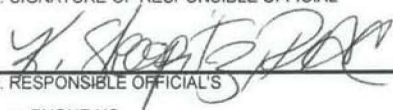


TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE		1. DATE SUBMITTED 11/26/2012	3. NDA/ANDA/AADA OR BLA/PLA/PMA Number: 202-236 Single product <input checked="" type="checkbox"/> Multiple products <input type="checkbox"/> For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.	
		2. LABEL REVIEW NO. (Biologics)		
NOTE: Form 2253 is required by law. Reports are required for approved NDAs and ANDAs (21 CFR 314.81)				
4. PROPRIETARY NAME DYMISTA		5. ESTABLISHED NAME azelastine hydrochloride and fluticasone propionate Prod. Code No.		
6. PACKAGE INSERT DATE and ID NO. (Latest final printed labeling) IN-023A6-01 04/2012		7. MANUFACTURER NAME: MEDA Pharmaceuticals, MEDA Pharmaceuticals Inc. License No. (Biologics)		
FDA/CBER USE ONLY				
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8. ADVERTISEMENT / PROMOTIONAL LABELING MATERIALS				
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Material Type (use FDA codes) a.	Dissemination/ Publication Date b.	Applicant's Material ID Code and/or description c.	Previous review No. if applicable / date (PLA Submissions) d.	COMMENTS:
PSL	11/26/2012	DYM-12-0240: AAM Physician's Deck		.pdf submitted
		<div style="background-color: yellow; padding: 10px; border: 1px solid black;"> <p style="font-size: 1.5em; margin: 0;">DYM-12-0240</p> <p style="font-size: 1.2em; margin: 0;">1851W 085 02</p> <p style="font-size: 1.2em; margin: 0;">47517814</p> </div>		
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9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT Kimberly Skopitz, RAC Manager, Regulatory Affairs			10. SIGNATURE OF RESPONSIBLE OFFICIAL 	
11. APPLICANT'S RETURN ADDRESS MEDA Pharmaceuticals Inc. 200 North Cobb Parkway, Bldg. 400, Suite 428 Marietta, GA 30062			12. RESPONSIBLE OFFICIAL'S a. PHONE NO. 770.916.3918 b. FAX NO. 678-718.3253	
			13. FOR CBER PRODUCTS ONLY: (Check one) <input type="checkbox"/> Part I/Draft <input type="checkbox"/> Part II/Final	

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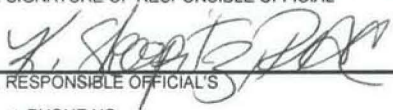
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-SUBJECT TO STIPULATED PROTECTIVE ORDER

**PLAINTIFFS'
TRIAL EXHIBIT**
PTX0917

MEDA_APTX03478897

CIP2085
 Argentum Pharmaceuticals LLC v. Cipla Ltd.
 IPR2017-00807

PTX0917-00001

TRANSMITTAL OF ADVERTISEMENTS AND PROMOTIONAL LABELING FOR DRUGS AND BIOLOGICS FOR HUMAN USE		1. DATE SUBMITTED		3. NDA/ANDA/AADA OR BLA/PLA/PMA	
		11/26/2012		Number: 202-236 Single product <input checked="" type="checkbox"/> Multiple products <input type="checkbox"/> For multiple products, submit completed form and specimen of advertising/promotional materials to one application of choice, and attach separate sheet addressing items 3-5 for remainder of products. Refer to No. 3 on instruction sheet.	
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9. TYPED NAME AND TITLE OF RESPONSIBLE OFFICIAL OR AGENT			10. SIGNATURE OF RESPONSIBLE OFFICIAL		
Kimberly Skopitz, RAC Manager, Regulatory Affairs					
11. APPLICANT'S RETURN ADDRESS			12. RESPONSIBLE OFFICIAL'S		
MEDA Pharmaceuticals Inc. 200 North Cobb Parkway, Bldg. 400, Suite 428 Marietta, GA 30062			a. PHONE NO.		
			770.916.3918		
			b. FAX NO.		
			678-718.3253		
			13. FOR CBER PRODUCTS ONLY: (Check one)		
			<input type="checkbox"/> Part I/Draft <input type="checkbox"/> Part II/Final		



An Advanced Treatment for
Symptom Relief of
Seasonal Allergic Rhinitis*

A Primer for
Physicians

DYMISTA™
(azelastine hydrochloride and
fluticasone propionate) Nasal Spray
137 mcg / 50 mcg per Spray

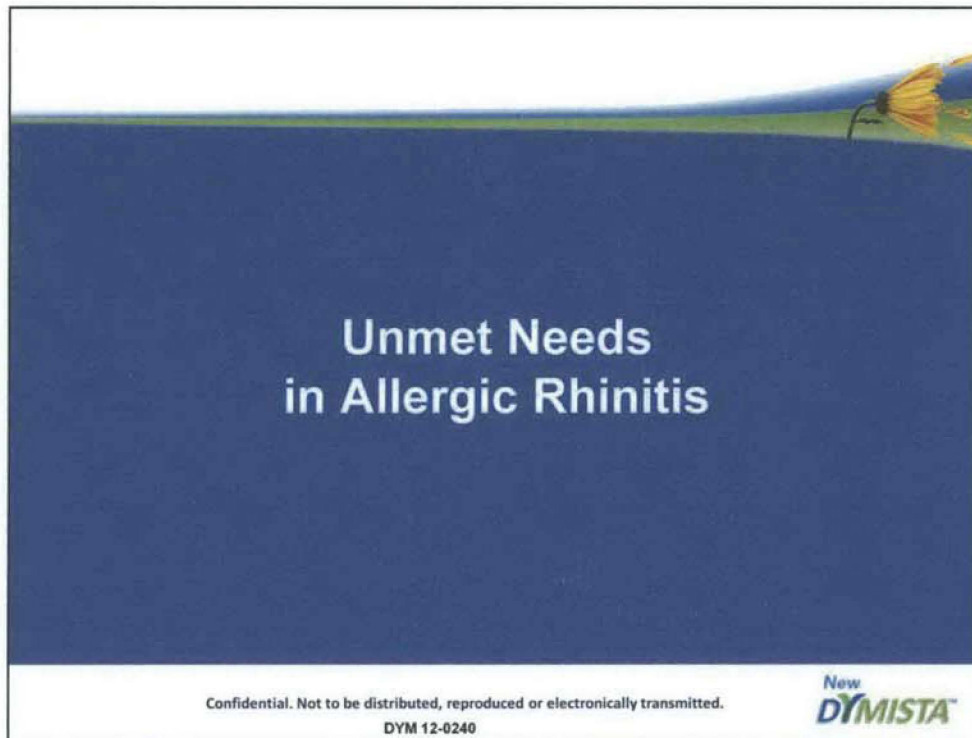
*In patients 12 years of age and older who require treatment with both
azelastine hydrochloride and fluticasone propionate for symptomatic relief.

The following presentation is provided by Meda Pharmaceuticals Inc,
and does not qualify participants for CME or other independent medical
education requirements. All materials presented are intended to be
consistent with FDA guidelines and supportive of the approved indication
and label for the product described herein.

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Cover Slide

Customized by Speaker and Date per meeting



We are now going to look at the unmet medical needs and some patient perspectives on SAR collected from market research.

