

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209529Orig1s000

OTHER REVIEW(S)

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: May 8, 2020

To: Nenita Crisostomo, RN
Senior Regulatory Health Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Kelly Jackson, PharmD
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Elvy Varghese, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): VESIcare LS (solifenacin succinate)

Dosage Form and Route: oral suspension

Application Type/Number: NDA 209529

Applicant: Astellas Pharma Global Development Inc., on behalf of Astellas Pharma US Inc.,

1 INTRODUCTION

On November 27, 2019, Astellas Pharma Global Development Inc., on behalf of Astellas Pharma US Inc., submitted for the Agency's review a Class 2 Resubmission for New Drug Application (NDA) 209529 for VESicare LS (solifenacin succinate) in response to a Complete Response letter issued on August 28, 2017 for three deficiencies for Chemistry, Manufacturing, and Controls. This NDA proposes an indication for the treatment of neurogenic detrusor overactivity in pediatric patients.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Bone, Reproductive and Urologic Products (DBRUP) on December 18, 2019 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for VESicare LS (solifenacin succinate) oral suspension.

2 MATERIAL REVIEWED

- Draft VESicare LS (solifenacin succinate) PPI received on November 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 1, 2020.
- Draft VESicare LS (solifenacin succinate) Prescribing Information (PI) received on November 27, 2019, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on May 1, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: May 4, 2020

To: Elena N. Boley, M.D.
Division of Urology, Obstetrics, and Gynecology (DUOG)

Nenita Crisostomo, RN
Senior Regulatory Health Project Manager

From: Elvy Varghese, PharmD,
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, PharmD
Team Leader, OPDP

Subject: OPDP Labeling Comments for VESICARE LS (solifenacin succinate) oral suspension

NDA: 209529

In response to DUOG consult request dated December 18, 2019, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for VESICARE LS (solifenacin succinate) oral suspension (Vesicare LS).

PI and PPI: OPDP's comments on the proposed labeling are based on the draft PI downloaded from the DUOG Vesicare LS SharePoint on May 1, 2020 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed PPI will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 6, 2020 (carton) and March 23, 202 (container) and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Elvy Varghese at (240) 402-0080 or Elvy.Varghese@fda.hhs.gov.

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ELVY M VARGHESE
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: April 9, 2020
Requesting Office or Division: Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number: NDA 209529
Product Name and Strength: VESicare LS (solifenacin succinate) oral suspension, 5 mg/5 mL (1 mg/mL)
Applicant/Sponsor Name: Astellas Pharma US, Inc.
OSE RCM #: 2019-2490-2
DMEPA Safety Evaluator: Justine Kalonia, PharmD
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on April 6, 2020 for VESicare LS. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised carton labeling for VESicare LS (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review and memorandum.^{ab}

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

^a Kalonia J. Label and Labeling Review for VESicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 02. RCM No.: 2019-2490.

^b Kalonia J. Label and Labeling Memorandum for VESicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 26. RCM No.: 2019-2490-1.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON APRIL 6, 2020

Carton labeling

(b) (4)



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/s/

JUSTINE H KALONIA
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Memorandum: March 26, 2020
Requesting Office or Division: Division of Urology, Obstetrics, and Gynecology (DUOG)
Application Type and Number: NDA 209529
Product Name and Strength: VESicare LS (solifenacin succinate) oral suspension,
5 mg/5 mL (1 mg/mL)
Applicant/Sponsor Name: Astellas Pharma US, Inc.
OSE RCM #: 2019-2490-1
DMEPA Safety Evaluator: Justine Kalonia, PharmD
DMEPA Team Leader: Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on March 23, 2020 for VESicare LS. The Division of Urology, Obstetrics, and Gynecology (DUOG) requested that we review the revised container label and carton labeling for VESicare LS (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised carton labeling is unacceptable from a medication error perspective. The principal display panel (that is, the panel with the red text) is cluttered, which hinders readability of critical information.

3 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

^a Kalonia J. Label and Labeling Review for VESicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 02. RCM No.: 2019-2490.

We recommend the following be implemented prior to approval of this NDA 209529:
The principal display panel (that is, the panel with the red text) of the carton labeling is cluttered, which hinders readability of critical information. Consider relocating the equivalency and recommended dosage statements to another panel on the carton labeling to improve the readability of other critical information, or address this concern by other means.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	March 2, 2020
Requesting Office or Division:	Division of Bone, Reproductive and Urologic Products (DBRUP)
Application Type and Number:	NDA 209529
Product Name and Strength:	VESicare LS (solifenacin succinate) oral suspension, 5 mg/5 mL (1 mg/mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
FDA Received Date:	11/27/2019
OSE RCM #:	2019-2490
DMEPA Safety Evaluator:	Justine Kalonia, PharmD
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

As part of the approval process for VESicare LS (solifenacin succinate) oral suspension, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that we review the proposed VESicare LS prescribing information (PI), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

2 REGULATORY HISTORY

Astellas submitted NDA 209529 on February 28, 2017. However, the application received a complete response on August 28, 2017. Therefore, Astellas resubmitted NDA 209529 on November 27, 2019.

3 MATERIALS REVIEWED

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C - N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

4 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), container label, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) – General			
1.	The strength is expressed as 1 mg/mL throughout the PI.	Inconsistent with the strength expression on the container label and carton labeling [i.e., 5 mg/5 mL (1 mg/mL)].	Consider revising the strength expression in the PI to 5 mg/5 mL (1 mg/mL) for consistency with the container labels and carton labeling.
Prescribing Information (PI) – Section 2 Dosage and Administration			
1.	In Section 2.1 of the PI, Table 1 contains the error-prone abbreviation, >, to	The symbol, >, appears on ISMP's List of Error-Prone Abbreviations, Symbols, and	Consider replacing the symbol, >, with the intended meaning (i.e.,

Table 2. Identified Issues and Recommendations for Division of Bone, Reproductive and Urologic Products (DBRUP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	describe the weight range in kg (i.e., > 15 to 30, > 30 to 45, > 45 to 60, and > 60).	Dose Designations because this symbol is often mistaken as the opposite of intended.	greater than) to prevent misinterpretation and confusion. For example, revise "> 15 to 30" to read: "greater than 15 to 30"
Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	Section 16 is missing appropriate information to facilitate identification (i.e., the description of the color of the suspension). The color of the suspension is described in Section 3 as "white to off-white-colored."	Appropriate information to facilitate identification of the dosage form (e.g., color) is required in Section 16 to comply with 21 CFR 201.57(c)(17)(iii).	We recommend adding the product description "white to off-white colored" to Section 16. For example, "VESIcare LS is supplied as a white to off-white-colored 1 mg/mL aqueous suspension..."
2.	The container label and carton labeling contain the statement "dispense in a tight light-resistant container" which suggests that the product is light-sensitive. However, Section 16 is missing this special handling and storage (i.e., the product is sensitive to light) information.	Special handling and storage conditions, such as sensitivity to light, are required in Section 16 to comply with 21 CFR 201.57(c)(17)(iv).	If applicable, we recommend adding the special handling and storage conditions that reflect the product's "sensitivity to light" to Section 16. For example, revise "Store in original bottle," to read "Store in original bottle to protect from degradation. Dispense in a tight light-resistant container. Discard any unused product 28 days after opening the original bottle."
3.	The description of the package configuration (i.e., (b) (4) (b) (4)) lacks clarity.	Can be improved.	We recommend revising the description of the package configuration (b) (4) (b) (4) to read: "Carton containing one bottle", or a similar statement.
Prescribing Information – Section 17 Patient Counseling			
1.	Section 17 is missing instructions to use an oral dosing syringe to measure	Evidence suggests use of an oral syringe may decrease the risk of wrong dose errors. In a	We recommend adding the following statement to Section 17:

Table 2. Identified Issues and Recommendations for Division of Bone, Reproductive and Urologic Products (DBRUP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	the dose. The labeling of oral liquids that are not co-packaged with a dosing device should provide a statement instructing the patient or caregiver to use an oral dosing syringe to measure the dose.	study conducted by Yin et al. ^a , investigators found that use of oral syringes was associated with less dosing errors than oral dosing cups, particularly when used to measure smaller doses (i.e., less than 5 mL).	"Instruct patients or caregivers to use an oral dosing syringe to correctly measure the prescribed amount of medication. Inform patients that oral dosing syringes may be obtained from their pharmacy."
Patient Information			
2.	The "How should I take VESicare LS?" section of the Patient Information is missing the instruction to shake well before use.	May contribute to wrong technique medication errors, which could result in overdose or underdose.	We recommend adding the following instructions to the "How should I take VESicare LS?" section of the Patient Information: "Shake the VESicare LS bottle well before each use."
3.	The "How should I take VESicare LS?" section of the Patient Information is missing instructions to use an oral dosing syringe to measure the dose. The labeling of oral liquids that are not co-packaged with a dosing device should provide a statement instructing the patient or caregiver to use an oral dosing syringe to measure the dose.	Evidence suggests use of an oral syringe may decrease the risk of wrong dose errors. In a study conducted by Yin et al. ^a , investigators found that use of oral syringes was associated with less dosing errors than oral dosing cups, particularly when used to measure smaller doses (i.e., less than 5 mL).	We recommend adding the following instructions to the "How should I take VESicare LS?" section of the Patient Information: "Use an oral dosing syringe to correctly measure your dose. Ask your pharmacist for an oral dosing syringe if you do not have one."
4.	The "How should I store VESicare LS?" section of the Patient Information states: (b) (4) (b) (4)	Can be improved for consistency with the container label and carton labeling to explicitly state the intended action (i.e., discard remaining VESicare LS 28 days after first opening).	Consider revising the statement (b) (4) to read: "Throw away VESicare LS oral suspension 28 days (4 weeks) after first opening", or a similar statement.

^a Yin HS, Parker RM, Sanders LM, et al. Liquid Medication Errors and Dosing Tools: A Randomized Controlled Experiment. *Pediatrics*. 2016; 138(4): e20160357.

Table 2. Identified Issues and Recommendations for Division of Bone, Reproductive and Urologic Products (DBRUP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	However, the container label and carton labeling state “discard remaining VESicare LS 28 days after first opening”.		

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The (b) (4) statement can be improved.	To ensure consistency with the Physician Labeling Rule (PLR) formatted Prescribing Information.	Revise the statement, (b) (4) (b) (4) (b) (4) to read “Recommended Dosage: See prescribing information.”
2.	The expiration date format is not defined.	We are unable to assess the proposed expiration date format from a medication safety perspective (e.g., risk for deteriorated drug medication errors).	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
3.	The instruction to “Discard remaining VESicare LS 28 days after first opening” lacks prominence (it is	The statement “discard 28 days after first opening” may be overlooked, which could result	Increase the prominence of this important information. For example, consider moving the statement “Discard

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	small and not easily identifiable) on the container label and carton labeling.	in the product being used past the 28-day expiration.	remaining VESicare LS 28 days after first opening” and the placeholder to write the discard after date to the principal display panel (PDP) of the carton labeling. Additionally, consider moving the statement “Discard remaining VESicare LS 28 days after first opening” to the PDP of the container label. Or, address this concern by other means (e.g., utilize color, boxing, or bolding).
4.	The instruction “shake well” lacks prominence.	We are concerned that the instruction “shake well” may be overlooked, which may cause incorrect dosing. Based on our post marketing experience, this is known to occur in dispensing suspensions from the stock bottle by pharmacy staff. ^b	Increase prominence of “Shake the bottle well before use” on the container label and carton labeling.
Carton Labeling			
1.	The presence of the equivalency statement “Each 1 mL contains 1 mg of solifenacin succinate equivalent to 0.75 mg solifenacin” on five panels of the carton labeling creates visual clutter.	May hinder the readability of critical information on the carton labeling.	Implement changes to the carton labeling to decrease visual clutter. For example, consider including the equivalency statement on the principal display panel only, or address this concern by other means.
2.	As currently presented, there is no product identifier on the carton labeling.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and	We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product’s labeling. The DSCSA guidance on product identifiers recommends that the human-readable portion be

^b Institute for Safe Medication Practices. 2004 Jul. Shake well before dispensing. ISMP Med Saf Alert Community/Ambulatory Care. 3(7):3-4.

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		<p>homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively.</p> <p>The draft guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf</p>	<p>located near the 2D data matrix barcode and recommends the following format:</p> <p>NDC: [insert products NDC] SERIAL: [insert products' serial number] LOT: [insert product's lot number] EXP: [insert product's expiration date]</p>
3.	Lacks identification of a placeholder for the lot number and expiration date.	The lot number and expiration date are required on the immediate container and carton labeling per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively.	Ensure that the lot number and expiration date are present on the carton labeling and container label in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17. Please provide the intended expiration date format for evaluation.
Container Label			
1.	The container label and carton labeling contain the statement "dispense in a tight light-resistant container" which suggests that the product is light sensitive. However, a "protect from light" statement is not on the container label or carton labeling.	A "protect from light" statement should be on the container label to comply with USP Chapter 659 Packaging and Storage Requirements.	If applicable, add a "protect from light" statement to the container label in accordance with USP Chapter 659.
General			
1.	To aid in our review, we request you submit five placebo only intend-to-market samples of your proposed product (carton containing 150 mL bottle) to the Agency. Address the samples to the following: OSE Sample Steward ATTN: Oyinlola (Lola) Fashina Food and Drug Administration 10903 New Hampshire Avenue, Bldg. 22, Room 4477 Silver Spring, MD		

Table 3. Identified Issues and Recommendations for Astellas Pharma US, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	Use zip code 20903 if shipping via United States Postal Service (USPS) Use zip code 20993 if sending via any other carrier other than USPS (e.g., UPS, DHL, FedEx)		
	Please instruct the package carrier that a signature is NOT required for delivery if the package is dropped off at the designated inbox.		
	Please confirm receipt of this communication and include the delivery carrier's tracking number for the package in your response.		

5 CONCLUSION

Our evaluation of the proposed VESicare LS prescribing information (PI), container label, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Astellas Pharma US, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Error! Reference source not found. presents relevant product information for VESicare LS that Astellas Pharma US, Inc. submitted on November 27, 2019, and Vesicare.

Product Name	VESicare	VESicare LS																		
Initial Approval Date	November 19, 2004	N/A																		
Active Ingredient	solifenacin succinate	solifenacin succinate																		
Indication	Muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.	Muscarinic antagonist indicated for treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years to less than 18 years																		
Route of Administration	oral	oral																		
Dosage Form	tablet	suspension																		
Strength	5 mg, 10 mg	5 mg/5 mL (1 mg/mL)																		
Dose and Frequency	5 mg tablet taken once daily, and if well tolerated may be increased to 10 mg once daily	<table border="1"> <thead> <tr> <th>Weight range (kg)</th> <th>Starting dose (mL)¹</th> <th>Maximum dose (mL)¹</th> </tr> </thead> <tbody> <tr> <td>9 to 15</td> <td>2</td> <td>4</td> </tr> <tr> <td>> 15 to 30</td> <td>3</td> <td>5</td> </tr> <tr> <td>> 30 to 45</td> <td>3</td> <td>6</td> </tr> <tr> <td>> 45 to 60</td> <td>4</td> <td>8</td> </tr> <tr> <td>> 60</td> <td>5</td> <td>10</td> </tr> </tbody> </table> <p><small>1. The oral suspension formulation of VESicare LS has a concentration of 1 mg/mL.</small></p>	Weight range (kg)	Starting dose (mL) ¹	Maximum dose (mL) ¹	9 to 15	2	4	> 15 to 30	3	5	> 30 to 45	3	6	> 45 to 60	4	8	> 60	5	10
Weight range (kg)	Starting dose (mL) ¹	Maximum dose (mL) ¹																		
9 to 15	2	4																		
> 15 to 30	3	5																		
> 30 to 45	3	6																		
> 45 to 60	4	8																		
> 60	5	10																		
How Supplied	Both 5 mg and 10 mg: <ul style="list-style-type: none"> • Bottle of: 30, 90, or 500 • Unit Dose Blister Pack: 7 (sample) or 100 	Carton containing one 150 mL bottle																		
Storage	Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F - 86°F) [see USP Controlled Room Temperature].	Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F-86°F) [see USP Controlled Room Temperature]. Store in original bottle. Discard any unused product 28 days after opening the bottle.																		
Container Closure	unit dose blister packages and high-density polyethylene (HDPE) bottles	amber polyethylene terephthalate (PET) bottles, which are capped with child-resistant high-density polyethylene-polypropylene caps with a pulp and vinyl seal liner																		

APPENDIX B. PREVIOUS DMEPA REVIEWS

On December 10, 2019, we searched for previous DMEPA reviews relevant to this current review using the terms, "VESicare LS", "NDA 209529", and "solifenacin". Our search identified 3 previous reviews^{c,d,e}, and we confirmed that our previous recommendations were implemented.

