary objectives: (1) to evaluate relative bioavailability of 548 mcg ——— M (new formulation) compared to the same dose of Astelin® (approved commercial formulation) and (2) to evaluate dose proportionality of two different doses (548 mcg and 822 mcg) of ' ——— M. This was particularly necessary because it is known from the literature that sorbitol decreases bioavailability of certain drugs following oral administration. This has been attributed to several factors including altering GI permeability, inhibiting intestinal transporter(s) and so on. ——— is an intranasal formulation with ' ——— (w/v) sorbitol concentration. The impact on systemic drug exposure of the presence of sorbitol at this level following intranasal administration is unknown.

The pharmacokinetic parameters of azelastin and its major metabolite, desmethylazelastine following intranasal administration of ——— M and Astelin® are listed in Table 3. The data revealed that systemic exposure of azelastin as well as desmethylazelastine, as evidenced by mean C_{max} and AUC, from ——— M, was numerically slightly lower compared to Astelin®. All other pharmacokinetic parameters including time to peak plasma concentration (T_{max}), elimination half-life ($T_{1/2}$), intranasal clearance (CL/F) were comparable between the two formulations. Visual inspection of plasma concentration-time plots for azelastine (Figure 6) and desmethylazelastine (Figure 7) further supports the above conclusion. The relative exposure data from ——— M (with sorbitol) compared to Astelin® (without sorbitol) seems to be in line with the known impact of sorbitol in oral formulations of other drugs.

Table 3. Mean \pm SD pharmacokinetic parameters of azelastine and desmethylazelastine following 2 sprays of Astelin® and _____TM solution per nostril

PK parameters	Azelastine		Desmethylazelastine	
	Astelin® (marketed)	_____ TM (new)	Astelin® (marketed)	_____ TM (new)
AUC _{0-t} (pg.hr/mL)	5903 \pm 2264	4917 \pm 1394	1873 \pm 553	1634 \pm 603
AUC _{0-inf} (pg.hr/mL)	6122 \pm 2373	5122 \pm 1546	2615 \pm 779	2131 \pm 609
AUC _{0-inf} /D (pg.hr/mL/(μ g/kg))	839 \pm 329	704 \pm 207	357 \pm 108	292 \pm 72
C _{max} (pg/mL)	235 \pm 88	200 \pm 67	24 \pm 7.8	23 \pm 11
C _{max} /D (pg/mL/(μ g/kg))	32 \pm 12	27 \pm 7.9	3.3 \pm 1.1	3.1 \pm 1.3
T _{max} (hr)*	4.0 (0.25-6.0)	3.0 (0.5 – 4.0)	24 (24-72)	24 (12 – 96)
T _{1/2} (hr)	24 \pm 6.0	22 \pm 7.5	60 \pm 22	52 \pm 21
V _d /F (L/kg)	48 \pm 26	50 \pm 36	261 \pm 120	272 \pm 140
CL/F (mL/min/kg)	25 \pm 18	26 \pm 9.5	53 \pm 24	61 \pm 16

* median (range)

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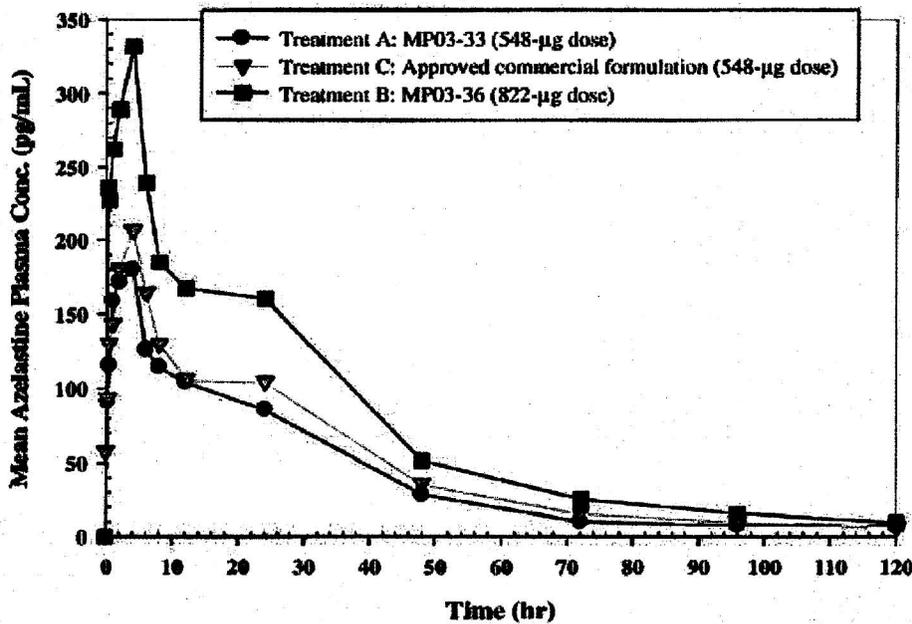


Figure 6: Mean azelastine plasma concentration-time profiles following single intranasal administration (2 sprays per nostril) of 548 mcg TM (MP03-33), 548 mcg Astelin® (approved commercial formulation) and 822 mcg TM (MP03-36).

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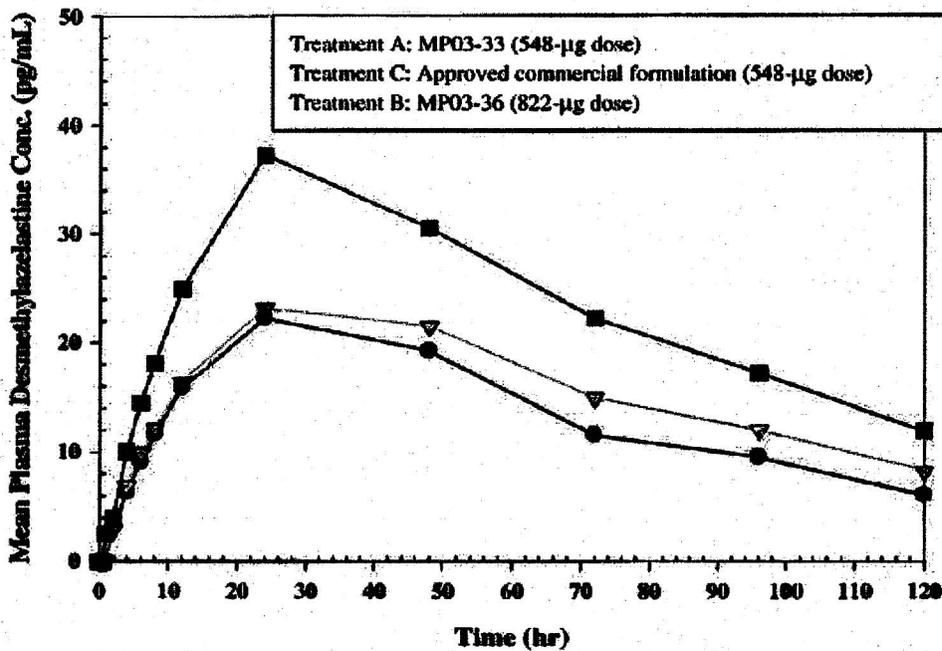


Figure 7: Mean desmethylazelastine plasma concentration-time profiles following single intranasal administration (2 sprays per nostril) of 548 mcg TM (MP03-33), 548 mcg Astelin® (approved commercial formulation) and 822 mcg TM (MP03-36).

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