AR—Frequently Underestimated and Inadequately Treated¹

- **44%** of patients not fully satisfied with current prescription allergy medication believe their allergy medication does not provide symptom relief quickly enough²
- **74%** of patients use multiple therapies trying to achieve symptom control³
- Patients frequently experience severe symptoms while on therapy and are dissatisfied and nonadherent to currently available therapy^{4,5}

1. Maurer M, Zuberbier T. *Allergy*. 2007;62:1057-1063.

2. Harris Interactive survey of U.S. adult allergy patients. Commissioned by the Asthma and Allergy Foundation of America, October 10-17, 2005.

3. Demoly P, et al. *Allergy*. 2002;57(6):546-554.

4. Valovirta E, et al. *Curr Opin Allergy Clin Immunol*. 2008;8:1-9.

5. Loh CY, et al. *Allergy*. 2004;59(11):1168-1172.

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Many patients do not respond sufficiently to treatment

There are many patients who do not respond to therapy regardless of what is used to treat their symptoms.

There exists several challenges when treating our AR patients. They include:

1. Onset—Patients want something that works fast

2. Approximately 75% of patients suffering from AR use multiple therapies, increasing costs—**Patients want something that is effective**

3. Patient dissatisfaction with current treatment is a leading cause of increased costs and adherence—**Patients are still experiencing severe symptoms and are still seeking relief**

Survey Methodology:

Harris Interactive conducted the online survey on behalf of AAFA from October 10-17, 2005, using its Chronic Illness Panel database. Total survey sampling includes a national sample of 1214 U.S. adults aged ≥18 years who have been diagnosed with seasonal allergies and are currently using prescription allergy medication to treat their allergies.

Data are weighted to be representative of adults aged ≥18 years who have been diagnosed with seasonal allergies and are currently using prescription allergy medication. Weighting was based on age within sex, education, race/ethnicity, region, income, and propensity to be online. In theory, with probability samples of this size, one can say with 95% certainty that the overall results have a sampling error of ± 4.3 percentage points.

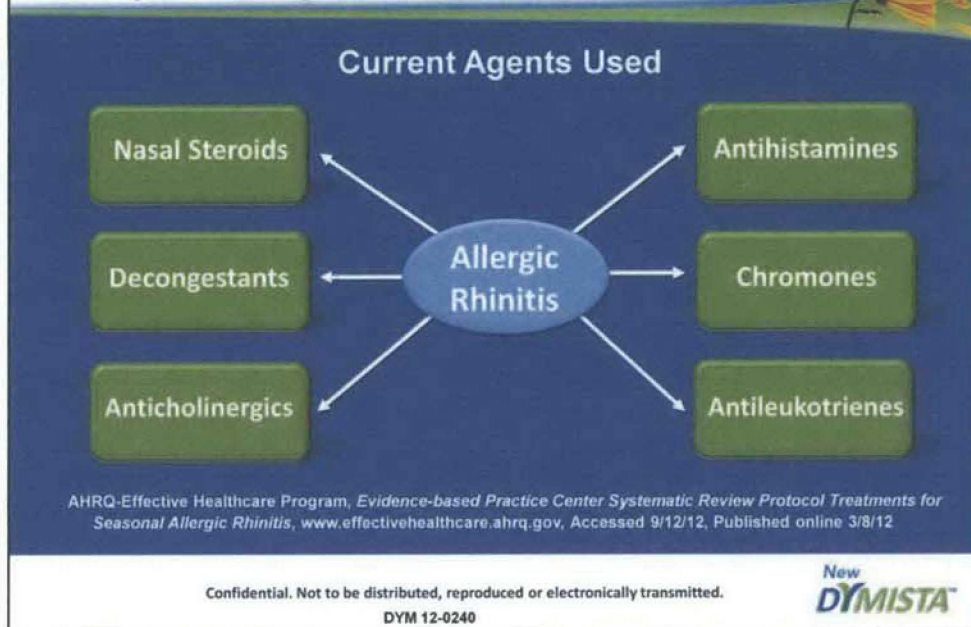
Sampling error for the sub-samples of patients who see a health care professional for seasonal

allergies (n=1194), patients who are not satisfied with their current prescription allergy medication (n=348), and patients who are not satisfied with the allergy care provided by their doctor or health care provider (n=242) is higher and varies. This online sample is not a probability sample.



We will now review some of the current therapeutic options to treat and manage SAR.

Management of Rhinitis: Multiple Therapeutic Options



As noted previously, as many as 75% of patients use multiple therapies to achieve symptom control.

These are the major therapeutic classes of drugs used to treat SAR.

Speaker opens a discussion with the audience:

What are the agents you routinely employ? Why?

Patients Use Multiple Medications Looking for Relief

What gives patients *MORE* relief?

- Oral antihistamine + nasal antihistamine
- Oral antihistamine + nasal steroid
- Antileukotriene + nasal steroid

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Can you provide some insight on your therapy selection?

Recall—Approximately 75% of patients suffering from AR use multiple therapies, leading to issues of increased costs.

How can we become more efficient in our management of SAR?

Oral Antihistamines Plus Intranasal Antihistamine: Lack of Additive Benefit

- Studies have examined the benefit of using an intranasal antihistamine with oral antihistamines in rhinitis:
 - Loratadine + Azelastine¹
 - Fexofenadine + Azelastine²
- The 2 studies above did not show improvement over the monotherapy with Azelastine in any of the study efficacy variables
- Studies have examined the benefit of using an intranasal steroid with an oral antihistamine or leukotriene antagonists in rhinitis:
 - Beclomethasone + astemizole³
 - Fluticasone + loratadine⁴
 - Fluticasone + levocetirizine⁵
 - Fluticasone + cetirizine, and fluticasone + montelukast⁶
- None of the 4 studies listed above concluded that the use of multiple agents was more effective than a nasal steroid alone

1. Berger WE, et al. *Ann Allergy Asthma Immunol.* 2003;91:205-211.
2. LaForce CF, et al. *Ann Allergy Asthma Immunol.* 2004;93:154-159.
3. Juniper EF, et al. *J Allergy Clin Immunol.* 1999;83:927-933.
4. Ratnes PR, et al. *J Fam Pract.* 1998;47:118-122.
5. Barnes ML, et al. *Clin Exp Allergy.* 2006;36:676-684.
6. Di Lorenzo G, et al. *Clin Exp Allergy.* 2004;34:259-267.

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Speaker Note: Please briefly review the methodology, primary efficacy variable, and results with the audience. It is important for them to appreciate the lack of added benefits to polypharmacy for SAR patients.

Study Designs:

Berger

Two-week, multicenter, placebo-controlled, randomized, double-blind study in patients with moderate-to-severe symptoms of seasonal allergic rhinitis.

Following a 1-week, open-label lead-in period, during which the patients received loratadine 10 mg daily, those patients who met the symptom qualification criteria (<25% to 33% improvement taking loratadine) were randomized to treatment with (1) azelastine nasal spray 2 sprays per nostril twice daily plus placebo capsule once daily, (2) azelastine nasal spray 2 sprays per nostril twice daily plus loratadine 10 mg tablets once daily, (3) desloratadine 5 mg tablets once daily plus placebo nasal spray 2 sprays per nostril twice daily, or (4) placebo nasal spray 2 sprays per nostril twice daily plus placebo capsule once daily.

The primary efficacy variable was the change from baseline to day 14 in the total nasal symptom score, consisting of runny nose, sneezing, itchy nose, and nasal congestion symptom scores recorded twice daily (am and pm) in patient diary cards.