OSE RCM #	Review Date	Summary of Recommendations
2017-564	May 22, 2017	We reviewed the proposed Prescribing Information (PI) labeling, container label and carton labeling. We provided recommendations to the Division and the Sponsor. The revisions are addressed in OSE RCM # 2017-564-1
2017-564-1	May 22, 2017	We reviewed the revised carton labeling and container label. We provided recommendations to the Sponsor to revise the expiration date format.
2017-564-2	June 5, 2017	We reviewed the revised expiration date format and found it acceptable.

^c Rider, B. Label and Labeling Review for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 22. RCM No.: 2017-564.

^d Rider, B. Label and Labeling Packaging Review MEMO for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 22. RCM No.: 2017-564-1.

^e Rider, B. Label and Labeling Packaging Review MEMO for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JUN 5. RCM No.: 2017-564-2.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^f along with postmarket medication error data, we reviewed the following VESicare LS labels and labeling submitted by Astellas Pharma US, Inc. on November 27, 2019:

- Container label
- Carton labeling
- Prescribing Information (image not shown)

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^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

JUSTINE H KALONIA
03/02/2020 01:39:18 PM

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03/02/2020 01:45:57 PM

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: August 29, 2017

To: Nenita Crisostomo, Regulatory Project Manager
Division of Bone, Reproductive and Urologic Products (DBRUP)

From: Jina Kwak, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments for solifenacin succinate oral suspension

NDA: 209529

This memo is in response to DBRUP labeling consult request dated March 20, 2017. Reference is made to a Complete Response letter that was issued on August 28, 2017. Therefore, OPDP defers comment on the proposed labeling at this time, and request that DBRUP submit a new consult request during the subsequent review cycle. If you have any questions, please contact Jina Kwak at (301) 796-4809 or jina.kwak@fda.hhs.gov

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/s/

JINA KWAK
08/29/2017

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

REVIEW DEFERRAL MEMORANDUM

Date: August 11, 2017

To: Hylton V. Joffe, MD
Director
Division of Reproductive and Urologic Products (DRUP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Patient Labeling Reviewer, Team Leader
Division of Risk Management

From: Twanda Scales, MSN/Ed., RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Patient Package Insert (PPI) and
Instructions for Use (IFU)

Drug Name: VESIcare (solifenacin succinate)

Dosage Form and Route: oral suspension

Application
Type/Number: NDA 209529

Applicant: Astellas Pharma US, Inc. (Astellas)

1 INTRODUCTION

On February 28, 2017, Astellas submitted for the Agency's review an Original New Drug Application (NDA 209529) for solifenacin succinate, oral suspension for treatment of neurogenic detrusor overactivity (NDO) in pediatric patients.

Solifenacin succinate was originally approved, November 19, 2004, under NDA 021518 VESIcare 5 mg and 10mg tablets for the treatment of overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency in adults. A request for the proposed proprietary name VESIcare LS was submitted by the Applicant on January 27, 2017 and February 28, 2017 and conditionally approved by the Agency on May 24, 2017.

On March 21, 2017, the Division of Bone, Reproductive and Urologic Products (DBRUP) requested that DMPP review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for VESIcare LS (solifenacin succinate) oral suspension.

This memorandum documents the DMPP review deferral of the Applicant's proposed PPI and IFU for VESIcare LS (solifenacin succinate) oral suspension.

2 CONCLUSIONS

Due to outstanding facility deficiencies, DBRUP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

TWANDA D SCALES
08/11/2017

MARCIA B WILLIAMS
08/11/2017



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation Research
Office of New Drugs – ODE IV
Division of Pediatric and Maternal Health

10903 New Hampshire Avenue
Silver Spring, MD 20993
Telephone 301.796.2200
Fax 301.796.9744

MEMORANDUM: PEDIATRIC REVIEW

From: Melanie E. Bhatnagar, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)
Office of Drug Evaluation IV (ODE IV)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
John J. Alexander, MD, MPH, Deputy Director
DPMH/ODEIV/OND

To: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Subject: NDA submission in response to a Written Request (WR)

Drug: VESicare LS (solifenacin succinate) oral suspension (1 mg/mL)

NDA: 209529

Applicant: Astellas Pharma US, Inc.

Proposed Indication: VESicare LS is a muscarinic antagonist indicated for the treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older.

Materials Reviewed:

- Documents entered into DARRTS under NDA 209529
 - DPMH consult request dated 3/13/17
 - Division of Transplant and Ophthalmology Products (DTOP) review dated 6/23/17
 - Interdisciplinary Review Team (IRT) for QT Studies review dated 6/23/17
 - Applicant's proposed labeling dated 2/28/17 and 5/17/17
- Documents entered into DARRTS under IND 058135
 - Proposed Pediatric Study Request (PPSR) dated 3/23/12
 - WR dated 7/27/12
- Documents entered into DARRTS under NDA 021518
 - WR Amendments 1, 2, and 3 respectively dated 9/14/12, 4/17/14, and 12/12/14
 - DPMH Memorandum dated 12/16/14
- VESicare labeling revised March 2017 (accessed from FDALabel on 6/28/17)

Consult Request

DBRUP consulted DPMH to provide guidance on the preparation of documents for review by the Pediatric Review Committee and the Pediatric Exclusivity Board. DPMH also provided a review of pediatric use information in labeling based on DBRUP's review and assessment of the pediatric study data.

Regulatory History

On February 28, 2017, Astellas Pharma submitted NDA 209529 for VESicare LS (solifenacin succinate) oral suspension with the proposed indication of treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older. FDA approved VESicare (solifenacin succinate) oral tablets on November 19, 2004 under NDA 021518 for the treatment of adults with overactive bladder (OAB) with symptoms of urge urinary incontinence, urgency, and urinary frequency.¹

With initial U.S. approval of VESicare in 2004, DBRUP granted the applicant a partial waiver of study requirements under the Pediatric Research Equity Act (PREA) for pediatric patients birth to 4 years of age. DBRUP described the difficulty defining a diagnosis of OAB in pediatric patients birth to 4 years of age as the basis for waiving these studies.² Studies in the remaining pediatric population were deferred and a PREA Post-Marketing Requirement (PMR) was issued to evaluate treatment of OAB in pediatric patients 5 years to 17 years of age.¹

On March 23, 2012, the applicant submitted a PPSR to FDA seeking issuance of a WR to evaluate use of solifenacin succinate for treatment of NDO in pediatric patients 5 years to less than 18 years of age.³ DBRUP issued the applicant a WR on July 27, 2012⁴ which subsequently underwent three amendments that have previously been reviewed by DPMH.⁵ In summary, the WR was amended to modify the secondary endpoints, to reduce the number of patients required in the efficacy study, and to revise the statistical plan to combine all age groups in the analysis. DBRUP issued the third and final amended WR on December 12, 2014.⁶ The following two studies are included in the WR⁶:

- 1) Study 1: A multi-center, open-label, single-dose study to evaluate pharmacokinetics (PK), safety, and tolerability of solifenacin succinate oral suspension in pediatric patients aged 5 years to less than 18 years with NDO.
- 2) Study 2: A phase 3, open-label, baseline-controlled, multi-center, sequential dose titration study to assess the long-term efficacy and safety and PK of solifenacin succinate oral suspension in pediatric patients aged 5 years to less than 18 years with NDO.

¹ VESicare Approval Letter dated 11/19/04, accessed from DARRTS under NDA 021518

² Pediatric Page dated 11/19/04, accessed from DARRTS under NDA 021518

³ Proposed Pediatric Study Request dated 3/23/12, accessed from DARRTS under IND 058135

⁴ Written Request dated 7/27/12, accessed from DARRTS under IND 058135

⁵ DPMH Memorandum dated 12/16/14, accessed from DARRTS under NDA 021518

⁶ Written Request Amendment 3 dated 12/12/14, accessed from DARRTS under NDA 021518

The WR notably focuses on the use of solifenacin succinate in pediatric patients with NDO rather than OAB, the approved adult indication. In a November 2, 2005 meeting, DBRUP recommended the pediatric studies only be conducted in patients with neurologic disease.⁷ NDO is defined as detrusor overactivity in the setting of a relevant neurologic condition.⁴ DBRUP has previously agreed studies in NDO will satisfy the PREA PMR issued for VESicare.⁸

Background

In accordance with the WR, the applicant developed a new age-appropriate oral suspension formulation of solifenacin succinate. In the current NDA submission, the applicant provides data supporting approvability from the following pediatric clinical studies using the solifenacin succinate oral suspension:

- 1) Study 905-CL-079: Multi-center, open-label, single-dose study to evaluate PK, safety, and tolerability of solifenacin succinate in pediatric patients aged 5 years to less than 18 years with NDO
- 2) Study 905-CL-074: Phase 3, open-label, baseline-controlled, multi-center, sequential dose-titration study to assess the PK, long-term efficacy, and safety of solifenacin succinate in pediatric patients aged 6 months to less than 5 years with NDO
- 3) Study 905-CL-047: Phase 3, open-label, baseline-controlled, multi-center, sequential dose-titration study to assess the long-term efficacy and safety and PK of solifenacin succinate in pediatric patients aged 5 years to less than 18 years with NDO

Although the applicant is seeking product approval in patients 2 years of age and older, Study 905-CL-074 was open to enrollment of pediatric patients down to 6 months of age and 4 patients aged 6 months to less than 2 years received treatment.

Several key safety variables were specifically monitored in Study 905-CL-074 and Study 905-CL-047.⁶ The effect of VESicare LS on ocular accommodation in pediatric patients was assessed in Study 905-CL-047 with objective measurements at baseline and week 12.⁹ Although the applicant reported no adverse effects on vision in the study, DTOP reviewed the data provided by the applicant and concluded the information was both unreliable and inadequate to make an assessment.¹⁰ DTOP did not recommend adding procedures for ocular monitoring or vision testing during product use in labeling. Abnormalities in ocular accommodation are anticipated with use of anti-muscarinic drugs.¹¹ In the adult phase 3 program, the percentage of patients experiencing blurred vision was 3.8% in patients treated with VESicare at 5 mg dosages (n = 578) and 4.8% in patients treated with VESicare at 10 mg dosages (n = 1233), compared to 1.8% in patients receiving placebo (n = 1216).¹¹

⁷ November 2, 2005 Meeting Minutes dated 11/23/05, accessed from DARRTS under NDA 021518

⁸ Information Request dated 1/20/06, accessed from DARRTS under NDA 021518

⁹ Protocol 905-CL-047 Version 3.2, accessed from DARRTS under IND 058135

¹⁰ DTOP Consult Review dated 6/23/17, accessed from DARRTS under NDA 209529

¹¹ Section 6 Adverse Reactions VESicare labeling revised March 2017, accessed from FDA Label on 6/28/17

Prolongation of the QTc interval has been observed in adults receiving dosages of solifenacin succinate three times the therapeutic exposure.¹² In Study 905-CL-047, 4 pediatric patients met discontinuation criteria specified in the protocol for QT prolongation.¹³ Once the protocol was amended to increase the precision of the baseline QT measurement by averaging 2 pretreatment values, no additional pediatric patients met the discontinuation criteria. When the amendment was retrospectively applied for the 4 pediatric patients meeting discontinuation criteria, only 1 patient continued to meet criteria. The Interdisciplinary Review Team for QT Studies reviewed the current application and concluded that use of VESicare LS at the proposed dosages for pediatric patients is unlikely to have a clinically relevant effect on the QTc interval.¹³

After reviewing the NDA submission, DBRUP concluded the data are adequate to support the safety and efficacy of solifenacin succinate in pediatric patients 2 years to less than 18 years of age for the treatment of NDO. DBRUP intends to send a Complete Response (CR) Letter to the applicant due to drug product quality issues related to a change in manufacturing of one of the excipients. In terms of the adequacy of the applicant's response to the WR, DBRUP believes the applicant fairly responded to the terms and recommended granting pediatric exclusivity. On July 25, 2017, the Pediatric Exclusivity Board agreed with DBRUP's assessment and granted pediatric exclusivity to the applicant. DPMH recommended the CR letter reiterate the applicant's obligation under the Best Pharmaceuticals for Children Act (BPCA) to market VESicare LS oral suspension within 1 year of FDA's public notification granting pediatric exclusivity to the applicant. DBRUP intends to send a letter informing the applicant that the pediatric studies included in NDA 209529 have fulfilled the PREA PMR issued to the applicant in 2004 with initial U.S. approval of VESicare tablets under NDA 021518.

Discussion of Pediatric Use Labeling

Because the indication and target patient population differ between VESicare tablets and VESicare LS oral suspension, the applicant chose to create separate labeling for VESicare LS. As such, each of the products should be considered individually for the purposes of labeling. The VESicare LS labeling will include only the indication for treatment of NDO in pediatric patients 2 years to less than 18 years of age, so the entire labeling will contain a summary of the information essential for the safe and effective use in pediatric patients as required by 21 CFR 201.57(c)(9)(iv).¹⁴

If a new safety signal was identified or if a known adverse reaction occurred more frequently or with greater severity in the pediatric clinical studies of VESicare LS, that important safety information would need to be conveyed in subsection 8.4 (Pediatric Use) of VESicare labeling. Because DBRUP identified no new safety concerns in the pediatric clinical studies, no changes are necessary for the VESicare labeling, except in subsection 8.4 (Pediatric Use) which should be expanded to state "The safety and effectiveness of VESicare in pediatric patients have not

¹² Section 12 Clinical Pharmacology VESicare labeling revised March 2017, accessed from FDA Label on 6/28/17

¹³ Interdisciplinary Review Team (IRT) for QT Studies Consultation: QTc Evaluation dated 6/23/17 (accessed from DARRTS under NDA 209529)

¹⁴ February 2013 Draft Guidance for Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling

been established for the treatment of OAB” because the OAB indication has not been studied in pediatric patients.

Recommendations for Labeling

At an internal meeting held on July 20, 2017, DPMH provided high-level recommendations for DBRUP to consider when including pediatric use information in labeling, including revising Section 6 (Adverse Reactions) to be specific to pediatric clinical trial and post-marketing experience. DPMH suggested providing additional details in Section 6 regarding the pediatric clinical trial experience with QT prolongation with use of solifenacin to more adequately convey the findings described in the IRT QT Studies consultation.

DPMH also discussed the need for juvenile animal toxicology studies to be included in Subsection 8.4 (Pediatric Use) if DBRUP determines they are clinically relevant. Dose-related increased mortality occurred in juvenile mice exposed to solifenacin before weaning, starting at postnatal day 10, with doses that achieved a pharmacological effect.¹⁵ The increase in mortality was not observed for juvenile mice exposed to solifenacin after weaning, starting at postnatal day 21.¹⁵ DBRUP clinical and pharmacology-toxicology agreed the findings from these juvenile mice studies were not relevant for use in pediatric patients because of differences in brain development in mice compared to humans. The development of the blood-brain barrier and the pattern of neurogenesis and associated development of muscarinic receptors may continue for up to weeks postnatally in juvenile mice, whereas they are complete at birth in humans.¹⁶

Excerpts from the applicant’s proposed VESicare LS labeling dated May 17, 2017 for Section 1 (Indications and Usage) and Subsection 8.4 (Pediatric Use) are copied below with recommended edits from the DPMH Pediatric Team. Labeling additions are proposed as underlined text and proposed deletions as strikethroughs in the relevant text. Final labeling decisions will not be made in this review cycle because the application will be receiving a CR. Final labeling decisions in the next review cycle may not fully reflect changes suggested in this review.

1 INDICATIONS AND USAGE

VESicare LS (b) (4) (solifenacin succinate) is a muscarinic antagonist indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients ~~aged 2 years and older~~ (b) (4).

Reviewer Comment: Because this product was not studied in adults with NDO, consider revising to more specifically define the ages in the indication statement and throughout labeling.