1. Berger WE, et al. *Ann Allergy Asthma Immunol.* 2003;91:205-211.

LaForce:

This was a multicenter, randomized, double blind, placebo controlled, 2-week study in patients with moderate-to-severe seasonal allergic rhinitis.

The study began with a 1-week, open-label lead-in period, during which patients received fexofenadine, 60 mg twice daily. Patients who improved less than 25% to 33% with fexofenadine were randomized to treatment with (1) azelastine nasal spray 2 sprays per nostril twice daily plus placebo capsules twice daily, (2) azelastine nasal spray 2 sprays per nostril twice daily plus fexofenadine 60 mg tablets twice daily, or (3) placebo nasal spray 2 sprays per nostril twice daily plus placebo capsules twice daily.

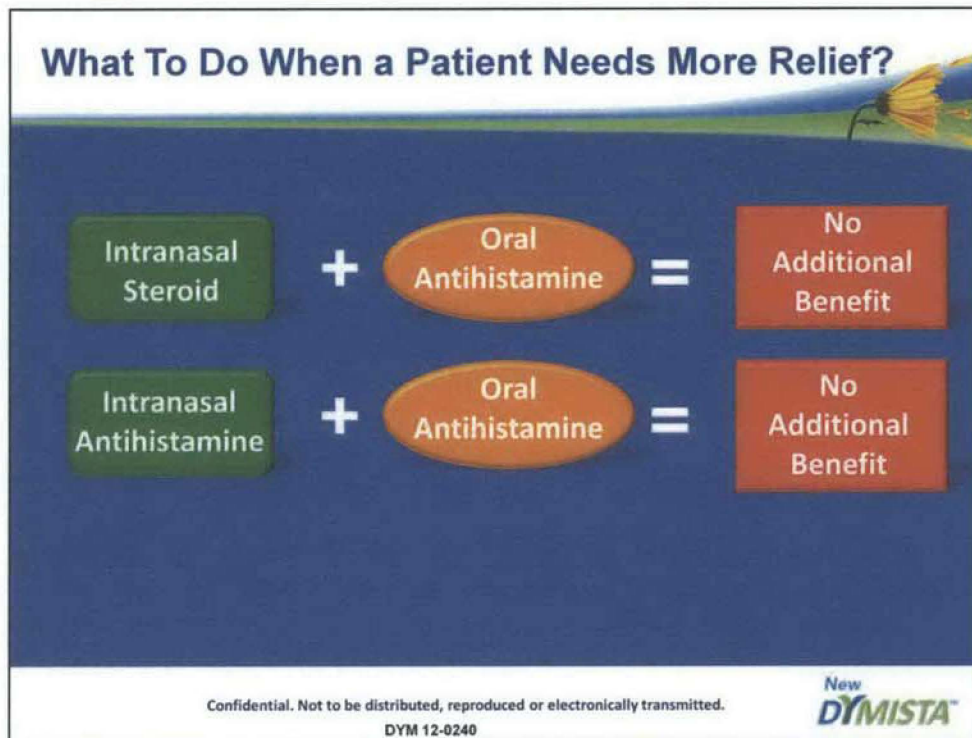
The primary efficacy variable was the change from baseline to day 14 in the total nasal symptom score (TNSS), consisting of runny nose, sneezing, itchy nose, and nasal congestion symptom scores.

2. LaForce CF, et al. *Ann Allergy Asthma Immunol.* 2004;93:154-159.

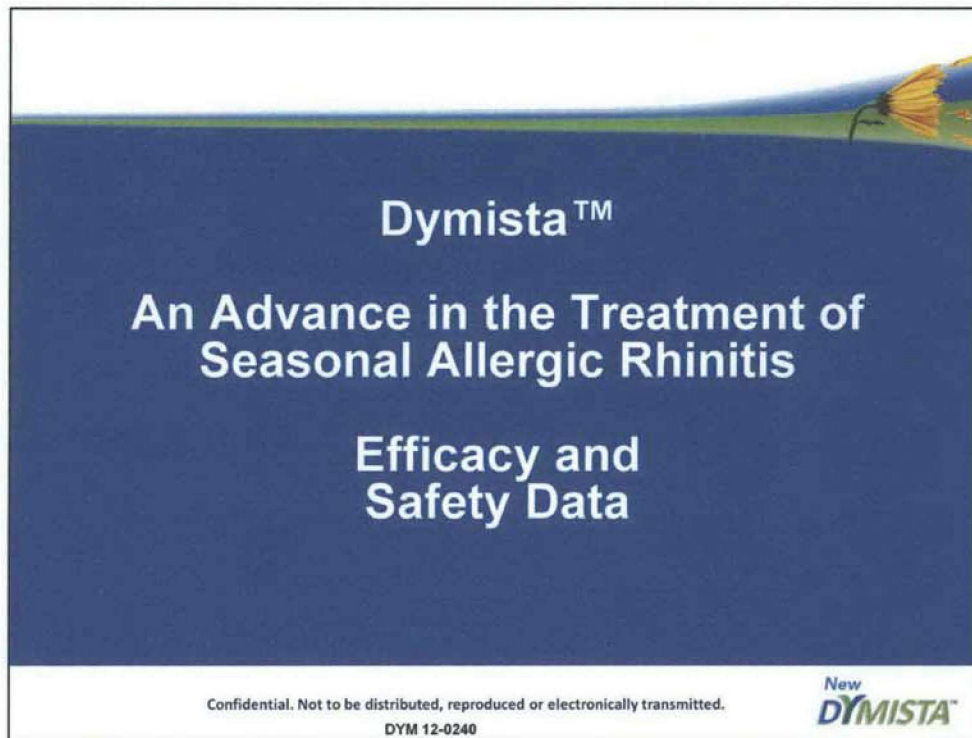
Speaker Note: Please initiate a discussion around these therapeutic choices for treating AR.

Have you experienced similar results?

What agents do you think would provide a benefit to your patients? Why?



Is there a reason why we do this?

The slide features a dark blue background with a white border. At the top right, there is a small graphic of a yellow flower with a green stem and leaves. The text is centered in white. The title 'Dymista™' is at the top, followed by 'An Advance in the Treatment of Seasonal Allergic Rhinitis' and 'Efficacy and Safety Data'. At the bottom, there is a white bar containing a confidentiality notice, the code 'DYM 12-0240', and the 'New DYMISTA™' logo.

Dymista™

**An Advance in the Treatment of
Seasonal Allergic Rhinitis**

**Efficacy and
Safety Data**

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We will now review some of the clinical data on Dymista™.

A Comprehensive Clinical Program Designed To Demonstrate Significant Superiority

- **Objectives:**

- **Directly compare** the efficacy and safety of Dymista™ in patients with SAR to:
 - Azelastine HCl
 - Fluticasone propionate
 - Placebo
- Assess the long-term safety of Dymista™ in patients with chronic rhinitis
- Follow the most recent regulatory guidance

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The 3 pivotal studies were designed to evaluate the efficacy and safety of Dymista™ to the 2 components of Dymista™, azelastine HCl and fluticasone propionate, in a **head-to-head comparison** for rapid and more complete symptom relief of SAR.

A long-term safety (12-month) study was conducted comparing Dymista™ to commercially available fluticasone propionate.

The FDA recently provided guidance to industry on the clinical trial design for new formulations of 2 or more drugs when each drug alone has activity and can be administered individually.¹

Reference

1. Center for Drug Evaluation and Research Guidance for Industry. Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combinations. December 2010.