¹⁵ Subsection 13.2 Animal Toxicology and/or Pharmacology of the applicant’s proposed labeling dated 5/17/17

¹⁶ Pharmacology/Toxicology NDA Review dated 7/28/17 accessed from DARRTS under NDA 209529

8.4 Pediatric Use

The safety and effectiveness of VESicare LS have been established in pediatric patients 2 years ^{(b) (4)} for treatment of NDO. The safety and effectiveness of VESicare LS have not been established in pediatric patients less than 2 years of age.

(b) (4)

Reviewer Comment: For products with pediatric indications, the pediatric information must be placed in all relevant sections of labeling as required by 21 CFR 201.57(c)(9)(iv). When a drug is approved for use only in pediatric patients and not in adults, the entire labeling will contain a summary of the information essential for the safe and effective use in pediatric patients. In order to avoid redundancy in labeling, only a brief pediatric use statement summarizing the approved pediatric indication and any limitations on pediatric use should be described in the Pediatric Use subsection of labeling along with appropriate cross-references. Appropriate pediatric use statements to include in labeling are described in 21 CFR 201.57(c)(9)(iv). Details pertaining to the pediatric clinical studies will be conveyed in Section 14 (Clinical Studies) and should be cross-referenced in the Pediatric Use subsection. The pediatric use statement adequately conveys the approved NDO indication and the limitations for use in pediatric patients less than 2 years of age.

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/s/

MELANIE E BHATNAGAR
08/01/2017

MONA K KHURANA
08/02/2017

JOHN J ALEXANDER
08/02/2017

Clinical Inspection Summary

Date	August 2, 2017
From	Roy Blay, Ph.D., Reviewer Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations (OSI)
To	Nita Crisostomo, RPM Guodong Fang, Clinical Reviewer Mark Hirsch, Clinical Team Leader Division of Bone, Reproductive, and Urologic Products (DBRUP)
NDA #	NDA 209529
Applicant	Astellas Pharma
Drug	Solifenacin (Vesicare)
NME	No
Therapeutic Classification	Antispasmodic (anticholinergic)
Proposed Indication	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients
Consultation Request Date	March 16, 2017
Summary Goal Date	August 11, 2017
Action Goal Date	August 28, 2017
PDUFA Date	August 28, 2017

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Hoebeke, Vande Walle, and Baka-Ostrowska were inspected in support of this NDA.

Discrepancies in the secondary efficacy endpoint of bladder compliance were noted at the sites of Drs. Hoebeke and Dr. Baka Ostrowska in addition to some recordkeeping deficiencies at the latter site and are discussed in further detail below. Nevertheless, based on the overall results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication. The pending classification of all three inspections is No Action Indicated (NAI).

2. BACKGROUND

The Applicant submitted this NDA to support the use of Vesicare (solifenacin) in the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients.

Inspections were requested for the following protocols in support of this application:

Protocol 905-CL-047, entitled “A Phase 3, Open-label, Baseline-controlled, Multicenter, Sequential Dose Titration Study to Assess the Long-term Efficacy and Safety, and the Pharmacokinetics of Solifenacin Succinate Suspension in Patients from 5 to Less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO)”

This was an open-label, baseline-controlled, sequential dose titration study. Subjects were treated with sequential doses of solifenacin oral suspension for 12 weeks (titration period) to determine each subject’s optimal dose, after which a fixed dose of solifenacin oral suspension was given for at least 40 weeks (fixed-dose assessment period).

The objectives of this open-label study were to evaluate the efficacy, safety and pharmacokinetics of solifenacin oral suspension in pediatric patients with NDO, aged 5 years to < 18 years.

The primary endpoint for this study was the change from baseline to week 24 of treatment in maximum cystometric capacity (MCC).

Protocol 905-CL-047 was conducted at 21 study sites with the enrollment of 55 subjects who had valid baseline and post-baseline measurements for the primary endpoint.

Protocol 905-CI-074, entitled “A Phase 3, Open-label, Baseline-controlled, Multi-center, Sequential Dose-titration Study to Assess the Pharmacokinetics, Long-term Efficacy and Safety of Solifenacin Succinate Suspension in Children from 6 Months to less than 5 Years of Age with Neurogenic Detrusor Overactivity”

The objectives, study design, and primary efficacy endpoint were the same as in Protocol 905-CI-047.

Protocol 905-CI-074 was conducted at eight sites with the enrollment of 22 subjects who had valid baseline and post-baseline measurements for the primary endpoint.

Rationale for Site Selection

The clinical sites of Drs. Hoebeke and Vande Walle were chosen as substitute sites for that of Dr. Bolong in the Philippines due to travel restrictions. Dr. Baka-Ostrowska’s site was selected for inspection because it enrolled a relatively large number of subjects between the two pivotal Phase 3 studies. None of these clinical investigators had a history of inspection.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
Site # 3201 Piet Hoebeke, M.D. Gent University Hospital De Pintelaan 185, Urologie Gent, Belgium 9000	905-CL-047/ 6 subjects	5-7 Jul 2017	NAI Pending final classification
Site #3203 Johan Vande Walle, M.D. Gent University Hospital De Pintelaan 185, Urologie Gent, Belgium 9000	905-CL-074/ 1 subject	3-4 Jul 2017	NAI Pending final classification
Site # 4801 Malgorzata Baka-Ostrowska, M.D. Aleja Dzieci Polskich 20 Klinika Urologii Dzieciecej Oddzial Urologii Dzieciecej, Building "E" Warszawa, Poland 04-730	905-CI-047/ 24 subjects 905-CI-074/ 7 subjects	19-23 Jun 2017	NAI Pending final classification

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

For both Dr. Hoebeke (Protocol 905-CL-047) and Dr. Baka-Ostrowska (Protocols 905-CL-047 and 905-CI-074), discrepancies were noted between source data and CRFs with regard to the secondary efficacy endpoint of bladder compliance, which is based on the interpretation of urodynamic tracing reports. The sponsor's written response to the field investigators explained that the CI's assessment of bladder compliance was recorded in the CRF; however, the data line listings provided by the sponsor contained the assessment of bladder compliance by a centralized reader, as specified in the protocol. The sponsor's explanation was discussed extensively with the DBRUP clinical review team and found acceptable by them.

1. Piet Hoebeke, M.D.

For Protocol 905-CL-047, 12 subjects were screened, six subjects were enrolled, one subject discontinued the study, and five subjects completed the study.

The study records for all 12 subjects were reviewed, including, but not limited to, adverse event reporting and the primary efficacy endpoint. There was no evidence of under-reporting of adverse events, and the primary efficacy endpoint was verifiable.

A Form FDA 483 was not issued at the conclusion of the inspection.

2. Johan Vande Walle, M.D.

For Protocol 905-CI-074, one subjects was screened, enrolled, and completed the study.

The incorrect version of the consent form was initially signed for this subject, but this was corrected at the following study visit. Although the subject completed the study, no urodynamic assessments were made after Visit 5, which was before the primary efficacy endpoint. The clinical investigator explained that the subject's baseline urodynamic measurements were "not consistent".

A Form FDA 483 was not issued at the conclusion of the inspection.

3. Malgorzata Baka-Ostrowska, M.D.

Protocol 905-CL-047

For this study, 26 subjects were screened and 15 subjects were enrolled, all of whom completed the study.

The study records for all 15 subjects enrolled were reviewed, including, but not limited to adverse event reporting and the primary efficacy endpoint. There was no evidence of under-reporting of adverse events, and the primary efficacy endpoint was verifiable.

Protocol 905-CI-074

For this study, eight subjects were screened and seven subjects were enrolled, all of whom completed the study.

The study records for all eight subjects were reviewed, including, but not limited to, adverse event reporting and the primary efficacy endpoint. There was no evidence of under-reporting of adverse events, and the primary efficacy endpoint was verifiable.

Recordkeeping deficiencies were noted for both studies with respect to the maintenance of the enrollment log (the field investigator had to request that the CI produce a "final enrollment log" with complete information), a lack of ECG interpretation by the site for some subjects prior to review by the central reader, and overwritten entries in the drug accountability logs.

A Form FDA 483 was not issued at the conclusion of the inspection.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Phillip Krostein, M.D.
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Good Clinical Practice Assessment Branch
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Kassa Ayalew, M.D., M.P.H
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Good Clinical Practice Assessment Branch
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cc:

Central Doc. Rm.\NDA 209529
DBRUP\Division Director\Hylton Joffe
DBRUP\Team Leader\Mark Hirsch
DBRUP\Medical Officer\Guodong Fang
DBRUP\Project Manager\Nita Crisostomo
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Phillip Kronstein
OSI\DCCE\GCPAB\Reviewer\Roy Blay
OSI\DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
08/02/2017

PHILLIP D KRONSTEIN
08/02/2017

KASSA AYALEW
08/02/2017

Interdisciplinary Review Team for QT Studies Consultation: QTc Evaluation

NDA	209529
Brand Name	
Generic Name	Solifenacin oral suspension
Sponsor	Astellas
Indication	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older.
Dosage Form	Oral suspension (1 mg/mL)
Drug Class	Muscarinic receptor antagonist
Therapeutic Dosing Regimen	Once daily weight-based dosing range: 9 to 15 kg: 2–4 mg >15 to 30 kg: 3–5 mg >30 to 45 kg: 3–6 mg >45 kg: 4–8 mg
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	40 mg in adults
Submission Number and Date	001, February 28, 2017
Review Division	DBRUP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

1 SUMMARY

Astellas submitted a NDA for solifenacin for the treatment of neurogenic detrusor activity in pediatric patients aged 2 years and older.

In study 905-CL-047, there were 4 discontinuations due to patients meeting a protocol specified discontinuation criteria for QTc (e.g., change from baseline of QTcB exceeding 30 ms). Following the amendment to increase the precision of the baseline QTcB estimate by averaging the 2 pretreatment values, there were no further discontinuations due to QTc prolongation and when the amendment was retrospectively applied to the data from the 4 subjects who discontinued, only 1 patient still met the criteria. Subsequent to these discontinuations the sponsor conducted an analysis of intrasubject variability and modified ongoing study protocols to define the baseline QTcB as an average of multiple pre-dose ECGs rather than a single ECG. We agree with the protocol amendment that the sponsor implemented.

Evaluation of the QTc outlier data from the Phase 3 pediatric studies did not show any patients with QTcB intervals greater than 480 ms or change from QTcB interval greater than 60 ms. The applicability of these QTc prolongation thresholds in pediatrics is not known and the timing of ECG collection relative to dosing was not controlled, which limits the interpretation. However, the absence of cardiac adverse events related to QTc prolongation is reassuring.

To better understand the potential for QTc prolongation in pediatrics due to solifenacin exposure with the proposed doses, we reviewed a prior thorough QT study for solifenacin in adults and developed a concentration-QTc model. This analysis showed a concentration-dependent increase in QTc for solifenacin, with a 90% upper bound of approximately 11 ms (Table 2) at suprathreshold exposures in pediatrics.

Overall, based on the data collected in this program and the predicted QTc effect using the concentration-QTc relationship developed from the TQT study in adults, it does not appear likely that solifenacin will have a clinically relevant effect on the QTc interval at the proposed doses in pediatric patients.

2 PROPOSED LABEL

Reviewer's Comment: The sponsor is proposing to use the same QTc language as included in the reference product, while this approach is appropriate we propose to revise the language so that it is consistent with current QTc labeling practices. We defer final labeling decisions to the Division.

Cardiac Electrophysiology

(b) (4)

3 BACKGROUND

3.1 PRODUCT INFORMATION

Solifenacin is a competitive muscarinic receptor antagonist with high affinity for M3-receptors. The muscarinic M3-receptor antagonistic effect is considered as the main mechanism of solifenacin-induced relaxation of the urinary bladder.

A pediatric development program has been conducted for solifenacin to establish safety and efficacy in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 2 years and older. The data demonstrate that solifenacin increases bladder capacity and reduces both involuntary detrusor contractions and incontinence in pediatric patients with an acceptable safety and tolerability profile.

The proposed indication for solifenacin oral suspension is for treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older.

3.2 MARKET APPROVAL STATUS

Solifenacin is currently approved in the United States for treatment of overactive bladder in adults (NDA 021518, approved 19 Nov 2004).

3.3 PRECLINICAL INFORMATION

No additional safety pharmacology studies were conducted to support the pediatric indication. Appendix 6.1 summarizes the key features of solifenacin's cardiac safety pharmacology.

3.4 TQT STUDY

The sponsor conducted a TQT study prior to the implementation of the ICH E14 guideline and the formation of the QT IRT.

The effect of 10 mg and 30 mg solifenacin on the QT interval was evaluated at the time of peak plasma concentration of solifenacin in a multi-dose, randomized, double-blind, placebo and positive controlled (moxifloxacin 400 mg) study. Patients were randomized to 1 of 2 treatment groups after receiving placebo and moxifloxacin sequentially. One group (n = 51) went on to complete 3 additional sequential periods of dosing with 10, 20, and 30 mg solifenacin while the second group (n = 25) completed a sequence of placebo and moxifloxacin in parallel. Patients were female volunteers aged 19 to 79 years. The 30 mg dose of solifenacin (3 times the highest recommended dose) was chosen in this study because this dose results in a solifenacin exposure that covers those observed upon co-administration of 10 mg VESicare with potent cytochrome P450 3A4 inhibitors (e.g., ketoconazole 400 mg). Due to the sequential dose escalating nature of the study, baseline ECG measurements were separated from the final QT assessment (of the 30 mg dose level) by 33 days. The median difference from baseline in heart rate associated with the 10 and 30 mg doses of solifenacin compared with placebo was -2 and 0 beats/minute, respectively. Because a significant period effect on QTc was observed, the QTc effects were analyzed using the parallel placebo control arm rather than the pre-specified intra-patient analysis. Representative results are shown in [Table 8]

Table 8 Change (90% CI) from Baseline in QTc (ms) at T_{max} (Relative to Placebo)

Drug/Dose	Fridericia's Formula (using Mean Difference)
Solifenacin 10 mg	2 (-3, 6)
Solifenacin 30 mg	8 (4, 13)

The results displayed are those derived from the parallel design portion of the study and represent the comparison of Group 1 to time-matched placebo effects in Group 2.

CI: confidence interval; QTc: QT interval corrected for heart rate.

Source: Prescribing Information for VESicare (solifenacin succinate) tablets, NDA 021518.

Reviewer's comment: The IRT conducted a concentration-QTc analysis of these data with results presented in section 5. This relationship is used to bridge the drug-induced QTc prolongation to pediatrics by exposure with the proposed dosing regimen.

3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of solifenacin's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

Data reviewed include:

- TQT study in healthy adult women (R905-CL-043, NDA021518)
- Summary of clinical safety, NDA209529
- QT Research Report, NDA209529
- US Package Insert, NDA209529

4.2 CLINICAL ECG DATA

The sponsor conducted an evaluation of the effects of solifenacin on QTc in children and adolescents for the 2 open-label studies in pediatric patients with NDO (Studies 905-CL-074 and 905-CL-047) and for the phase 3 studies in pediatric patients with OAB, which provide relevant supportive data (Studies 905-CL-076 and 905-CL-077).

All ECGs were centrally reviewed by a cardiologist.

4.2.1 ECG Methodology

A 12-lead ECG was performed in triplicate one minute apart while the subject in the supine position, after the subject has been lying quietly for at least 5 minutes. Recordings were made at a speed of 25 mm/s and all leads included at least four complexes. A sampling frequency of at least 500 Hz was used. ECG traces will be evaluated by a central laboratory.

The final ECG reports sent by the central laboratory were reviewed by the Investigator and were used for immediate safety assessment and subject care since there might be slight changes from the initial analysis produced by the ECG machines. If QTc interval exceeded 480 ms or an increase from baseline between 30 and 60 ms was observed, then repeat ECGs was performed. If, after central cardiologist review, the QTc interval exceeded 500 ms, or if the QTc interval was prolonged by greater than 60 ms relative to baseline, the subject was withdrawn from the study.

- 905-CL-074: Visits 1, 2, 3, 4, 5, 6, 7, 8 and 9 (Screening, baseline, week 3, week 6, week 9, week 12, week 24, week 36 and 52/EoT)
- 905-CL-047: Visits 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 (Screening, start washout, baseline, week 3, week 6, week 9, week 12, week 24, week 36 and 52/EoT).
- 905-CL-076: Visits 1, 2, 3, 4, 5, 6 and 7 (Screening, start of single-blind placebo run-in, baseline, week 3, week 6, week 9 and week 12/EoT).
- 905-CL-077: Visits 9, 10, 11, 12, 13, 14 (week 15, week 18, week 21, week 24, week 36, week 52/EoT).