Robust Sample Size and Comparative Trials To Demonstrate Significant Superiority

- **Over 4000 patients studied**
 - The largest body of evidence **directly comparing** the effectiveness of anti-rhinitis medications*
- **Trials**
 - One real-world clinical trial
 - Three Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group trials
 - One long-term, open-label safety study

*The 4 most recent drugs approved for AR had the following number of patients enrolled in their pivotal clinical trials: Patanase (1,598); Veramyst (1,829); Xyzal (2,412); Astepro 0.15% (3,077). None of these clinical trials involved head to head comparisons to current therapies.¹

1. <http://www.centerwatch.com>, Accessed September 11, 2012.

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The clinical development program for Dymista™ enrolled over 4000 patients, surpassing the clinical programs used for approval of the 4 most recently approved drugs for the treatment of AR.

***The 4 most recent drugs approved for AR had the following number of patients enrolled in their pivotal clinical trials: Patanase (1598); Veramyst (1829); Xyzal (2412); Astepro 0.15% (3077). None of these clinical trials involved head-to-head comparisons to current therapies.¹**

Each of the clinical trials designed for Dymista™ involved active comparators. The next slide provides a listing of the comparators used in each trial. The total enrollment for the Dymista™ clinical trials totaled 4617 for all comparator trials.

Patient Inclusion: Pivotal Trials

- ≥ 12 years old with a ≥ 2 -year history of SAR
- Positive skin-prick test to relevant pollen
- Defined by baseline rTNSS and nasal congestion scores
 - rTNSS score of 8 out of 12 per assessment
 - Nasal Congestion greater than or equal to 2 out of 3
- At least one of the following: disruption of sleep, emotional distress, work and school interference

rTNSS: Reflective total nasal symptom score—runny nose, itchy nose, nasal congestion, and sneezing was assessed twice daily. Each symptom rated on a scale from 0–3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe (maximum 12 points per assessment). Total possible score is 24 per day.

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The clinical trial program for Dymista™ Nasal Spray included four 2-week, randomized, double-blind, placebo- and active-controlled, parallel-group, clinical studies: MP4001, MP4002, MP4004, and MP4006. These studies share several characteristics:

Study population: patients aged ≥ 12 years with symptomatic seasonal allergic rhinitis

All had positive skin-prick tests to relevant pollen

All patients had rTNSS scores of at least 8 out of 12 and a nasal congestion score of 2 out of 3

At least one of the following: disruption of sleep, emotional distress, work and school interference

Speaker review rTNSS with the audience if needed

Efficacy and Tolerability of DYMISTA Were Evaluated in 3 Well-Designed, Head-to-Head, Pivotal Studies

1. Dymista PI.
Sect 14.1/p15/¶7-8 & p17/¶1 & table 2.

- 3 head-to-head studies^{1,2}
– More than 3300 patients with SAR

Pivotal Studies	Study Design	4 Study Arms			
MP 4002 MP 4004 MP 4006	Randomized, double-blind, multicenter	DYMISTA	Fluticasone (DYMISTA vehicle)	Azelastine (DYMISTA vehicle)	Placebo (DYMISTA vehicle)

Please see Important Risk Information on slide 15.

1. Dymista [package insert]. Somerset, NJ: MEDA Pharmaceuticals Inc; 2012.

2. Data on file. MEDA Pharmaceuticals Inc.

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2. DOF. 4002
CSR, Synopsis. P 4.¶5 & 10; p5/¶1 & 4.

4004 CSR,
Synopsis. P 4.¶7;
p 5/¶3 & 6.

4004 CSR,
Synopsis. P 4.¶6;
p 5/¶2 & 5.

Efficacy and Tolerability of DYMISTA Were Evaluated in 3 Well-Designed, Head-to-Head, Pivotal Studies

1. Dymista PI.
Sect 14.1/p15/¶7-8 & p17/¶1 & table 2.

Key Takeaway:

In a robust clinical development program, DYMISTA was evaluated in 3 head-to-head studies that enrolled more than 3300 patients with SAR^{1,2}

Efficacy and tolerability of DYMISTA were compared with those of fluticasone, azelastine, and placebo (total of 4 study arms)

Additional Information:

Note that in these studies, fluticasone and azelastine were delivered using the same vehicle as DYMISTA

In all studies, DYMISTA, fluticasone, and azelastine were administered as 1 spray per nostril twice daily

The study population was 12 to 78 years of age

2. DOF. 4002
CSR, Synopsis. P 4.¶5 & 10; p5/¶1 & 4.

4004 CSR,
Synopsis. P 4.¶7;
p 5/¶3 & 6.

4004 CSR,
Synopsis. P 4.¶6;
p 5/¶2 & 5.

References:

1. Dymista [package insert]. Somerset, NJ: MEDA Pharmaceuticals Inc; 2012.

2. Data on file. MEDA Pharmaceuticals Inc.

Primary Endpoint

- Change from baseline in 12-hour rTNSS for the entire 14-day study period
 - Baseline-average of all combined rTNSS scores over 7-day placebo lead-in period
 - Patients used diary cards to record severity of their symptoms

rTNSS: Reflective total nasal symptom score- runny nose, itchy nose, nasal congestion, and sneezing was assessed twice daily. Each symptom rated on a scale from 0–3: 0 = none, 1 = mild, 2 = moderate, and 3 = severe (maximum 12 points per assessment). Total possible score is 24 per day.

Meltzer EO, et al. *Allergy Asthma Proc.* 2012;33(4):324-332.

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Primary endpoint: change from baseline to Day 14 in combined 12-hour AM and PM rTNSS

Baseline-average of all combined rTNSS scores over 7-day placebo lead-in period, including the AM day 1 diary scores (predosing)

Patients used diary cards to record severity of their symptoms

Secondary Endpoints

- Change from baseline in 12-hour reflective individual symptoms scores for the entire 14-day study period
 - Individual symptoms (nasal congestion, runny nose, itchy nose, and sneezing)
- Onset of action
 - Scored at 15 and 30-minute intervals over 4 hours at first dose
- Change from baseline to Day 14 in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)
 - Activities, sleep, practical problems, emotional
 - Eye symptoms, nasal symptoms, non-nose/eye symptoms

Meltzer EO, et al. *Allergy Asthma Proc.* 2012;33(4):324-332.

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Selected secondary endpoints:

Change from baseline to Day 14 in individual symptom scores

Onset of action

Change from baseline in the RQLQ (overall score and 7 individual domains) in subjects aged ≥ 18 years

Individual symptom scores—Recorded change from baseline for individual symptom (nasal congestion, runny nose, itchy nose, and sneezing)

Onset of action—Determined at the first office visit for each patient—nasal symptoms were scored at 15- to 30-minute intervals after the first dose of study medication during a 4-hour observation period.