Reviewer's comment: In general, the collection of safety ECGs in Phase 3 studies is adequate for categorical outlier analysis; however, the limitation is post-treatment ECGs were collected without controlling for the collection time relative to dosing of solifenacin.

4.2.2 Adverse Events and Treatment Discontinuation Due to QTc Prolongation

In all Phase 3 studies, treatment was discontinued if an on-treatment QTcB value exceeded 460 ms or change from baseline QTcB value exceeded 30 ms. Because of a higher rate of discontinuation due to change from baseline QTcB exceeding 30 ms in Study 905-CL-076, all protocols were amended to define baseline QTcB interval as the average of pre-treatment QTcB intervals. The SAPs for Studies 905-CL-076, 905-CL-077, 905-CL-074 and 905-CL-047, the baseline QTcB measure for the mean and

categorical analyses of QTcB used the average of the screening/start of washout and baseline measures.

- **In Study 905-CL-074**, the study specified that solifenacin should be discontinued if QTcB interval exceeded 460 ms or the QTcB interval was prolonged by greater than 30 ms relative to baseline. The protocol also specified the visit 2/baseline QTcB measurement was the baseline measure to which postbaseline QTcB values would be compared and that ECG measurements were to be taken in triplicate. Global protocol amendment 3 was implemented in version 4.0 of the protocol and specified that the baseline mean QTcB should be calculated by averaging of the QTcB means from visits 1/screening and 2/baseline (i.e., both pretreatment visits).
- **In Study 905-CL-047**, the calculation of baseline mean QTcB was revised for the discontinuation criterion as was done for Study 905-CL-074. Global substantial amendment 2 was implemented in version 2.0 of the protocol and specified that the measurement of baseline QTcB should be calculated by averaging the mean value from the visit 2/start of washout (or visit 1/screening, if visits 1/screening and 2/start of washout were combined) and visit 3/baseline ECG triplicates instead of using the QTcB mean from visit 3/baseline only.
- **In Study 905-CL-076/-077**, ECG measurements were made on visit 1 (screening), visit 2 (start of single-blind placebo run-in) and visit 3 (designated baseline visit). The version of the protocol under which patients were initially entered into the study (version 2.0) specified the visit 3 QTcB measurement as the baseline measure to which postbaseline QTcB values would be compared. This was subsequently amended (version 3.0) to use the average of the visit 2 and visit 3 measures as the baseline measure to which postbaseline QTcB values would be compared. The analysis of **Study 905-CL-077** was based on the integration of data from Study 905-CL-076 and Study 905-CL-077.

The results of the random effects model analysis conducted with the pretreatment QTcB measurements during the course of Study 905-CL-076 demonstrated that the observed numbers of discontinuations and associated TEAEs were in line with those estimated to occur in the absence of any solifenacin treatment effect on QTcB interval (6.25% based on the original criterion). Furthermore the random effects model analysis demonstrated that taking an average of the screening/start of washout and baseline triplicate measures of QTcB in Study 905-CL-076 would provide a more precise estimate of the baseline and thus lead to fewer inappropriate discontinuations driven by intrasubject variance in repeat QTcB measurements (3.24%). Whilst these results were obtained from analysis of the OAB patient dataset, the findings were considered to be equally applicable to studies in NDO patients.

Reviewer's Comment: We agree with the protocol amendments to define baseline QTcB as the average of all pre-treatment QTcB values to account for normal variation in the QTc. The sponsor's random effects analysis of intrasubject variability in study 905-CL-076 (described in Appendix 1 of Section 5.3.5.3 QTc Report) supports averaging these values.

In Study 905-CL-074, there were no treatment discontinuations due to QTc prolongation and no “ECG QT prolonged” AEs were reported. There were no TEAEs that were considered potentially related to QT prolongation.

In Study 905-CL-047, there were 4 TEAE of QT prolongation. All of the patients with a TEAE of QTc prolongation were discontinued from the study as they met the protocol-specified discontinuation criterion for this parameter. Following the amendment to increase the precision of the baseline QTcB estimate by averaging the 2 pretreatment values, there were no further discontinuations due to QTc prolongation and when the amendment was retrospectively applied to the data from the 4 subjects who discontinued, only 1 patient still met the criteria. There were no additional TEAEs reported during the study that were considered to be potentially related to QT prolongation.

In Study 905-CL-076, there were 10 patients who reported “ECG QT prolonged” AEs are listed in [Table 49]. For all these patients, the AE was reported before the baseline QTcB mean was recalculated. Most of these patients were discontinued from the study as they met the protocol-specified discontinuation criterion of an increase in QTcB exceeding 30 ms from baseline (1 placebo-treated child vs 4 solifenacin-treated children and 1 placebo-treated adolescent vs 2 solifenacin-treated adolescents). None of the patients experienced any untoward event in relation to the ECG observations (e.g., no arrhythmias, palpitations or other effects were reported).

Table 49 Summary of ECG QT Prolonged Reported as AEs

Patient ID	Age /Sex	Treatment	Onset Timing	Severity	Relationship	Outcome	Action Taken	QTcB Value (ms)
Children (Aged 5 to less than 12 Years)								
(b) (6)	6/M	Solifenacin	During DB Period	Mild	Probable	Not recovered	Drug withdrawn	B: 394.8 V4: 424.7 EoT: 414.3
	9/M	Solifenacin	During DB Period	Mild	Probable	Recovering	Drug withdrawn	B: 406.0 V5: 447.3 EoT: 424.3
	6/M	Placebo	During DB Period	Mild	Possible	recovered	Dose reduced	B: 393.5 V5: 380.3 V6: 398.3 UNS: 404.0
	7/M	Placebo	During DB Period	Mild	Probable	Recovered	Drug withdrawn	B: 392.8 V6: 416.0 EoT: 388.7
	8/F	Solifenacin	During DB Period	Mild	Possible	recovered	Drug withdrawn	B: 376.3 V5: 413.3 EoT: 397.7
	11/F	Solifenacin	During DB Period	Mild	Possible	recovered	Dose not changed	B: 430.0 V5: 456.0 EoT: 449.3
	8/F	Solifenacin	During DB Period	Mild	Not related	recovered	Drug withdrawn	B: 352.3 V5: 368.7 EoT: 407.3
Adolescents (Aged 12 to less than 18 Years)								
(b) (6)	16/F	Placebo	During DB Period	Mild	Possible	Unknown	Drug withdrawn	B: 382.7 V6: 399.0 UNS: 377.3 EoT: 387.7
	13/F	Solifenacin	During DB Period	Mild	Probable	Recovered	Drug withdrawn	B: 407.3 V4: 435.7 UNS: 431.0 EoT: 412.0
	13/F	Solifenacin	During DB Period	Mild	Not related	Recovered	Drug withdrawn	B: 410.7 V4: 431.3 EoT: 420.3

The baseline value is the mean of the triplicate means at visit 2 and visit 3 (Amendment 2).

AE: adverse event; B: baseline visit, DB: double-blind; UNS: unscheduled visit; ECG: electrocardiogram; EoT: end of treatment.

Source: Appendices 13.2.7.1 and 13.2.8.3.1

In Study 905-CL-077, there were 14 TEAE reports (9 females/5 males), with the PT “ECG QT” prolonged in the study, 10 in children and 4 in adolescents. Of these, 12 events resulted in discontinuation of study drug driven by the discontinuation criterion in the protocol of a greater than 30 ms increase in mean QTcB interval compared to baseline. Of these patients, one had an increase in categorical QTcB of more than 460 ms. Of the remaining events, one resulted in discontinuation based on an erroneous evaluation of the data against the discontinuation criteria and one was an observation that was made at the final study visit in a patient who had already completed study treatment. All these events were reported with a possible or probable relationship with study drug by the investigator [Table 36]. There were no increases in mean QTcB compared to baseline of more than 40 ms in the study. None of the 14 TEAE reports of ECG QT prolonged were associated with any clinical symptoms or tachyarrhythmia.

Table 36 Summary of ECG QT Prolonged Reported as TEAEs (All Subjects Who Received at Least One Dose of Open-label Solifenacin)

Patient ID/Age/Sex	Treatment 905-CL-076	Severity/Relationship/ Outcome	Action Taken	QTcB Value (ms)
Children (Aged 5 to Less Than 12 Years)				
(b) (6)	Placebo	Mild/Possible/ Recovered	Drug withdrawn	B (V3): 381.3 B (V2 + V3): 389.3 Day 42†: 419.3 EoOL/Day 63†: 409.3
(b) (6)	Placebo	Mild/ Possible/ Not recovered	Drug withdrawn	B (V3): 385.7 B (V2 + V3): 390.7 Day 36†: 423.0 EoOL/Day 64†: 419.0
(b) (6)	Placebo	Mild/Possible/ Recovered	Drug withdrawn	B (V3): 393.3 B (V2 + V3): 393.0 Day 166†: 437.7 EoOL/Day 215†: 394.7
(b) (6)	Placebo	Mild/Probable/ Not recovered	Drug withdrawn	B (V3): 425.3 B (V2 + V3): 416.5 Day 63†: 464.0 EoOL/Day 84†: 433.7
(b) (6)	Solifenacin	Mild/Probable/ Not recovered	Drug withdrawn	B (V3): 415.0 B (V2 + V3): 421.0 Day 96†: 450.3 EoOL/Day 133†: 445.0
(b) (6)	Solifenacin	Moderate/Possible/ Not recovered	Drug withdrawn	B (V3): 347.3 B (V2 + V3): 359.2 Day 126†: 376.3
(b) (6)	Placebo	Mild/Probable/ Recovered	Drug withdrawn	B (V3): 396.3 B (V2 + V3): 406.5 Day 84†: 426.7 EoOL/Day 119†: 406.0
(b) (6)	Solifenacin	Mild/Probable/ Recovered	Drug withdrawn	B (V3): 427.0 B (V2 + V3): 427.5 Day 168†: 458.0 EoOL/Day 189†: 436.0
(b) (6)	Solifenacin	Mild/Possible/ Not recovered	Dose not Changed	B (V3): 423.3 B (V2 + V3): 418.8 EoOL/Day 365†: 451.0
(b) (6)	Solifenacin	Mild/Possible/ Recovered	Drug withdrawn	B (V3): 410.0 B (V2 + V3): 420.7 Day 128†: 450.0 EoOL/Day 134†: 432.7
Adolescents (Aged 12 to Less Than 18 Years)				
(b) (6)	Solifenacin	Mild/Probable/ Recovered	Drug withdrawn	B (V3): 390.0 B (V2 + V3): 401.7 Day 168†: 421.3 EoOL/Day 189†: 403.8
(b) (6)	Solifenacin	Mild/Probable/ Recovered	Drug withdrawn	B (V3): 395.0 B (V2 + V3): 406.5 Day 82†: 428.0 EoOL/Day 91†: 415.7
(b) (6)	Solifenacin	Mild/Probable/ Recovered	Drug withdrawn	B (V3): 384.3 B (V2 + V3): 401.7 Day 168†: 417.7 EoOL/Day 173†: 397.3

Table continued on next page

Patient ID/Age/Sex	Treatment 905-CL-076	Severity/Relationship/ Outcome	Action Taken	QTcB Value (ms)
(b) (6)	Placebo	Mild/Probable/ Recovered	Drug withdrawn	B (V3):398.0 B (V2 + V3): 395.8 Day 62†: 429.0 EoOL/Day 83†: 413.0

B (V3): The baseline value is the mean of the triplicate means at visit 3.

B (V2 + V3): The baseline value is the mean of the triplicate means at visit 2 and visit 3 (Amendment 3 dated 23 Sep 2013).

† Day is relative to the first dose of solifenacin treatment and corresponds to the onset date of the TEAE.

B: baseline; EoOL: end of open-label period; TEAE: treatment-emergent adverse event.

Source: Appendices 13.2.8.3.5 and 13.2.7.6.1

4.2.3 Categorical Outlier Analysis

Study 905-CL-074

All patients had a categorized absolute QTcB value < 450 ms at baseline except for 1 child for which a baseline QTcB of 455 ms was measured [Table 40]. At EoT, all patients had a categorized absolute QTcB value < 450 ms. Two children had a change from baseline to EoT in absolute QTcB between 30 and < 60 ms. No change from baseline > 60 ms was reported.

Table 40 Summary of Categorized Absolute Value of QTcB and Categorized Change from Baseline in QTcB (SAF)

Criteria	Number of patients (%)				
	All Patients (Aged 6 Months to < 5 Years)				
	Total Solifenacin	PED2.5	PED5	PED7.5	PED10
Value at Baseline (ms)					
n			23		
< 450			22 (95.7)		
450 to < 480			1 (4.3)		
480 to < 500			0		
≥ 500			0		
Value at EoT (ms)					
n	22	0	1	6	15
< 450	22 (100)	0	1 (100)	6 (100)	15 (100)
> 450	0	0	0	0	0
Change from Baseline to EoT (ms)					
n	22	0	1	6	15
< 0	9 (40.9)	0	0	2 (33.3)	7 (46.7)
0 to < 30	11 (50.0)	0	0	4 (66.7)	7 (46.7)
30 to < 60	2 (9.1)	0	1 (100)	0	1 (6.7)
≥ 60	0	0	0	0	0

The mean of the triplicate is summarized. The Baseline value is the mean of the triplicate means at visit 1 and visit 2. Each ECG value is assigned to the dose group of the last dose taken prior to the ECG being performed.

The value at the final visit is the most recent non-missing post-baseline value at or prior to visit 9. The total number of patients in each dose group is the number who ever received that dose in the course of the study.

EoT: end of treatment; NA: not applicable; n: number of patients; PED: pediatric equivalent dose; QTcB: QT interval corrected for heart rate by Bazett's formula; SAF: safety analysis set.

Source: Tables 12.6.4.2, 12.6.4.3.1 and 12.6.4.4.1

Study 905-CL-047

All patients had a categorized absolute QTcB value < 450 ms at baseline [Table 40]. At week 52, all patients but 1 had a categorized absolute QTcB value < 450 ms; 1 adolescent had a change from baseline to week 52 in absolute QTcB between 30 and < 60 ms. No change from baseline > 60 ms was reported.

Table 40 Summary of Categorized Absolute Value of QTcB and Categorized Change from Baseline in QTcB (SAF)

Criteria	Number of Patients (%)		
	Children (Aged 5 Years to < 12 Years)	Adolescents (Aged 12 Years to < 18 Years)	All Patients (Aged 5 Years to < 18 Years)
Value at Baseline (ms)			
n	42	34	76
< 450	42 (100)	34 (100)	76 (100)
Value at Week 52 (ms)			
n	30	27	57
< 450	30 (100)	26 (96.3)	56 (98.2%)
> 450 to < 480	0	1 (3.7)	1 (1.8%)
Change from Baseline to Week 52 (ms)			
n	30	27	57
< 0	15 (50)	14 (51.9)	29 (50.9)
0 to < 30	15 (50)	12 (44.4)	27 (47.4)
30 to < 60		1 (3.7)	1 (1.8)

A triplicate of ECGs was performed at each study visit and was required to be repeated in certain instances. If 2 or more values were equally close and on the same day, the mean was used for continuous variables or the worst observed case for categorical variables. The mean of the triplicate was summarized. The baseline value was the mean of the triplicate means at visit 2 and visit 3.

ECG: electrocardiogram; NA: not applicable; n: number of patients; QTcB: QT interval corrected for heart rate by Bazett's formula; SAF: safety analysis set.

Source: Table 12.6.4.3.1 and 12.6.4.4.1

Study 905-CL-076

All patients had an absolute QTcB value < 450 ms at baseline. Only 1 patient had a change in the categorized absolute QTcB value between baseline and EoT; a solifenacin-treated child had an absolute QTcB value between 450 to < 480 ms at EoT (patient 3812187 with a QTcB value of 451 ms). One placebo-treated child, 2 solifenacin-treated children and 2 solifenacin-treated adolescents had a change from baseline to EoT in absolute QTcB value between 30 to < 60 ms. No patient had a change from baseline > 60 ms.

Table 48 Summary of Categorized Absolute Value of QTc by Study Week - Bazett's Correction and Categorized Change from Baseline in QTc by Study Week - Bazett's Correction (SAF)

Criteria	Children (Aged 5 to less than 12 Years)		Adolescents (Aged 12 to less than 18 Years)	
	Placebo (n = 73)	Solifenacin (n = 73)	Placebo (n = 19)	Solifenacin (n = 22)
Value at Baseline (ms)				
n	73	73	19	22
< 450	73 (100.0%)	73 (100.0%)	19 (100.0%)	22 (100.0%)
450 to < 480	0	0	0	0
480 to < 500	0	0	0	0
≥ 500	0	0	0	0
Value at EoT (ms)				
n	73	72	19	21
< 450	73 (100.0%)	71 (98.6%)	19 (100.0%)	21 (100.0%)
450 to < 480	0	1 (1.4%)	0	0
480 to < 500	0	0	0	0
≥ 500	0	0	0	0
Change from Baseline to EoT (ms)				
n	73	72	19	21
< 0	31 (42.5%)	30 (41.7%)	7 (36.8%)	11 (52.4%)
0 to < 30	41 (56.2%)	40 (55.6%)	12 (63.2%)	8 (38.1%)
30 to < 60	1 (1.4%)	2 (2.8%)	0	2 (9.5%)
≥ 60	0	0	0	0

Results are based on the baseline calculation resulting from Amendment 2 [Appendix 13.1.1].

The baseline value is the mean of the triplicate means at visit 2 and visit 3.

The value at the final visit is the most recent nonmissing postbaseline value at or prior to week 12.

EoT: end of treatment; QTc: QT interval corrected for heart rate; SAF: safety analysis set.

Source: Tables 12.6.4.3.1 and 12.6.4.4.1

Study 905-CL-077

Categorical analyses of QTcB demonstrated that 5 patients had a measured mean QTcB interval greater than or equal to 450 ms at the final observation [Table 38]. There was no incidence of a patient with a mean QTcB > 480 ms (maximal mean QTcB interval observed was 464 ms). One of these QTcB intervals greater than or equal to 450 ms was observed at the dose of PED5, 2 at the dose of PED7.5 and 2 at the PED10 dose.

Table 38 Summary of Categorized Absolute Value of QTc - Bazett's Correction and Categorized Change From Baseline in QTc - Bazett's Correction (SAF)

Criteria	Children (Aged 5 to Less Than 12 Years) All Solifenacin n =118	Adolescents (Aged 12 to Less Than 18 Years) All Solifenacin n =29
Value at Baseline (ms)		
n	118	29
< 450	118 (100.0%)	29 (100.0%)
450 to < 480	0	0
480 to < 500	0	0
≥ 500	0	0
Value at Final Visit (ms)†		
n	116	29
< 450	111 (95.7%)	29 (100.0%)
450 to < 480	5 (4.3%)	0
480 to < 500	0	0
≥ 500	0	0
Change From Baseline to Final Visit (ms)†		
n	116	29
< 0	38 (32.8%)	11 (37.9%)
0 to < 30	73 (62.9%)	17 (58.6%)
30 to < 60	5 (4.3%)	1 (3.4%)
≥ 60	0	0

A triplicate of ECGs were performed at each study visit and were required to be repeated in certain instances. The mean of the triplicate is summarized. The baseline value is the mean of the triplicate means at visit 2 and visit 3.

† The value at the final visit is the most recent value after first dose of solifenacin up to and including visit 14.

ECG: electrocardiogram; QTc: QT interval corrected for heart rate; SAF: safety analysis set.

Source: Tables 12.6.4.3.1 and 12.6.4.4.1

Reviewer's Comment: There were no incidences of patients with QTcB values exceeding 480 ms or 60 ms change from baseline in all Phase 3 studies conducted in children. None of the children or adolescents experienced a cardiac AEs related to QTc prolongation. Overall, there is no clinically significant increases in QTc interval.

5 REVIEWERS' ASSESSMENT

5.1 CLINICAL PHARMACOLOGY ASSESSMENTS

A thorough QT study was previously conducted for solifenacin, which included two doses of solifenacin: 10 and 30 mg (therapeutic and suprathreshold doses respectively) as well as placebo and moxifloxacin. This review will only focus on the solifenacin and placebo arm, and the development of a concentration-QTc model to predict the QTc prolongation at pediatric exposures.

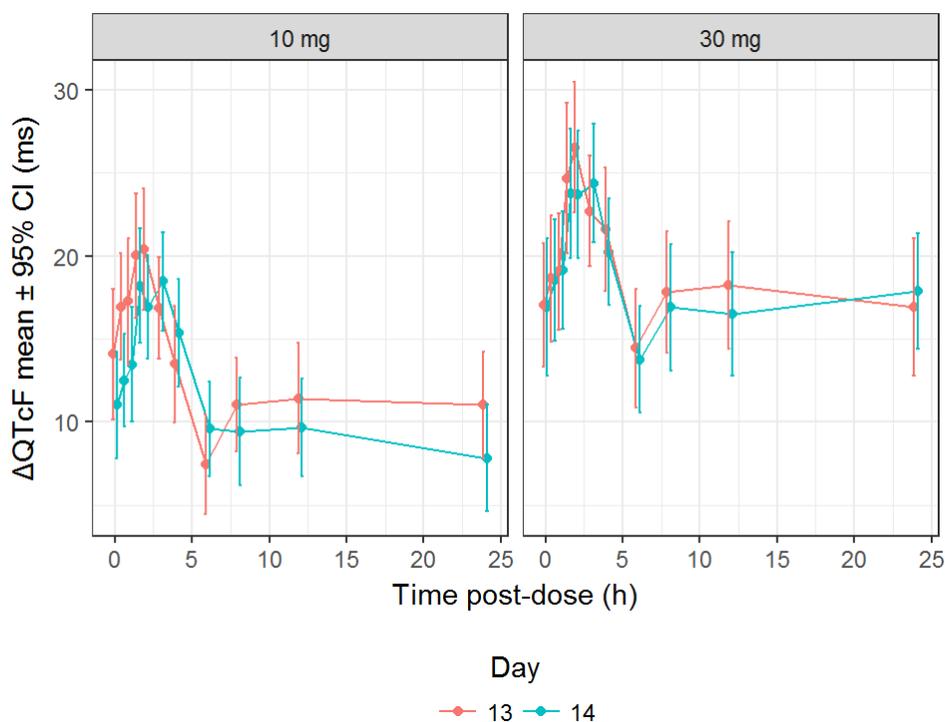
The study included two treatment groups with dosing in five sessions (Figure 1). Between sessions 1 and 2 a washout of at least 3 days was included, but there were no washout between sessions 2 through 5. Therefore, starting with session 3 the design of the study is similar to a traditional parallel thorough QT study with the exception of moxifloxacin dosing on day 14 of sessions 3 and 5.

Figure 1: Study overview

	Treatment Group A	Treatment Group B
Session 1	1-day baseline (no drug) moxifloxacin (400 mg) on Day 1	
Session 2	1-day baseline (no drug) placebo on Day 1	
Session 3	1-day baseline (no drug) solifenacin 10 mg UID x 14 days	1-day baseline (no drug) placebo UID x 13 days; moxifloxacin (400 mg) on Day 14
Session 4	solifenacin 20 mg UID x 5 days	placebo UID x 5 days
Session 5	solifenacin 30 mg UID x 14 days	placebo UID x 13 days; moxifloxacin (400 mg) on Day 14

The study has one important limitation, which is that solifenacin PK was only collected on day 14 in sessions 3 and 5, which is the moxifloxacin dosing day in the placebo arm. The lack of a PK collection on day 13, complicates the use of concentration-QTc analysis to analyze the data. However, based on the pharmacokinetics of solifenacin it is expected that the PK, as well as QTc profile, on day 13 and 14 to be similar. To evaluate this assumption the reviewer compared the QTc time-profile between days 13 and 14 for 10 and 30 mg (Figure 2). As seen in the figure the time-profile in Δ QTc is generally similar between days 13 and 14 for each dose group.

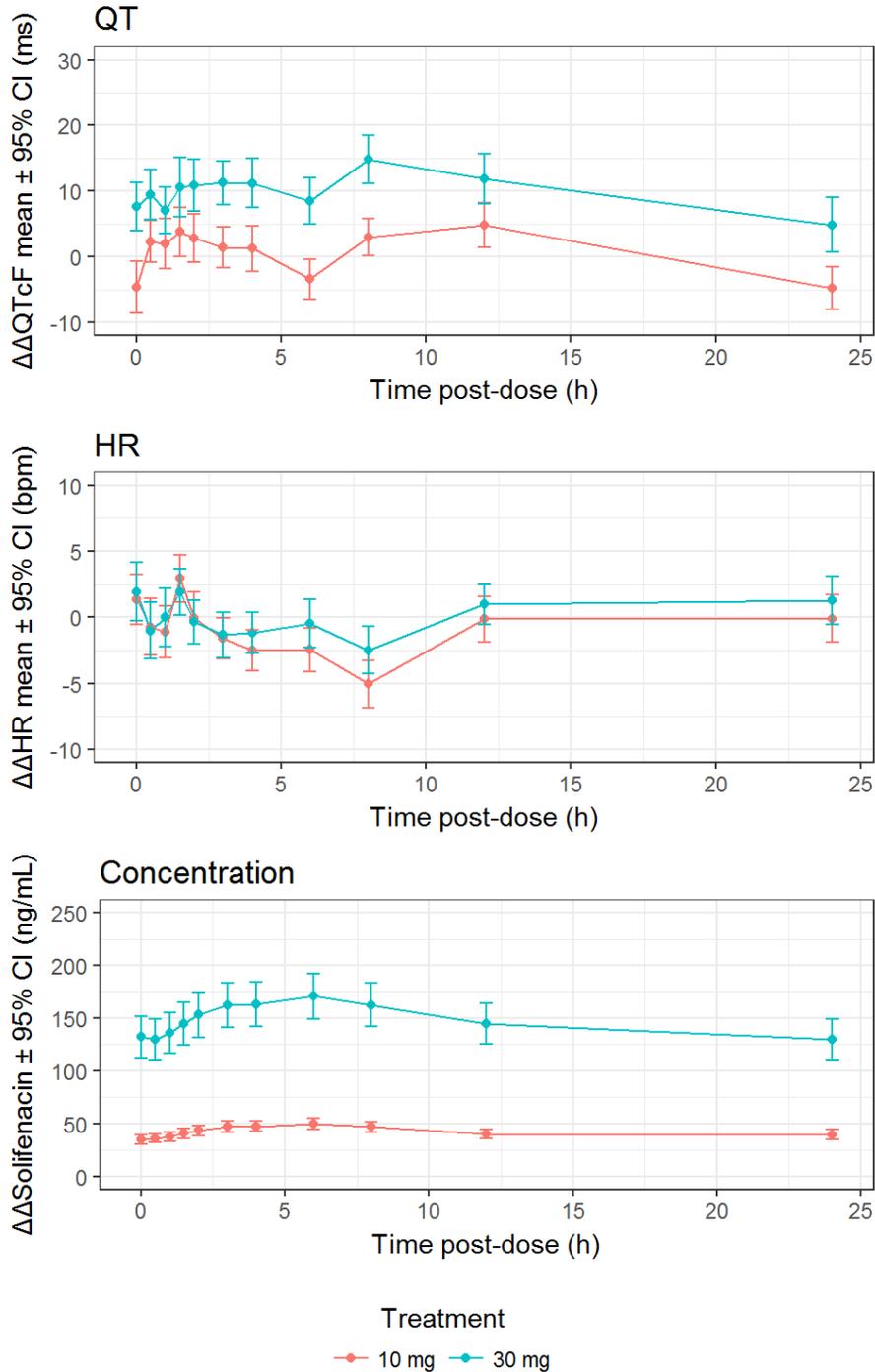
Figure 2: Comparison of the Δ QTc time-profile for day 13 and 14 for 10 mg (left) and 30 mg (right)



Before conducting the concentration-QTc analysis, an exploratory analysis was conducted to evaluate the changes in HR and to assess if there was a delay between QTc interval changes and solifenacin concentration. This analysis is shown in Figure 3 and

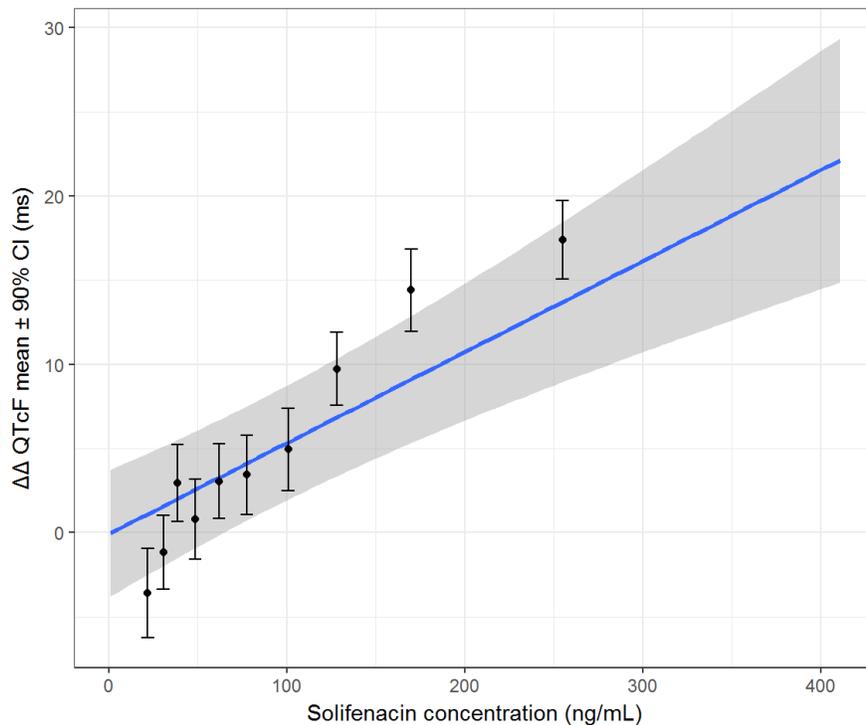
suggests an absence of a delay between solifenacin concentration and QTc interval changes. In addition, no significant increases or decreases in heart rate were observed for solifenacin. The absence of heart rate changes supports the use of Fridericia's correction for assessing the changes in the QTc interval.

Figure 3: Evaluation of the relationship between $\Delta\Delta\text{QTc}$ (top row), $\Delta\Delta\text{HR}$ (middle row) and solifenacin concentration (bottom row).



The relationship between solifenacin concentration and QTc was modeled with a linear mixed effects model that included change from baseline in QTc as the dependent variable and treatment and time as fixed categorical effects and baseline QTc centered at the population mean and concentration (set to zero for placebo) as continuous covariates. The model also included a random effect on the intercept and slope by subject. The concentration values used in the analysis was from day 14 and the QTc values were from day 13, as supported by the initial analysis described above (Figure 2). The goodness-of-fit for the model is shown in Figure 4, which shows a linear concentration-dependent relationship for solifenacin for the QTc interval.

Figure 4: Goodness-of-fit plot for the model. The observed $\Delta\Delta\text{QTcF}$ is grouped into 10 bins for the treatment data. The solid black line and shaded area represent mean \pm 90 % confidence interval.



The $\Delta\Delta\text{QTc}$ effect predicted using the concentration-QTc model was similar to the $\Delta\Delta\text{QTc}$ reported in the label that was computed using a by-time analysis (Table 1).

Table 1: Comparison of the $\Delta\Delta\text{QTc}$ estimated using by-time or concentration-QTc analysis

	Concentration (ng/mL)	By-time (ms)	Concentration- QTc (ms)
10 mg	38	2 (-3 to 6)	2.0 (-1.5 to 5.5)
30 mg	132	8 (4 to 13)	7.0 (3.5 to 10.6)

The concentration-QTc model was used to compute the predicted mean $\Delta\Delta\text{QTc}$ in pediatrics based at therapeutic and supratherapeutic concentrations (with a CYP3A

inhibitor) (Table 2). In this analysis, the weight band with the maximum mean C_{\max} (>30 to 45 kg: 51.6 ng/mL based on study CL-047) was used as maximum therapeutic concentration and the suprathreshold concentration was based on that weight band. Based on this analysis it can be observed that the upper bound at the suprathreshold dose barely exceeds 10 ms, similar to what was observed in adults (Table 1).