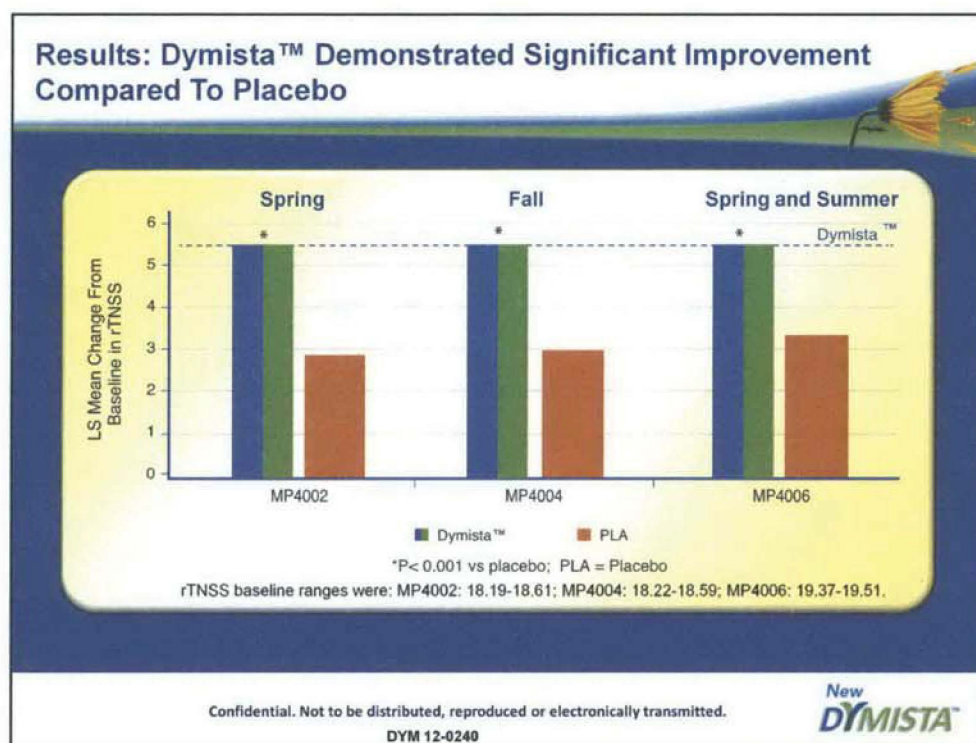
Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ)

28 items in 7 domains (activities, sleep, non-nose/eye symptoms, practical problems, nasal symptoms, eye symptoms, and emotional) evaluated on a 7-point scale where 0=no impairment and 6=maximum impairment.

Administered to patients aged ≥ 18 years.

An overall RQLQ score is calculated from the mean of all items in the instrument.

A change from baseline of at least 0.5 points is considered a clinically meaningful improvement.



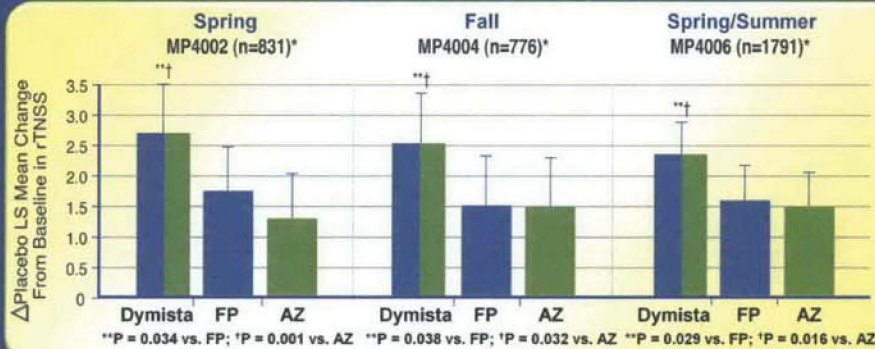
This graph represents the first part of the combination rule that Dymista™ was to be compared to placebo.

It also represents the typical study design of recently approved AR therapies.¹

1. <http://www.centerwatch.com/>, Accessed 8.30.12

Dymista™ showed improvement in rTNSS regardless of the allergy season when compared to placebo.

Results: Dymista™ Demonstrated Significant Improvement Compared To Fluticasone Propionate and Azelastine HCl



Across the development program Dymista™ demonstrated a 40% to 67% improvement over fluticasone

*Placebo subtracted

rTNSS=reflective total nasal symptom score; IN=intranasal; FP=fluticasone propionate; AZ=azelastine HCl.

1. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.

2. Data on file. Meda Pharmaceuticals.

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This slide represents the findings of the 3 pivotal studies with respect to the primary endpoint rTNSS.

Across the 3 pivotal clinical trials, the improvement with Dymista™ ranged from 40% to 67% greater improvement relative to either comparator^{1,2}

The azelastine HCl and fluticasone propionate comparators used the same device and vehicle as Dymista™ and are not commercially marketed²

Results shown are placebo subtracted

Speaker Note: You may initiate a discussion on the data seen in the slide above.

What are your thoughts regarding this data?

Are there patients under your care that may be candidates for Dymista™ now? Why?

What would Dymista™ be replacing? Why?

1. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.

2. Data on file. Meda Pharmaceuticals.

FDA Regulatory Guidance for Approval

“Two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effects...”

Code of Federal Regulations, Title 21, Volume 5, Revised as of April 1, 2012, 21CFR300.50.

18

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The FDA recognized that creating formulations of existing agents used together as a new single agent holds great promise for advancing patient care. Innovative drug, biological product, device combinations have the potential to make treatments safer, more effective, or more convenient or acceptable to patients.

Results: Rapid Symptom Relief

Patients want rapid symptom relief from their seasonal allergy treatment¹

Nasal Symptom Reduction: Statistically Superior at 30 Minutes^{2,3}



* Data shown are from study MP 4004. Onset of action was defined as the first time point at which Dymista was statistically superior to placebo in the mean change from baseline in instantaneous TNSS and was sustained thereafter.¹

1. Marple BF, et al. *Otolaryngol Head Neck Surg*. 2007; 136:S107-S124.
2. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.
3. Data on file. Meda Pharmaceuticals Inc.

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Within 30 minutes of administration of Dymista™, patients began to experience significant relief of their nasal symptoms.

How important is rapid relief to your patients? What impact will this have on your practice/prescribing for SAR?

References

1. Marple BF, Fornadley JA, Patel AA, et al. Keys to successful management of patients with allergic rhinitis: focus on patient confidence, compliance, and satisfaction. *Otolaryngol Head Neck Surg*. 2007;136:S107-S124.
2. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.
3. Data on file. Meda Pharmaceuticals Inc.

Results: Improved Quality Of life^{1,2}

Treatment with Dymista™ resulted in significant improvement in health-related quality of life (RQLQ) variables compared to placebo*

- Activities, sleep, practical problems, emotional
- Eye symptoms, nasal symptoms, non-nose/eye symptoms

RQLQ-Rhinoconjunctivitis Quality of Life Questionnaire

* Differences in health-related RQLQ score vs those of active comparators did not reach the level of clinical importance.¹

1. Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.
2. Data on file (MP 4004). Meda Pharmaceuticals Inc.

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Are these typical quality of life issues that your AR patients present with? How do you address them currently?

This information is supportive of the more complete symptom relief seen with Dymista™.

In the 3 pivotal trials, Dymista™ demonstrated a statistically significant greater decrease from baseline in the overall RQLQ than placebo

Ranged from -0.55 (95% CI: -0.72, -0.39) to -0.80 (95% CI: -1.05, -0.55)

The treatment differences between Dymista™ Nasal Spray and the monotherapies were less than the minimum important difference of 0.5 points.