Table 2: Predicted $\Delta\Delta QTc$ in pediatrics based on concentration- QTc model

	Mean $\Delta\Delta QTc$ (ms)	90% CI (ms)
Therapeutic, 51.6 ng/mL	2.7	-0.7 to 6.2
Suprathreshold (CYP3A), 144.5 ng/mL	7.7	4.1 to 11.3

5.2 CLINICAL ASSESSMENTS

5.2.1 Safety assessments

None of the adverse events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in studies 905-CL-074, 905-CL-047, 905-CL-076 and 905-CL-077.

5.2.2 ECG assessments

No ECGs were uploaded to the FDA ECGWarehouse.

5.2.3 PR and QRS Interval

In the TQT study, no QRS prolongation was observed at 10 and 30 mg, however, modest concentration-dependent PR prolongation (8 ms [90% CI: 4.5 to 13.0]) was observed at the 30 mg dose.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY AND CARDIAC SAFETY

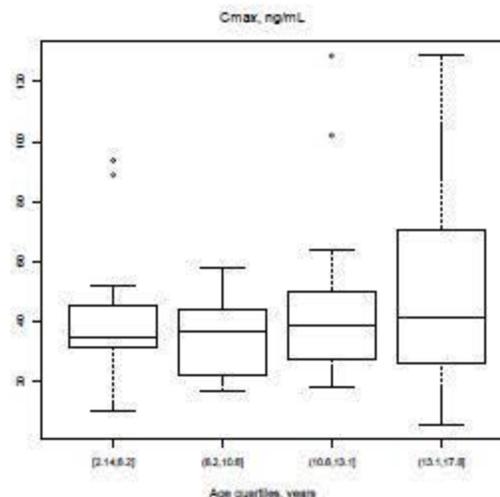
Table 1. Highlights of Clinical Pharmacology and Cardiac Safety

<p>Therapeutic dose and exposure</p>	<p>In the solifenacin pediatric development program, patients were dosed with pediatric equivalent doses (PED) based on body weight to achieve a similar steady state exposure (AUC) to that observed in adults dosed with 5 or 10 mg once daily; the corresponding pediatric doses were identified as PED5 or PED10. The proposed dosing table for labeling was also constructed based on this principle. The resulting maximum dosing regimen for pediatric patients is PED10.</p> <p>The mean (%CV) C_{max} and AUC at the maximum proposed dosing regimen of PED10 for pediatric patients are provided in Table 1.</p> <p>Table 1 Mean (CV%) C_{max} and AUC at PED10 for Pediatric Patients</p> <table border="1" data-bbox="453 642 1308 743"> <thead> <tr> <th></th> <th>C_{max} (ng/mL)</th> <th>AUC (ng.h/mL)</th> </tr> </thead> <tbody> <tr> <td>Single Dose†</td> <td>34.57 (56.4%)</td> <td>1794 (104.5%)</td> </tr> <tr> <td>Steady State‡</td> <td>47.36 (51.8%)</td> <td>940.63 (59.7%)</td> </tr> </tbody> </table> <p>† Study 905-CL-075, n = 13, patients with OAB aged 5 years to less than 18 years. The single doses administered to achieve plasma concentrations that were representative for steady state exposures were 3-fold higher than the calculated PED10.</p> <p>‡ Studies 905-CL-074 and 905-CL-047, n = 54, patients with NDO aged 2 years to less than 18 years. NDO: neurogenic detrusor overactivity; PED: pediatric equivalent dose; OAB: overactive bladder.</p>		C_{max} (ng/mL)	AUC (ng.h/mL)	Single Dose†	34.57 (56.4%)	1794 (104.5%)	Steady State‡	47.36 (51.8%)	940.63 (59.7%)																																																																
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<p>Principal adverse events</p>	<p>The most frequently reported treatment-emergent adverse event (TEAE) in the phase 3 neurogenic detrusor overactivity (NDO) population was urinary tract infection (30.5%) [Table 2]; patients performing clean intermittent catheterization commonly report this adverse event.</p> <p>Table 2 Incidence (> 5% Incidence in Total Group) of TEAEs, 52 Weeks of Treatment (SAE); Phase 3 Population</p> <table border="1" data-bbox="453 1115 1308 1692"> <thead> <tr> <th rowspan="3">MedDRA v19.0 SOC Preferred Term</th> <th colspan="4">ISS Pool / Study; Number of Patients (%)</th> </tr> <tr> <th>Phase 3 NDO Population</th> <th colspan="2">905-CL-076 / 905-CL-077</th> <th>Phase 3 Population Total†</th> </tr> <tr> <th>Solifenacin Open-label (NDO) n = 95</th> <th>Solifenacin Double-blind + Solifenacin Open-label (OAB) n = 73</th> <th>Placebo Double-blind + Solifenacin Open-Label (OAB) n = 75</th> <th>(OAB and NDO) n = 243</th> </tr> </thead> <tbody> <tr> <td>Overall</td> <td>61 (64.2)</td> <td>58 (79.5)</td> <td>65 (86.7)</td> <td>184 (75.7)</td> </tr> <tr> <td colspan="5">Gastrointestinal Disorders</td> </tr> <tr> <td>Constipation</td> <td>7 (7.4)</td> <td>11 (15.1)</td> <td>8 (10.7)</td> <td>26 (10.7)</td> </tr> <tr> <td>Diarrhoea</td> <td>4 (4.2)</td> <td>8 (11.0)</td> <td>4 (5.3)</td> <td>16 (6.6)</td> </tr> <tr> <td colspan="5">General Disorders and Administration Site Conditions</td> </tr> <tr> <td>Pyrexia</td> <td>4 (4.2)</td> <td>3 (4.1)</td> <td>8 (10.7)</td> <td>15 (6.2)</td> </tr> <tr> <td colspan="5">Infections and Infestations</td> </tr> <tr> <td>Gastroenteritis</td> <td>3 (3.2)</td> <td>6 (8.2)</td> <td>8 (10.7)</td> <td>17 (7.0)</td> </tr> <tr> <td>Influenza</td> <td>2 (2.1)</td> <td>3 (4.1)</td> <td>8 (10.7)</td> <td>13 (5.3)</td> </tr> <tr> <td>Nasopharyngitis</td> <td>6 (6.3)</td> <td>8 (11.0)</td> <td>16 (21.3)</td> <td>30 (12.3)</td> </tr> <tr> <td>Upper Respiratory Tract Infection</td> <td>6 (6.3)</td> <td>2 (2.7)</td> <td>7 (9.3)</td> <td>15 (6.2)</td> </tr> <tr> <td>Urinary Tract Infection ‡</td> <td>29 (30.5)</td> <td>9 (12.3)</td> <td>10 (13.3)</td> <td>48 (19.8)</td> </tr> </tbody> </table> <p><i>Table continued on next page</i></p>	MedDRA v19.0 SOC Preferred Term	ISS Pool / Study; Number of Patients (%)				Phase 3 NDO Population	905-CL-076 / 905-CL-077		Phase 3 Population Total†	Solifenacin Open-label (NDO) n = 95	Solifenacin Double-blind + Solifenacin Open-label (OAB) n = 73	Placebo Double-blind + Solifenacin Open-Label (OAB) n = 75	(OAB and NDO) n = 243	Overall	61 (64.2)	58 (79.5)	65 (86.7)	184 (75.7)	Gastrointestinal Disorders					Constipation	7 (7.4)	11 (15.1)	8 (10.7)	26 (10.7)	Diarrhoea	4 (4.2)	8 (11.0)	4 (5.3)	16 (6.6)	General Disorders and Administration Site Conditions					Pyrexia	4 (4.2)	3 (4.1)	8 (10.7)	15 (6.2)	Infections and Infestations					Gastroenteritis	3 (3.2)	6 (8.2)	8 (10.7)	17 (7.0)	Influenza	2 (2.1)	3 (4.1)	8 (10.7)	13 (5.3)	Nasopharyngitis	6 (6.3)	8 (11.0)	16 (21.3)	30 (12.3)	Upper Respiratory Tract Infection	6 (6.3)	2 (2.7)	7 (9.3)	15 (6.2)	Urinary Tract Infection ‡	29 (30.5)	9 (12.3)	10 (13.3)	48 (19.8)
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Investigations				
ECG QT Prolonged	4 (4.2)	7 (9.6)	9 (12.0)	20 (8.2)
Nervous System Disorders				
Headache	4 (4.2)	10 (13.7)	8 (10.7)	22 (9.1)
<p>† The Total (OAB and NDO) 52 weeks treatment group consists of results from all patients in the phase 3 population, including placebo-treated periods.</p> <p>‡ The category urinary tract infection includes MedDRA preferred terms of Escherichia urinary tract infection, urinary tract infection bacterial, urinary tract infection enterococcal and urinary tract infection pseudomonal.</p> <p>The Phase 3 NDO population includes Studies 905-CL-047 and 905-CL-074. The Phase 3 population includes Studies 905-CL-076, 905-CL-077, 905-CL-047 and 905-CL-074.</p> <p>SOCs and preferred terms within each SOC are organized by ascending alphabetical order.</p> <p>ECG: electrocardiogram; ISS: integrated summary of safety; n: number of patients; NDO: neurogenic detrusor overactivity; OAB: overactive bladder; SAF: safety analysis set.</p> <p>Source: ISS Table 13.4.11.2 and Table 13.4.2.2.1</p> <p>The most frequently reported drug-related TEAE was constipation (7.4%). In the phase 3 NDO population, 4 adverse events (4.2% patients) of electrocardiogram (ECG) QT prolonged were reported. All of the patients with a TEAE of QT prolongation were discontinued as they met the strict protocol-specified discontinuation criterion for this parameter. There were no further discontinuations due to QT prolongation and no new TEAEs of ECG QT prolonged after a protocol amendment was implemented to increase the accuracy of the baseline QTc measure. No dose-limiting adverse events were observed in pediatric clinical studies with solifenacin. The maximum tolerated dose in adults was 40 mg (Study 905-CL-022). At a dose of 50 mg the neurological adverse event of tremor led to discontinuation of treatment.</p>				
Maximum dose tested	Single Dose	The maximum single dose tested in the pediatric population was PED10 (Study 905-CL-075). The accumulation ratio of solifenacin was anticipated to be approximately 3. Therefore, to achieve plasma concentrations after a single dose that were representative for steady state exposures, the actual single doses administered in single-dose Study 905-CL-075 were 3-fold higher than the calculated single doses. This adjustment led to actual doses in the range of 3 to 27 mg.		
	Multiple Dose	The maximum multiple dose tested in the pediatric population was PED10 once daily (Studies 905-CL-047 and 905-CL-074). This led to actual doses in the range of 1.6 to 10 mg. Total study duration was 52 weeks.		

Exposures Achieved at Maximum Tested Dose	Single Dose	The mean C_{max} (%CV) at the maximum single dose tested in the pediatric population was 34.57 (56.4%) ng/mL (PED10, adjusted for the 3-fold accumulation ratio, Study 905-CL-075, n = 13). The mean AUC_{inf} (%CV) at the maximum single dose tested in the pediatric population was 1794 (104.5%) ng/mL.h (PED10, adjusted for the 3-fold accumulation ratio, Study 905-CL-075, n = 13).
	Multiple Dose	The mean (%CV) C_{max} at the maximum multiple dose tested in the pediatric NDO population aged 2 years and older was 47.36 (51.8%) ng/mL (PED10, Studies 905-CL-047 and 905-CL-074, n = 54). The mean (%CV) AUC_{0-24} at the maximum multiple dose tested in the pediatric NDO population aged 2 years and older was 940.6 (59.7%) ng.h/mL (PED10, Studies 905-CL-047 and 905-CL-074, n = 54).
Range of linear PK	Linear pharmacokinetics was observed in the full range of doses that were administered in the pediatric population: this included single doses of PED2.5 to PED10, adjusted for the 3-fold accumulation ratio, up to an actual maximum single dose of 27 mg (Study 905-CL-075) and multiple doses of PED2.5 to PED10, up to an actual maximum multiple dose of 10 mg once daily (Study 905-CL-047). Linear pharmacokinetics was also observed up to 40 mg once daily for multiple dose administration in the adult population.	
Accumulation at steady state	The mean (%CV) accumulation at steady state in pediatric patients with NDO aged 2 years and older administered solifenacin once daily was 2.41 (42.1%) (Studies 905-CL-047 and 905-CL-074).	
Metabolites	One pharmacologically active metabolite M3 (4R-hydroxy solifenacin) and 3 pharmacologically inactive metabolites M2, M4 and M5 (N-oxide, 4R-hydroxy-N-oxide and N-glucuronide, respectively) have been found in human plasma after oral dosing. The active metabolite M3 occurs at low concentrations and is unlikely to contribute significantly to clinical activity. In addition, M3 inhibited approximately 10% of the IKr potassium current (considered not significant) at the maximum concentration (109 ng/mL) in the HERG cell assay; metabolites M2, M4 and M5 were not active in this assay. Only parent concentrations were determined in the pediatric population since there are no pharmacologically active metabolites that significantly contribute to the efficacy or safety.	
Absorption	Absolute/Relative Bioavailability	The absolute or relative bioavailability of solifenacin has not been determined in the pediatric population. In adults (Study 905-CL-009), the mean absolute bioavailability amounted to 88.0% with a 95% confidence interval [CI] of 75.8% to 102.1%.
	Tmax	The median t_{max} (range) for solifenacin in pediatric patients with NDO aged 2 years and older was 3.0 (2.0 to 6.0) hours (Studies 905-CL-047 and 905-CL-074). No metabolites have been measured in pediatric studies.

Distribution	Vd/F or Vd	The mean (%CV) apparent volume of distribution in pediatric patients with NDO aged 2 years and older was 234.5 (62.0%) L (Studies 905-CL-047 and 905-CL-074).
	% bound	The % bound has not been determined in the pediatric population. In adults (Study 905-CL-029), young males and females administered a dose of 5 mg, the mean (%CV) fraction unbound amounted to 1.917% (23.1%). At a dose of 10 mg, it was 2.130% (22.1%).
Elimination	Route	The routes of elimination have not been determined in the pediatric population. In adults (Study 905-CL-008), 69% of the radioactivity of a single dose of 10 mg ¹⁴ C-labeled solifenacin was excreted in urine and 27.4% in feces; 14.7% of the dose was excreted unchanged in urine. Therefore, metabolism is the major route of elimination, primarily via CYP3A4 (Studies 905-ME-011, 905-ME-060).
	Terminal t _{1/2}	The mean t _{1/2} (CV%) for solifenacin in pediatric patients with NDO aged 2 years and older was 30.3 (56.7%) h (Studies 905-CL-047 and 905-CL-074). No metabolites have been measured in pediatric studies.
	CL/F or CL	The mean (CV%) CL/F for solifenacin in pediatric patients with NDO aged 2 years and older was 5.83 (53.1%) L/h (Studies 905-CL-047 and 905-CL-074).
Intrinsic Factors	Age	Dosing was based on body weight in the solifenacin pediatric clinical studies (and in the proposed dosing table) to meet the target exposure (AUC) in adults (421 to 1896 ng h/mL with a median of 889.1 ng h/mL for a 10 mg dose/PED10). Weight and age are correlated thus a lack of relationship between age and exposure was expected. This is shown in Figure 1 for pediatric patients with NDO aged 2 years and older. Figure 1 C_{max} and AUC_{inf} versus Age



Sex	<p>As shown in Figure 2, there is no impact of sex on the exposure of pediatric patients with NDO aged 2 years and older.</p> <p>Figure 2 C_{max} and AUC_{inf} versus Sex</p>	

		<p style="text-align: center;">AUCinf, ng.h/mL</p> <p style="text-align: center;">Sex (0=males, 1=females)</p>
Race		<p>The effect of race on pharmacokinetics was not evaluated in the pediatric population based on the lack of impact of race in adults.</p> <p>In adults, no major differences between the pharmacokinetics in Japanese and Caucasian subjects were observed. In the population pharmacokinetic analysis of the phase 3 patient Studies 905-CL-013 and 905-CL-014, race was included as a covariate for explaining the inter-subject variability in CL/F (Caucasian, African-American, Hispanic, Asian, and other). No effect of race was found. The analysis of the trough levels obtained in the patient Study 905-CL-018 also showed that race had no effect.</p>
Hepatic & Renal Impairment		<p>No hepatic impairment studies have been performed in the pediatric population. In adult subjects (Study 905-CL-026) with moderate hepatic impairment, the following results were obtained (geometric mean ratio for impaired/healthy, 90% CI):</p> <ul style="list-style-type: none"> • C_{max}: 0.989 (0.70 to 1.40) • AUC_{inf}: 1.596 (1.05 to 2.43) <p>Adult patients with moderate hepatic impairment should be treated with caution and receive no more than 5 mg once daily.</p> <p>No renal impairment studies have been performed in the pediatric population. In adult subjects (Study 905-CL-016) with mild, moderate, and severe renal impairment, the following results were obtained (geometric mean ratio for impaired/healthy, 90% CI):</p> <ul style="list-style-type: none"> • Mild renal impairment C_{max} 113% (83.5% to 152%), AUC_{inf} 144% (98.3% to 211%) • Moderate renal impairment C_{max} 96.8% (71.7% to 131%), AUC_{inf} 128% (87.4% to 188%)

		<ul style="list-style-type: none"> Severe renal impairment C_{max} 123% (91.3% to 166%), AUC_{inf} 215% (147% to 316%) <p>Adult patients with severe renal impairment should be treated with caution and receive no more than 5 mg once daily.</p>
Extrinsic Factors	Drug interactions	<p>No drug interaction studies have been performed in the pediatric population.</p> <p>In adults, 2 studies have been performed with solifenacin as substrate with the CYP3A4 inhibitor ketoconazole. In Study 905-CL-010, 200 mg ketoconazole once daily resulted in a 1.43 (1.29 to 1.57) fold increase in C_{max}, and a 2.02 (1.83 to 2.23) fold increase in AUC_{inf}.</p> <p>In Study 905-CL-036, 400 mg ketoconazole once daily resulted in a 1.51 (1.45 to 1.58) fold increase in C_{max}, and a 2.82 (2.60 to 3.07) fold increase in AUC_{inf}.</p>
	Food Effects	<p>No food effect studies have been performed in the pediatric population.</p> <p>There was no food effect when adults who took the tablet formulation ate a standardized high-fat breakfast (Study 905-CL-003). Geometric mean ratios (fed/fasted) (90% CI) were 1.033 (0.953 to 1.120) for C_{max}; 1.040 (0.976 to 1.109) for AUC_{inf}.</p> <p>No food effect was observed when the preliminary suspension formulation (suspension A) was used (Study 905-CL-066). Geometric mean ratios (fed/fasted) (90% CI) were 87.52% (80.98% to 94.59%) for C_{max}, 107.26% (99.36% to 115.79%) for AUC_{inf}.</p>
Expected High Clinical Exposure Scenario	<p>A description of the worst case scenario can only be based on the data set available from adults. Assuming that the effects observed in adults of CYP3A4 inhibition, moderate hepatic impairment and severe renal impairment are independent, a maximum increase of 2.82 (CYP3A4 inhibition) x 1.596 (moderate hepatic impairment) x 2.15 (severe renal impairment) = 9.68-fold in AUC would be expected. These combined factors would result in an expected < 2-fold increase in C_{max} (single dose).</p> <p>With a dose of 5 mg, assuming dose linearity at doses above 40 mg, the resulting exposure in the scenario described above would be equivalent to that of a 48 mg dose. The highest tolerated multiple dose in adults was 40 mg (Study 905-CL-022).</p>	
Preclinical Cardiac Safety	<p>QT interval corrected for heart rate (QTc) prolongation is an important identified risk for solifenacin in adults and was designated as an adverse event (AE) of special interest for the pediatric program. No specific nonclinical (juvenile animal) studies were conducted to evaluate the preclinical cardiac safety in the pediatric population. No cardiac safety measurements were included in the nonclinical juvenile animal studies in the mouse, as it is technically not feasible to measure ECG in an animal of that size (dosing started at postnatal day [PND]10 or PND21).</p> <p>A summary of the in vitro and in vivo results, conducted to support the cardiac safety in the clinical adult population, is provided below.</p> <p>Electrophysiology studies were conducted to evaluate the effects of solifenacin on the human inwards rectifier potassium current (IKr) and on cardiac action potential parameters. Direct effects on the IKr channel were assessed in whole-cell patch clamp studies using Chinese hamster ovary cells expressing hERG, which transcribes</p>	

	<p>the IKr channel (Investigator's brochure, Version 6, Oct 2015). In this model, solifenacin inhibited the potassium current with a 50% inhibition (IC₅₀) of 0.27 μM (97.9 ng/mL). The maximum unbound concentration (C_{max,u}) for solifenacin in human plasma at the maximum approved human dose (10 mg/day) is 1.26 ng/mL in adults. This value is 78-fold higher than the IC₅₀ value (97.9 ng/mL) for inhibition of IKr currents in the hERG patch clamp assay.</p> <p>In isolated dog Purkinje fibers and isolated guinea pig papillary muscles, solifenacin did not affect action potential parameters at concentrations up to 0.3 μM, a concentration 87-fold higher than the C_{max,u} (1.26 ng/mL) in humans. Overall, the in vitro electrophysiology data indicate that solifenacin is not likely to affect cardiac action potential parameters including IKr at therapeutic plasma concentrations. This is because of the significantly higher concentration required to produce effects on the cardiac action potential and IKr compared with the concentration of unbound drug in plasma at the maximum approved human dose.</p> <p>Intravenous administration of solifenacin succinate to pentobarbital-anesthetized dogs at high doses (≥ 1 mg/kg) increased the respiration rate, decreased blood pressure and left ventricular pressure, and prolonged the PR interval on the ECG (905-PH-023). Decreased carotid arterial blood flow was observed at ≥ 3 mg/kg. At 10 mg/kg, complete atrioventricular block led to death in 1 dog. No significant changes in QT, QTc or QRS intervals were detected in the dog at intravenous doses up to 3 mg/kg.</p> <p>Other safety pharmacology studies conducted at pharmacological doses indicated that solifenacin did not have serious adverse effects on cardiovascular systems.</p> <p>In the 13-week repeat-dose oral toxicity studies in dogs, solifenacin induced changes in the ECG pattern at the maximum tolerated dose (18 mg/kg) (905-TX-007). P-wave, PR and QTc intervals were prolonged at the highest dose of 25/18 mg/kg (25 mg/kg dose was reduced to 18 mg/kg at week 7 due to the bad condition of the animals). The safety factor based on the C_{max,u} is approximately 17. There were no cardiovascular effects in the 52-week repeated dosing study in the dog; all ECG parameters were within normal limits for dogs (905-TX-008). Solifenacin did not induce histopathological changes in the hearts of the dogs in any of the animal species tested.</p>
<p>Clinical Cardiac Safety</p>	<p>The global pediatric clinical development program comprises 2 pharmacokinetic phase 1 studies (905-CL-079 in patients with NDO and 905-CL-075 in patients with overactive bladder [OAB]); 2 phase 3 studies in patients with NDO (905-CL-047 and 905-CL-074); and 2 phase 3 studies in patients with OAB (905-CL-076 and 905-CL-077), considered supportive for the understanding of safety.</p> <p>The phase 1 studies were single dose studies. In the phase 3 studies, patients were treated with sequential doses of solifenacin oral suspension for 12 weeks (titration period) to determine each patient's optimal dose. Doses were up- or down-titrated within the range PED2.5 to PED10. In Studies 905-CL-047 and 905-CL-074, the dose titration period was followed by a fixed-dose assessment period of at least 40 weeks in which all patients were treated with their optimal dose. For each study the cardiac safety events have been summarized per ICH E14 guidance (Table 3). Further details on dose and narratives for individual events are provided in the respective clinical study reports.</p> <p>Further details of the evaluation of the QTc interval in pediatric studies and the comparison of those results with those in obtained in phase 3 adults studies (Prescribing Information for VESicare® (solifenacin succinate) tablets, NDA 021518) are summarized in a research report submitted with the current NDA.</p>

(Research Report: QTc).

Table 3 Summary of Clinical Cardiac Safety

Cardiac Safety Events	Study 905-CL-X Number of Patients (SAF)					
	047 n = 76	074 n = 19	075 n = 42	076 n = 95	077 n = 147	079 n = 14
QT prolongation†	4	0	0	7	14	0
Syncope‡	0	0	0	0	2	0
Seizures§	0	0	0	1¶	0	0
Ventricular Arrhythmias	0	0	0	0	0	0
Ventricular Tachycardia	0	0	0	0	0	0
Ventricular Fibrillation	0	0	0	0	0	0
Flutter	0	0	0	0	0	0
Torsades de Pointes	0	0	0	0	0	0
Sudden Deaths	0	0	0	0	0	0

† Dose (number of QT prolongation events): PED5 (7); PED7.5 (7); PED10 (7)

‡ Dose (number of syncope events): PED10 (2)

§ Dose (number of seizure events): PED10 (1)

¶ This patient was subsequently diagnosed with autosomal dominant frontal lobe epilepsy.

SAF: safety analysis set.

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/s/

LARS JOHANNESSEN
06/23/2017

CHRISTINE E GARNETT
06/23/2017

Ophthalmology Consult Review of NDA 209529

Consult Request Date: April 11, 2017
Submission Date: February 28, 2017
Review completed: June 23, 2017

Product name: Solifenacin oral suspension, 1 mg/mL

Applicant: Astellas Pharma Global Development, Inc.

Drug Class: Muscarinic receptor antagonist

Requested: Please assist in the review of this pending NDA. This is a new dosage form studied in response to a Written Request in the pediatric population, 2yrs+, under a 6-month Priority review. This application is submitted by Astellas Pharma in EDR: \\CDSESUB1\evsprod\NDA209529\209529.enx. The PDUFA Goal Date is August 28, 2017.

The sponsor assessed ocular accommodation in Study 905-CL-047 and is submitted in this NDA. Although there appeared to be no adverse effects on vision and accommodation, we request that you review this portion of the application and provide any comments and recommendations by July 17, 2017. We appreciate your help in the review of this application. Thank you.

Note: This is a Consult Review and comments in this review are limited to areas of Ophthalmologic Concern.

Visual Effects Background:

Blurred vision was a commonly reported adverse event with solifenacin succinate in adults; in phase 3 studies, there was a pooled incidence of blurred vision in 3.8% in patients treated with solifenacin succinate 5 mg once daily and 4.8% of patients treated with solifenacin succinate 10 mg once daily compared with 1.8% of placebo treated patients.

Ocular irritation study findings in rabbits showed the active ingredient solifenacin succinate powder to be an ocular irritant in that species and indicate that care should be exercised when handling solifenacin succinate. No ocular irritation was observed in rabbits with the oral suspension. Eyes were to be rinsed immediately following exposure. The effects of solifenacin succinate on ocular accommodation were to be objectively assessed at baseline and on treatment in the present study.

Clinical Trial: A Phase 3, Open-Label, Baseline-controlled, Multicenter, Sequential Dose Titration Study to Assess the Long-Term Efficacy and Safety, and the Pharmacokinetics of Solifenacin Succinate Suspension in Patients from 5 to Less than 18 years of Age with Neurogenic Detrusor Overactivity (NDO). ISN/Protocol: 905-CL-047.
EudraCT number: 2011-000330-11. Protocol version: Final, dated 30 September 2011.

The primary objective was to evaluate the efficacy, safety and PK of solifenacin succinate suspension after multiple dose administration.

This was a phase 3, open-label, baseline-controlled, sequential study with an individual dose titration period followed by a fixed dose assessment period. Subjects were to continue their previous Neurogenic Detrusor Overactivity (NDO) therapy until visit 2 (start of washout) when it was stopped for a 14-day washout period. Study drug administration (orally via syringe) began the day after visit 3 and was followed by 1-3 dose titration steps (visits 4, 5 and 6/week 3, week 6 and week 9) to achieve the optimal dose. A fixed dose assessment period started at visits 3, 4, 5 or 6 depending on when the optimal dose for that subject had been reached and ended at visit 10 (week 52).

Visit Schedule:

	Visit 1 [§]	Visit 2 [§]	Visit 3	Visit 4 ^e	Visit 5 ^e	Visit 6 ^f	Visit 7	Visit 8	Visit 9	Visit 10/EoS ^m
	Screening	Start of Washout	Baseline	Week 3	Week 6	Week 9	Week 12	Week 24	Week 36	Week 52
Assessment	Up to 21 days prior to visit 2	Day - 14	Day -1	Day 21 (+/- 3 days)	Day 42 (+/- 3 days)	Day 63 (+/- 3 days)	Day 84 (+/- 3 days)	Day 168 (+/- 3 days)	Day 252 (+/- 3 days)	Day 364 (+/- 3 days)
ICF	X									
Inclusion/Exclusion	X	X _g	X _g							
Height and Weight	X		X					X		X
Medical History	X									
Previous and Current NDO	X	X	X	X	X	X	X	X	X	X
Vital Signs ^a	X	X	X	X	X	X	X	X	X	X
Physical Examination	X							X		X
12-Lead ECG	X	X	X	X	X	X	X	X	X	X
Hematology	X		X					X		X
Biochemistry	X		X					X		X
α1-AGP							X			
Urinalysis ^b	X	X	X	X	X	X	X	X	X	
Pregnancy test	X _h	X _i	X _h	X _i	X _i	X _i	X _i	X _h	X _i	X _h
PK ^c							X			
Renal Ultrasound			X							X
Cognitive testing	X _j	X	X				X	X		X
Refraction/Ocular		X	X				X			
QOL		X	X					X		X
AEs		X	X	X	X	X	X	X	X	X
Dispense Study Drug			X	X	X	X	X	X	X	
Titration assessment				X _e	X _e	X _f				
Diary		X	X	X	X	X	X	X	X	X
Urodynamics			X			X		X		X

[§] Visits occur concurrently for subjects participating in study 905-CL-079. Corresponding individual assessments will occur once only and results will be used for both studies. Visit 1 will coincide with the screening of study 905-CL-079; visit 3 will coincide to day 7 of study 905-CL-079.

- a) Pulse and blood pressure will be measured in triplicate. Temperature will also be measured.
 - b) Urine culture only done if sediment reading of bacteria at least ++ and leukocytes at least +.
 - c) Four blood samples for pharmacokinetics will be collected at the following time periods: Within 3 hrs prior to dosing (trough level), 1-3 hrs post dose, 4-5 hrs post dose and 7-10 hrs post dose.
 - d) Refraction will be assessed at visit 2 after instillation of cyclopentolate drops; accommodation will be measured at visits 3 and 7.
- d) Refraction will be assessed at visit 2 after instillation of cyclopentolate drops; accommodation will be measured at visits 3 and 7.

Refraction was assessed at visit 2 after instillation of cyclopentolate drops; accommodation was be measured at visits 3 and 7.

The **key safety variables** which will be specifically monitored during the study included change from baseline to visit 10 (week 52) in ocular accommodation testing.

Ocular Accommodation Assessment

The effects of solifenacin on ocular accommodation were assessed objectively using an open-field autorefractor. Refractive error assessment was made at the start-of-washout visit (visit 2) after instillation of cyclopentolate. Accommodation was assessed at baseline (visit 3) and at week 12 (visit 7). Accommodation was measured following correction with an optical appliance (spectacles or lens) of the refractive error measured at visit 2 in order to reach functional emmetropy. The endpoints measured were the accommodative response profile over (0 to 4.5 D) and the accommodative error index (AEI). These assessments were made according to the Schedule of Assessments, specified in Appendix 9, by a qualified optical practitioner with experience in measurement of visual accommodation in the pediatric population.

Appendix 9: Schedule of Assessment for Measurement of Visual Accommodation

Objective accommodation was measured with an open-field autorefractor that is able to present both distant and near targets. Refraction was measured while focusing on a distant target (0 D accommodative demand) and accommodation was assessed in response to presentation of a variety of near targets (from 0 to 4.5 D).

For the testing, room illumination was dimmed to maintain large pupils (0.1 lux). Subjects viewed accommodative targets through the 12.5 cm x 22 cm open field beam splitter of the autorefractor. Subjects viewed monocularly while the contralateral eye was occluded with an eye patch. The instrument software was set to a sensitivity of 0.01 D and a 0.0 mm vertex distance for measured refractions.

Subject's baseline refractive state was measured after instillation of cyclopentolate and the subject viewed the smallest line of letters that he or she could clearly read on a distance logMAR letter chart (or a spot light if the subject's visual acuity is less than 6/18) through the instrument beam splitter. The eye with the best distance acuity was used for further testing and the other eye was occluded. An initial test measurement was taken to ensure that the refraction measurements are on axis as off-axis measurements could have affected accuracy. The subject was asked to observe the just perceptible, dim measurement ring light and to locate a Maltese cross. If necessary, the chart was moved up or down to allow the subject to fixate on a letter that was close to his or her best acuity: This first measurement was not recorded. After the first measurement, the subject fixated on the selected Maltese cross for 3 additional measurements. The mean of these measurements was recorded as the subject's baseline refractive state. The correction (spectacle or contact lens) to make the child functionally emmetropic was placed before the eye prior to stimulating accommodation.