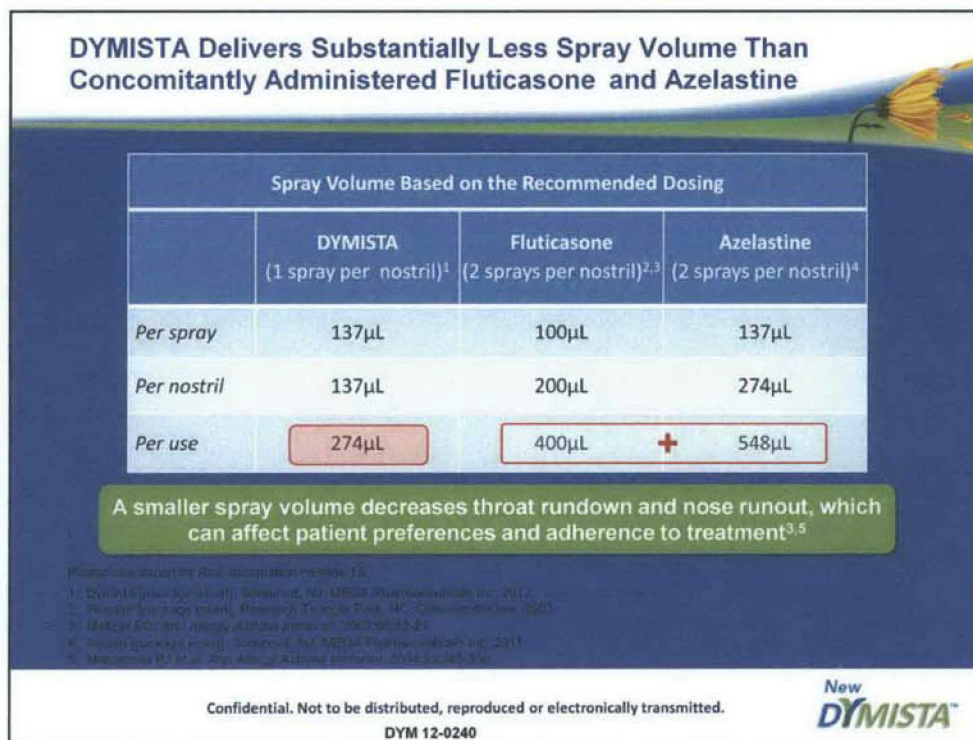
1. Dymista PI. Sect 3/p2¶¶6.

2. Flonase PI. 2004. p1/line 25; p11/lines 424-428.

4. Astelin PI. 2011. p1/¶3; p8/¶4.

3. Meltzer 2007. p 18/c2¶¶4; p19/c1¶¶1.

5. Mahadevia 2004. p 347/c1¶¶3.



DYMISTA Delivers Substantially Less Spray Volume Than Concomitantly Administered Fluticasone and Azelastine

1. Dymista PI. Sect 3/p2¶¶6.

Key Takeaway:

In comparison with the combination of fluticasone and azelastine—administered as 2 separate sprays— DYMISTA delivers substantially less volume in a single spray, which can minimize throat rundown and nose runout¹⁻⁴

2. Flonase PI. 2004. p1/line 25; p11/lines 424-428.

4. Astelin PI. 2011. p1/¶3; p8/¶4.

Additional Information:

Patient surveys show that throat rundown and nose runout can affect patient preferences and adherence to treatment^{4,5}

3. Meltzer 2007. p 18/c2¶¶4; p19/c1¶¶1.

It should be noted that practice guidelines state that there are inadequate data about the optimal interval between administration of an intranasal corticosteroid and an intranasal antihistamine, when administered as 2 separate sprays⁶

5. Mahadevia 2004. p 347/c1¶¶3.

6. Wallace 2008. p S19/table VI.

References:

1. Dymista [package insert]. Somerset, NJ: MEDA Pharmaceuticals Inc; 2012.

2. Flonase [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2003.
3. Meltzer EO. Formulation considerations of intranasal corticosteroids for the treatment of allergic rhinitis. *Ann Allergy Asthma Immunol.* 2007;96:12-21.
4. Astelin [package insert]. Somerset, NJ: MEDA Pharmaceuticals Inc; 2011.
5. Mahadevia PJ, Shah S, Leibman C, Kleinman L, O'Dowd L. Patient preferences for sensory attributes of intranasal corticosteroids and willingness to adhere to prescribed therapy for allergic rhinitis: a conjoint analysis. *Ann Allergy Asthma Immunol.* 2004;93:345-350.
6. Wallace DV, Dykewicz MS, Bernstein DI, et al. The diagnosis and management of rhinitis: an updated practice parameter. *J Allergy Clin Immunol.* 2008;122(2):S1-S84.

Results: Adverse Reactions

Adverse Reactions— $\geq 2\%$ Incidence in 2-Week Trials With
Dymista™ Nasal Spray

Adverse Reactions	1 spray per nostril twice daily			
	Dymista™ Nasal Spray (n=835)*	Azelastine Hydrochloride Nasal Spray (n=851)†	Fluticasone Propionate Nasal Spray (n=846)*	Vehicle Placebo (n=861)
Dysgeusia	30 (4%)	44 (5%)	4 (1%)	2 (>1%)
Headache	16 (2%)	20 (2%)	20 (2%)	10 (1%)
Epistaxis	18 (2%)	14 (2%)	14 (2%)	15 (2%)

Somnolence was reported in <1% of patients treated with Dymista™ Nasal Spray (6 of 853) or vehicle placebo (1 of 861)

*Safety population (n = 853), intent-to-treat population (n = 848).

†Not commercially marketed.

Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.

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New
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This table contains adverse reactions reported with frequencies greater than or equal to 2% and more frequently than placebo in patients treated with Dymista™ Nasal Spray in the seasonal allergic rhinitis controlled clinical trials.

In these trials, somnolence was reported in <1% of patients treated with Dymista™ Nasal Spray (6 of 853) or vehicle placebo (1 of 861).

MP4000: Long-Term Safety Trial (12 Month, Open Label)

PATIENT POPULATION	TREATMENT	ENDPOINTS
<ul style="list-style-type: none"> • Patients ≥ 12 years with PAR or VMR 	<ul style="list-style-type: none"> • Dymista™ n=405 (1 spray per nostril 2 times daily) • Fluticasone n=207 (2 sprays per nostril once per day) 	<p>PRIMARY ENDPOINT: To evaluate safety and tolerability of Dymista™ over a 1-year period</p> <p>SECONDARY ENDPOINT: Change in baseline in 12-hour rTNSS Change in Baseline from RQLQ</p>

Study was conducted in patients with perennial allergic rhinitis or vasomotor rhinitis*

*Dymista™ Nasal Spray, containing an H₁-receptor antagonist and a corticosteroid, is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

PAR=perennial allergic rhinitis; VMR=vasomotor rhinitis.

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- Study Design—randomized, 12-month, open-label, active-controlled, parallel-group study in subjects with perennial allergic rhinitis or vasomotor rhinitis

1-week screening period preceded the 12-month treatment period

Qualified subjects were randomized in a 2:1 ratio to treatment with:

Dymista™ (1 spray per nostril twice daily= total daily dose 548 mcg AZE; 200 mcg FP)

Fluticasone (2 sprays per nostril once daily=total daily dose 200 mcg)

- Clinic visits at months 1, 3, 6, 9, and 12
- Phone contact at months 2, 4, 5, 7, 8, 10, and 11
- Frequency of subject-reported adverse events
 - Monthly contact to review diary cards
- Focused nasal examinations
 - Baseline, months 1, 3, 6, 9, and 12
- Slit-lamp examination by an ophthalmologist
 - Baseline, months 6 and 12
- Laboratory assessments
 - Hematology, chemistry, urinalysis
 - Fasting AM serum cortisol levels at selected sites
 - Baseline, months 6 and 12

- Efficacy assessment
PM rTNSS baseline, daily over entire study period

Results: Long-Term Safety Trial

Key Findings

- Dymista™ was well tolerated—no evidence of adverse events that would preclude long-term use
- No significant adverse nasal examination findings
- No significant adverse ocular effects
- No clinically important changes from baseline in serum cortisol levels
- TNSS data indicated the efficacy of Dymista™ was maintained over the 1-yr study period

Berger W, et al. *J Allergy Clin Immunol*.129(2):AB 134: 2012.

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- The overall incidence of adverse reactions was 47% in the Dymista™ Nasal Spray treatment group and 44% in the fluticasone propionate nasal spray group.
- The most frequently reported adverse reactions ($\geq 2\%$) with Dymista™ Nasal Spray were headache, pyrexia, cough, nasal congestion, rhinitis, dysgeusia (2.5%), viral infection, upper respiratory tract infection, pharyngitis, pain, diarrhea, and epistaxis.
- In the Dymista™ Nasal Spray treatment group, 7 patients (2%) had mild epistaxis and 1 patient ($<1\%$) had moderate epistaxis. In the fluticasone propionate nasal spray treatment group, 1 patient ($<1\%$) had mild epistaxis. No patients had reports of severe epistaxis.
- Somnolence was reported in $<1\%$ of patients treated with Dymista™ Nasal Spray
- Less than 1% of treatment groups had adverse ocular effects
In the Dymista™ treatment group, 1 patient had increased intraocular pressure at Month 6. In addition, 3 patients had evidence of posterior subcapsular cataract at Month 6 and 1 at Month 12 (end of treatment).
In the fluticasone propionate treatment group, 3 patients had evidence of posterior subcapsular cataract at Month 12 (end of treatment).
- Effects of Dymista™ on the HPA axis were evaluated in a subset of patients
Mean fasting serum cortisol levels were similar between patients treated with Dymista™ and patients treated with fluticasone at baseline, Month 6, and Month 12

Dymista™: Rapid And More Complete Symptom Relief

The diagram illustrates that combining intranasal steroid with oral antihistamine or intranasal antihistamine with oral antihistamine results in no additional benefit. It also shows that Dymista (azelastine hydrochloride and fluticasone propionate) Nasal Spray is superior to monotherapy comparators.

DYMISTA™
 (azelastine hydrochloride and fluticasone propionate) Nasal Spray
 137 mcg/50 mcg per Spray

Superior to monotherapy comparators

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- Previous clinical studies have shown that there is not an additional benefit in using an:
 - Intranasal steroid with an oral antihistamine
 - Intranasal antihistamine with an oral antihistamine
- Market research has shown that patients want:
 - Rapid (under 30 minute) relief from their symptoms of SAR
 - Are willing to use multiple therapies to seek a more complete relief from the symptoms of SAR
 - Are dissatisfied with their current therapies, especially during severe episodes
- Dymista™ has demonstrated in clinical trials:
 - Rapid onset of relief within 30 minutes compared to placebo
 - Across the 3 pivotal clinical trials, Dymista has shown more complete relief vs. active comparators
 - Treatment with Dymista also resulted in significant improvement in health-related quality of life (QoL) variables vs placebo

Dymista™ Summary

- A unique fine mist formulation providing superior efficacy compared to ingredients found in first-line agents
- Rapid onset of action as early as 30 minutes*
- Significant improvement in TNSS vs fluticasone propionate or azelastine HCl
- Meaningful improvement in health-related quality of life variables
- Adverse reactions: In each of the 2-week pivotal trials, incidence and types of adverse reactions were comparable in all treatment groups (n = 3411)

Dymista™ provides *rapid and more complete relief* from seasonal allergic rhinitis symptoms vs fluticasone propionate or azelastine HCl comparator

*Vs placebo.

Dymista [package insert]. Somerset, NJ: Meda Pharmaceuticals Inc; 2012.

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Dymista™ is a unique fine mist formulation that contains both the antihistaminic properties of azelastine HCl and anti-inflammatory properties of fluticasone propionate

Dymista™ demonstrated significant improvement in:

TNSS vs monotherapy comparators*

RQLQ vs placebo

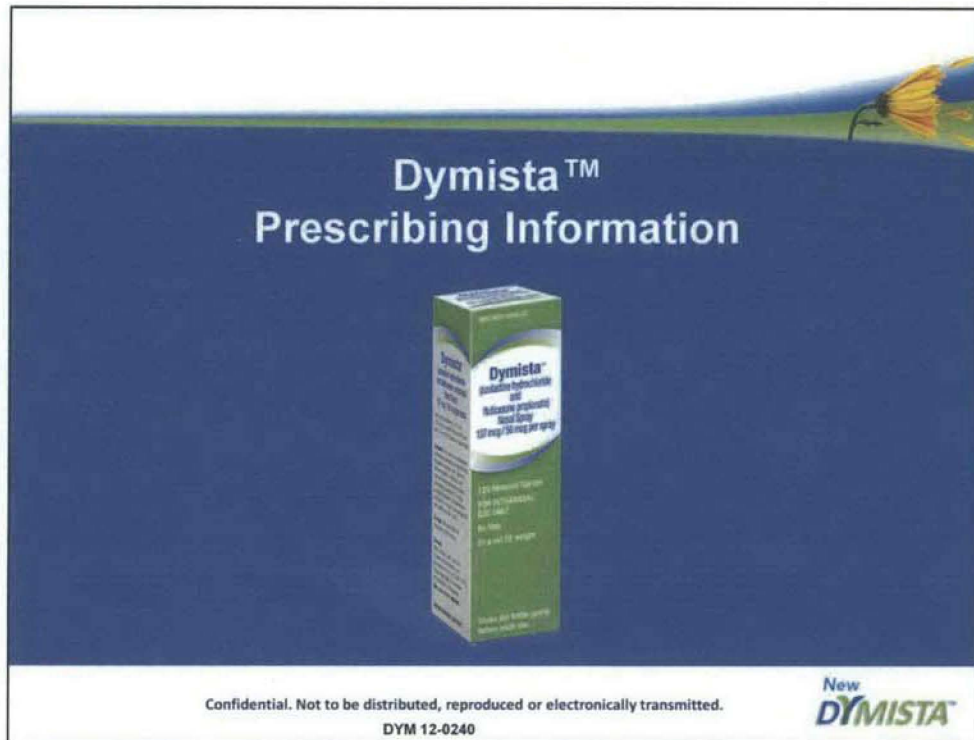
Onset of action vs placebo

Adverse reactions: In each of the 2-week pivotal trials, incidence and types of adverse reactions were comparable in all treatment groups (N=3411)

Conclusion:

Dymista™ provides *rapid and more complete relief* from seasonal allergic rhinitis symptoms vs. fluticasone propionate or azelastine HCl

*The azelastine HCl and fluticasone propionate comparators used the same device and vehicle as Dymista and are not commercially marketed.



We will now review some highlights of the prescribing information (PI) for Dymista™.

PIs to be distributed to the attendees.