To stimulate accommodation, the near target was moved closer to the subject in dioptric steps and the refraction measured at each step. The near target was mounted in front of the subject's line of sight on a near-point rod attached to a 5D Badal optometer, placed at distances corresponding to steps 0.5, 1.0, 2.0, 3.0, 4.0 and 4.5 D up to a minimum working distance of approximately 22 cm. An initial measurement was made, and the subject was again asked to find a Maltese cross that is close to the center of the measurement ring light. Subsequently, 3 refraction measurements were taken for each near target distance. Accommodation was calculated by subtracting the mean baseline with the refractive correction in place (calculated from the 3 measurements recorded for the far distance) from the 3 measurements at each near distance.

The endpoints measured were the accommodative response profile over 0 to 4.5 D and the AEI (accommodative error index).

Reviewer's Comment: *The procedure used in this study to evaluate accommodation is not a commonly used clinical measure. It is more common to evaluate accommodative amplitude in an individual. Accommodative amplitude is a measure of the maximum increase in diopter power that can be achieved at that time by the individual. Drug products which inhibit an individual's ability to accommodate will decrease the accommodative amplitude.*

The accommodative error index (AEI) was coined in a paper by Chauhan K and Charman WN in 1995 (Chauhan K, Charman WN. Single figure indices for the steady-state accommodative response. Ophthal Physiol Opt. 1995;15:217-221.) The AEI is based from an accommodation response-stimulus curve and is the mean of the magnitude of the response error divided by the correlation coefficient. As described in Dr. Chauhan's paper, steady-state accommodative responses can be characterized by a standard response-stimulus curve. The AEI is an attempt to represent this curve with a single number.



Chauhan1995.pdf

It is unclear why the applicant chose to measure the accommodation response-stimulus curve instead of the accommodative amplitude. Children, particularly those less than 12 years of age, typically have a very large accommodative amplitude. It is unclear whether a change in a child's ability to accommodate would be more evident from a change in the response-stimulus curve or from a change in the accommodative amplitude.

The accommodative response curves measured in this study do not appear to be informative. In many of the cases, it does not appear that the true refractive error was accurately obtained. The patterns of many of the curves, even at baseline where not as might have been expected.

The values used to generate the curves were based on triplicate measurements. The triplicate measurements were often very divergent, questioning the reliability of the measurement. The averaging of these divergent values was not appropriate.

In the applicant's analysis, a large number of accommodative response curves were ignored without acknowledging that they were ignored or documenting the reason for ignoring them.

Seventy-eight (78) subjects had accommodative response curves performed. All patients were supposed to have baseline, week 12 and week 52 measurements. Eighteen (18) had only baseline curves measures, sixty (60) had baseline and Week 12 curves measured but only eighteen (18) had baseline, Week 12 and Week 52 curves measured. None of the subjects with only baseline curves had an AEI value calculated. Sixteen (19) of the 60 with baseline and Week 12 curves did not have AEI values calculated including three (3) of the 18 with baseline, Week 12 and Week 52 measurements. Subjects without an AEI calculated were not included in any of the summary tables, graphs or analyses.

Summary:

1. The application does not contain reliable information concerning the drug product's effect on accommodation.
 - a. The choice of an accommodation response-stimulus curve instead of measuring the accommodative amplitude to measure a drug product's effect on accommodation is not supported. There is no evidence that this measure is capable of detecting a change in accommodation.
 - b. The choice to represent the accommodation response-stimulus curve with a calculated accommodative error index (AEI) is not supported. There is no evidence that this index will be reflective of a change in accommodative ability.
 - c. The variability of triplicate measurements used to construct the accommodation response-stimulus curve suggests that the collected values are not reliable measures of accommodation.
2. The analyses of accommodation failed to utilize all of the data collected on accommodation. Approximately one third of the accommodation data collected was not used in the analysis. There was no explanation for the exclusion of data. It is recommended that the applicant verify that there is not any other patient information collected during the study but not included in the analyses.
3. The applicant's claim that Study 905-CL-047 demonstrated improvement in "accommodative accuracy" is not supported, because the data is inconsistent. The claim that Solifenacin also did not have an effect on the slope of the MSE versus diopter stimulus is not supported because the data is inconsistent and there is no evidence to support the ability of the methodology used to detect a difference if a true difference was to be present.

Wiley A. Chambers, M.D.,
Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
06/23/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: June 5, 2017

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Application Type and Number: NDA 209529

Product Name and Strength: Vesicare LS (solifenacin succinate) oral suspension
1 mg/mL

Applicant/Sponsor Name: Astellas Pharma US, Inc.

Submission Date: May 31, 2017

OSE RCM #: 2017-564-1

DMEPA Primary Reviewer: Briana Rider, PharmD

DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised expiration date format for the carton labeling and container label for Vesicare LS (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we provided as part of a previous labeling review memorandum.^a

2 CONCLUSION

The revised expiration date format for the carton labeling and container labels for Vesicare LS is acceptable from a medication error perspective. We have no further recommendations at this time.

^a Rider, B. Label and Labeling Review Memorandum for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 22. RCM No.: 2017-564-1.

APPENDIX A. ASTELLAS PHARMA US, INC. MAY 31, 2017 RESPONSE TO INFORMATION REQUEST

<\\cdsesub1\evsprod\nda209529\0019\m1\us\1-14-1-1-draft-carton-container-exp.pdf>

In response, Astellas confirms that the expiration date will be expressed in a standard format, using three-letter text for the month (e.g., JAN) and four-digit numerals for the year (e.g., 2015).

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/s/

BRIANA B RIDER
06/05/2017

LOLITA G WHITE
06/05/2017

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 22, 2017
Requesting Office or Division:	Division of Bone, Reproductive, and Urologic Products (DBRUP)
Application Type and Number:	NDA 209529
Product Name and Strength:	Vesicare LS (solifenacin succinate) oral suspension 1 mg/mL
Product Type:	Single-Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Astellas Pharma US, Inc.
Submission Date:	February 28, 2017
OSE RCM #:	2017-564
DMEPA Primary Reviewer:	Briana Rider, PharmD
DMEPA Team Leader:	Lolita White, PharmD

1 REASON FOR REVIEW

This review evaluates the proposed labels and labeling for Vesicare LS (solifenacin succinate) oral suspension for areas of vulnerability that could lead to medication errors. The Division of Bone, Reproductive and Urologic (DBRUP) requested this review as part of their evaluation of NDA 022063 for Vesicare LS.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Prescribing Information (PI) labeling, container label and carton labeling for Vesicare LS (solifenacin succinate) oral suspension in support of NDA 209529 for risk of medication error. We identified the following areas of needed improvement that may contribute to medication errors:

Prescribing Information (PI):

1. We note that Table 1 in Section 2 – *Dosage and Administration* of the Full Prescribing Information (FPI) contains footnotes which present seemingly unnecessary information and may lead to confusion.

Carton Labeling and Container Label:

1. We note that the carton labeling and container label do not indicate where the lot and expiration date will be located. The lot number statement and expiration date are required on the immediate container and carton labeling per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively.

2. We note that the side panel states “Discard remaining VESicare LS™ 28 days after first opening.” However, the label can be optimized to help minimize the potential for the product to be used beyond 28 days after first opening.
3. As presented, the statement of strength (i.e., 1 mg/mL) is not consistent with other approved oral suspensions, which may contribute to medication errors due to miscalculations.
4. The net quantity statement appears in close proximity to the product strength on the container label and may contribute to confusion of product strength.
5. We note that the side panel states “shake the bottle [REDACTED] before use.” However, this critical information lacks prominence on the container label and may be easily overlooked.

4 CONCLUSION & RECOMMENDATIONS

We identified areas in the labels and labeling that are vulnerable to medication error and we recommend revision to minimize the risk for confusion, increase prominence of critical information and to ensure safe use and handling of the proposed product. We provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

4.1 RECOMMENDATIONS FOR THE DIVISION

2. Section 2 – *Dosage and Administration*

1.



4.2 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

We recommend the following be implemented prior to approval of this NDA:

A. Carton Labeling

1. We note that the carton labeling and container label do not indicate where the lot and expiration date will be located. The lot number statement and expiration

date are required on the immediate container and carton labeling per 21 CFR 201.10(i)(1) and 21 CFR 201.17, respectively. Ensure that the lot number and expiration date are present on the carton labeling and container label in accordance with 21 CFR 201.10(i)(1) and 21 CFR 201.17. Please provide the intended expiration date format for evaluation.

2. We note that the side panel states “Discard remaining VESicare LS™ 28 days after first opening.” We recommend adding the statement “Discard after ___/___/___” to allow space for pharmacy or other healthcare provider to write the post-opening expiration date on the label to help minimize the potential for the product to be used beyond 28 days after first opening. Additionally, the “___/___/___” statement will alert the healthcare provider to write a complete date (month, day, and year) on the container label.
3. As presented, the statement of strength (i.e., 1 mg/mL) is not consistent with other approved oral suspensions. To maintain consistency with other approved oral suspensions and to minimize the potential for medication errors due to miscalculations, the statement of strength should be expressed as the specified amount per 5 mL (i.e., 5 mg/5 mL). Please note that there should be space between the number and the metric measurement. The concentration per milliliter of the suspension should appear in close proximity to and with lesser prominence than the concentration per 5 mL on the principal display panel (PDP). The concentration statements should be presented as follows:

5 mg/ 5 mL
(1 mg/mL)

B. Container Label

1. The net quantity statement appears in close proximity to the product strength and may contribute to confusion of product strength. From post-marketing experience, the risk of numerical confusion between the strength and net quantity increases when the net quantity statement is located in close proximity to the strength statement. Relocate the net quantity statement away from the product strength.
2. We note that the side panel states “shake the bottle (b) (4) before use.” However, this information may be easily overlooked. To ensure that the product is prepared appropriately, add the following statement to in bold text to the principal display panel, “Shake well before use.”
3. See A.1, A.2, and A.3

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vesicare LS that Astellas Pharma US, Inc. submitted on February 28, 2017, and Vesicare.

Table 2. Relevant Product Information for Vesicare LS and Vesicare																	
Product Name	Vesicare LS	Vesicare															
Initial Approval Date	N/A	November 19, 2004															
Active Ingredient	solifenacin succinate	solifenacin succinate															
Indication	Muscarinic antagonist for the treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older.	Muscarinic antagonist indicated for the treatment of overactive bladder with symptoms of urinary incontinence, urgency, and urinary frequency.															
Route of Administration	Oral	Oral															
Dosage Form	Suspension	Tablet															
Strength	1 mg/mL	5 mg, 10 mg															
Dose and Frequency	Recommended dose is determined based on patient weight. <table border="1"> <caption>Table 1 Dose According to Patient Body Weight</caption> <thead> <tr> <th>Weight range (kg)</th> <th>Starting dose (mL)§¹</th> <th>Maximum dose (mL)§²</th> </tr> </thead> <tbody> <tr> <td>9 to 15</td> <td>2</td> <td>4</td> </tr> <tr> <td>> 15 to 30</td> <td>3</td> <td>5</td> </tr> <tr> <td>> 30 to 45</td> <td>3</td> <td>6</td> </tr> <tr> <td>> 45</td> <td>4</td> <td>8</td> </tr> </tbody> </table>	Weight range (kg)	Starting dose (mL)§ ¹	Maximum dose (mL)§ ²	9 to 15	2	4	> 15 to 30	3	5	> 30 to 45	3	6	> 45	4	8	Recommended dose is 5 mg once daily. If the 5 mg dose is well tolerated, the dose may be increased to 10 mg once daily.
Weight range (kg)	Starting dose (mL)§ ¹	Maximum dose (mL)§ ²															
9 to 15	2	4															
> 15 to 30	3	5															
> 30 to 45	3	6															
> 45	4	8															
How Supplied	150 mL bottles	5 mg, 10 mg <ul style="list-style-type: none"> • Bottle of 30 • Bottle of 90 Unit Dose Pack of 100 															
Storage	Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F - 86°F).	Store at 25°C (77°F) with excursions permitted from 15°C to 30°C (59°F - 86°F).															
Container Closure	150 mL amber polyethylene terephthalate (PET) bottles capped with child-resistant high-density polyethylene-polypropylene caps with a pulp and vinylseal liner.	High-density polyethylene (HDPE) bottles and blister packages.															

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 21, 2017, we searched the L:drive and AIMS using the terms, Vesicare LS to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous relevant reviews.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^a along with postmarket medication error data, we reviewed the following Vesicare LS labels and labeling submitted by Astellas Pharma US, Inc. on February 28, 2017.

- Container label
- Carton labeling
- Prescribing Information – no image

G.2 Label and Labeling Images

2 Pages Draft Labeling have been Withheld in Full as
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^a Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

BRIANA B RIDER
05/22/2017

LOLITA G WHITE
05/23/2017

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: May 22, 2017

Requesting Office or Division: Division of Bone, Reproductive, and Urologic Products (DBRUP)

Application Type and Number: NDA 209529

Product Name and Strength: Vesicare LS (solifenacin succinate) oral suspension
1 mg/mL

Applicant/Sponsor Name: Astellas Pharma US, Inc.

Submission Date: May 17, 2017

OSE RCM #: 2017-564-1

DMEPA Primary Reviewer: Briana Rider, PharmD

DMEPA Team Leader: Lolita White, PharmD

1 PURPOSE OF MEMO

The Division of Bone, Reproductive, and Urologic Products (DBRUP) requested that we review the revised carton labeling and container label for Vesicare LS (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we provided as part of a previous labeling review.^a

2 CONCLUSION

The revised Vesicare LS carton labeling and container label are unacceptable from a medication error perspective. In response to our May 3, 2017 recommendations^b, the Sponsor provided their intended expiration date format. The Sponsor indicated that the month of the expiry will be formatted either in a two character numeric format (e.g., 01) or in a three character alphabetic format (e.g., JAN). Based on postmarketing experience, we note that denoting the

^a Rider, B. Label and Labeling Review for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAY 22. RCM No.: 2017-564.

^b Crisostomo, N. DMEPA Information Request – Carton & Container Labeling for Vesicare LS (NDA 209529). Silver Spring (MD): FDA, CDER, OND, DBRUP (US); 2017 MAY 03.

month in a numerical format (e.g., 12) could lead to confusion, misinterpretation, and delays in treatment as the number could represent the day, month, or year.

3 RECOMMENDATIONS FOR ASTELLAS PHARMA US, INC.

We recommend the following be implemented prior to approval of this NDA 209529:

- A. We note that your May 17, 2017 response to our Information Request indicates that that the month of the expiry will be formatted either in a two character numeric format (e.g., 01) or in a three character alphabetic format (e.g., JAN). Based on postmarketing experience, we note that denoting the month in a numerical format (e.g., 12) could lead to confusion, misinterpretation, and delays in treatment as the number could represent the day, month, or year. (See *Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*) We recommend the expiration date be expressed in a standard format, using three-letter text for the month (e.g., JAN), two-digit numerals for the day (if included), and four-digit numerals for the year, as follows: MMMYYYY (e.g., JAN2015) or MMMDDYYYY (e.g., JAN012015). This will improve clarity for the intended users as they check the expiration date.

APPENDIX A. LABEL AND LABELING SUBMITTED ON MAY 17, 2017

Container labels

(b) (4)



Carton labeling

(b) (4)



APPENDIX B. ASTELLAS PHARMA US, INC. MAY 17, 2017 RESPONSE TO INFORMATION REQUEST

<\\cdsesub1\evsprod\nda209529\0014\m1\us\1-14-1-1-draft-carton-container-exp.pdf>

In response, the expiration date will be printed on-line at the time of manufacture of each lot of drug product. The month of the expiry will be formatted either in a two character numeric format (e.g., 01) or in a three character alphabetic format (e.g., JAN). In all cases, the year of expiry will be formatted in four character numeric format (e.g., 2017). The final format for the expiration date to be used on both the container and carton will be established at the time of labeling process validation.

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/s/

BRIANA B RIDER
05/22/2017

LOLITA G WHITE
05/23/2017