Indication and Usage

Dymista™ Nasal Spray, containing an H₁-receptor antagonist and a corticosteroid, is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

1. INDICATIONS AND USAGE	
2. 1. INDICATIONS AND USAGE	
3. Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.	
4. 2. DOSAGE AND ADMINISTRATION	
5. 2.1. Dosage Information	
6. 2.2. Important Administration Instructions	
7. 3. DOSAGE FORMS AND STRENGTHS	
8. 4. CONTRAINDICATIONS	
9. 5. WARNINGS AND PRECAUTIONS	
10. 6.2. Immunogenicity	

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Dymista™ Nasal Spray is indicated for the relief of the symptoms of seasonal allergic rhinitis (SAR) in patients 12 years of age and older who require treatment with both azelastine hydrochloride and fluticasone propionate for symptomatic relief.

Dosing and Administration

The recommended dosage of Dymista™ is 1 spray in each nostril administered 2 times per day (b.i.d.)

1. Indications and Usage	
1.1	INDICATIONS AND USAGE
1.1.1	Dymista Nasal Spray is indicated for the relief of symptoms of seasonal allergic rhinitis in patients 12 years of age and older who require treatment with both antihistamine hydrochloride and corticosteroid preparations for symptomatic relief.
2. Dosage and Administration	
2.1	Dosing Information
2.1.1	The recommended dose of Dymista Nasal Spray, 137 mcg/50 mcg, is 1 spray per nostril twice daily for seasonal allergic rhinitis. Each spray contains 137 mcg of azelastine hydrochloride and 50 mcg of fluticasone propionate (137 mcg/50 mcg).
2.1.2	Administer Dymista Nasal Spray by the intranasal route only.
3. Important Administration Instructions	
3.1	Important Administration Instructions
3.1.1	Important Administration Instructions
3.1.2	Important Administration Instructions
4. Warnings and Precautions	
4.1	WARNINGS AND PRECAUTIONS
4.1.1	Contraindications
4.1.2	Warnings
4.1.3	Precautions
4.1.4	Use in Specific Populations
4.1.5	Use in Pregnancy
4.1.6	Use in Lactation
4.1.7	Use in Pediatric Patients
4.1.8	Use in Geriatric Patients
4.1.9	Use in Patients with Renal Impairment
4.1.10	Use in Patients with Hepatic Impairment
4.1.11	Use in Patients with Glaucoma
4.1.12	Use in Patients with Hypertension
4.1.13	Use in Patients with Heart Disease
4.1.14	Use in Patients with Diabetes Mellitus
4.1.15	Use in Patients with Asthma
4.1.16	Use in Patients with Chronic Obstructive Pulmonary Disease
4.1.17	Use in Patients with Epilepsy
4.1.18	Use in Patients with Seizure Disorders
4.1.19	Use in Patients with Mental Illness
4.1.20	Use in Patients with Depression
4.1.21	Use in Patients with Anxiety Disorders
4.1.22	Use in Patients with Bipolar Disorder
4.1.23	Use in Patients with Schizophrenia
4.1.24	Use in Patients with Psychotic Disorders
4.1.25	Use in Patients with Personality Disorders
4.1.26	Use in Patients with Borderline Personality Disorder
4.1.27	Use in Patients with Narcissistic Personality Disorder
4.1.28	Use in Patients with Antisocial Personality Disorder
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4.1.99	Use in Patients with Borderline Narcissistic Personality Disorder
4.2	Use in Patients with Narcissistic Borderline Personality Disorder

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The recommended dosage is 1 spray in each nostril administered **2 times per day (b.i.d.)**.

Important Risk Information

- Patients may experience somnolence. Caution patients against engaging in hazardous occupations requiring complete mental alertness, such as driving or operating machinery
- Patients should avoid concurrent use of alcohol or other central nervous system (CNS) depressants because additional reductions in alertness and additional impairment of CNS performance may occur
- Because of the inhibitory effect of corticosteroids on wound healing, avoid use in patients with recent nasal ulcers, nasal surgery, or nasal trauma until healed
- Glaucoma, cataracts, and increased intraocular pressure may be associated with nasal corticosteroid use; therefore, close monitoring is warranted in patients with a change in vision and/or with a history of increased intraocular pressure, glaucoma, and/or cataracts
- Patients using corticosteroids may be susceptible to infections and may experience a more serious or even fatal course of chicken pox or measles. Dymista should be used with caution in patients with active or quiescent tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex

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Important Risk Information (cont'd)

- Systemic corticosteroid effects, such as hypercorticism and adrenal suppression, may occur with very high dosages or at the regular dosage in susceptible individuals. If such changes occur, discontinue Dymista gradually, under medical supervision
- Potent inhibitors of cytochrome P450 (CYP) 3A4 may increase blood levels of fluticasone propionate
- Ritonavir: coadministration is not recommended
- Other potent CYP3A4 inhibitors, such as ketoconazole: use caution with coadministration
- Intranasal corticosteroids may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth routinely of pediatric patients receiving Dymista
- In clinical trials, the most common adverse reactions that occurred with Dymista Nasal Spray, azelastine hydrochloride nasal spray, fluticasone nasal spray, and vehicle placebo groups, respectively were dysgeusia (4%, 5%, 1%, <1%), epistaxis (2% for each group), and headache (2%, 2%, 2%, and 1%)
- Pregnancy Category C: based on animal data; may cause fetal harm

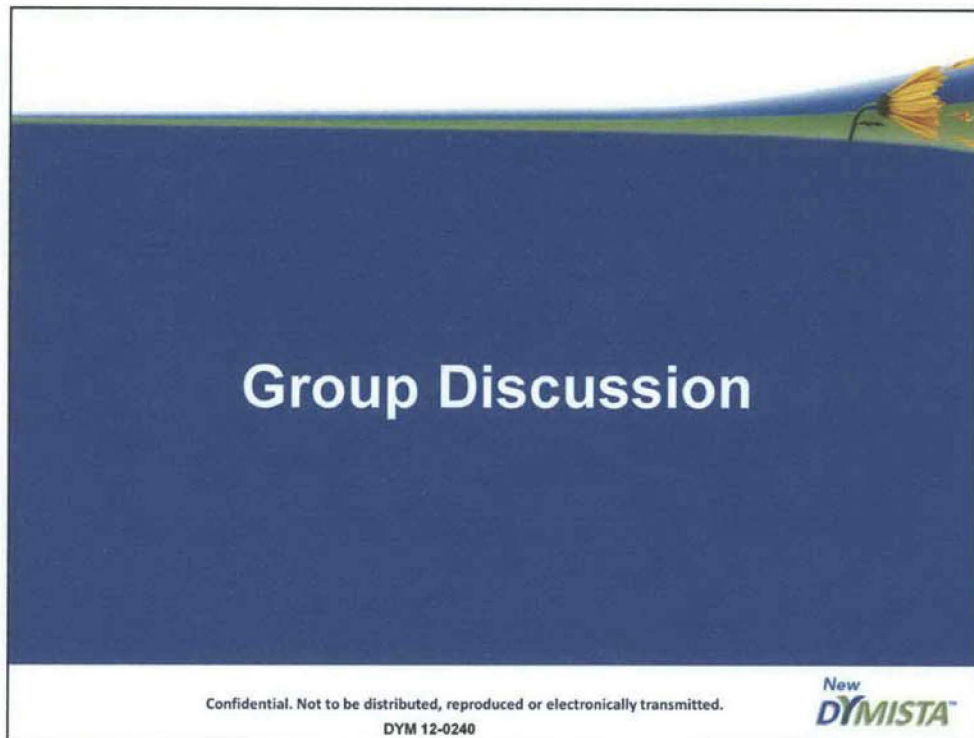
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Speaker opens up to the audience a discussion on the information just presented.