OFFICE OF CLINICAL PHARMACOLOGY REVIEW MEMORANDUM

NDA Number	209529
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Submission Type	Resubmission
Submission Date	11/27/2019
PDUFA Date	05/27/2020
Review type	Clinical Pharmacology Review Memorandum
Brand Name	VESIcare LS
Generic Name	Solifenacin succinate
Dosage Form and Strength	Solifenacin succinate oral suspension 1 mg/mL
Route of Administration	Oral
Proposed Indication	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Applicant	Astellas Pharma US, Inc.
Associated IND	IND 058135
Office of Clinical Pharmacology Review Team	Division of Cardiometabolic and Endocrine Pharmacology Jihong Shon, M.D., Ph.D. Lu Yanhui, Ph.D.

1. EXECUTIVE SUMMARY

Solifenacin is a competitive muscarinic antagonist that modulates smooth muscle contractility in the urinary bladder. The Applicant owns an oral tablet formulation of solifenacin succinate (VESIcare®, NDA021518) that is approved for the treatment of overactive bladder (OAB) in adults. The Applicant proposed a pediatric study plan for the use of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients (March 23, 2012) and a written response was provided by the Agency (July 27, 2012) to submit pharmacokinetic (PK), safety, and efficacy information of solifenacin succinate in pediatric patients with NDO.

Neurogenic detrusor overactivity (NDO) is a urodynamic dysfunction characterized by involuntary contraction of the bladder detrusor muscle during the filling phase, which results in elevated detrusor pressure and reduced bladder capacity and consequently cause several complications such as urinary tract infections, bladder stones, fibrosis, trabeculation, and autonomic dysreflexia. The Applicant has developed an oral suspension of solifenacin succinate for the treatment of NDO in pediatric patients and originally submitted a New Drug Application (NDA) for the pediatric patients aged 2 years and older on February 28, 2017. The Applicant proposed a weight-range adjusted dosing table for pediatric patients with NDO to achieve plasma exposures equivalent to those in adults with OAB at the approved doses (5 mg and 10 mg) of VESIcare® (Table 1).

The Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology III [the division where the clinical pharmacology review team resided prior to formation of Division of Cardiometabolic and Endocrine Pharmacology (DCEP)] and Division of Pharmacometrics completed reviewing the submitted clinical pharmacology information and concluded that the application was acceptable and recommended

approval from the clinical pharmacology standpoint (OFFICE OF CLINICAL PHARMACOLOGY REVIEW for NDA 209529 dated August 8, 2017 in DARRTS). In the previous review, the OCP recommended that the dosing table should be modified by adding a starting dose of 5 mg and a maximal dose of 10 mg for patients with body weight > 60 kg (Table 2.; Refer to Section 3. SUMMARY OF THE PRIOR OCP'S REVIEW). The Applicant accepted the recommendation and updated the prescribing information.

In the review process for the original submission, the Chemistry, Manufacturing, and Controls (CMC) review team identified three major deficiencies in the drug product specification and the manufacturing facility for the final product. Consequently, the Agency determined that the original NDA could not be approved (Complete Response Letter dated August 28, 2017).

The Applicant had resolved the CMC issues for the complete response and received feedback from the Agency on those issues via a Pre-NDA meeting and resubmitted the NDA on November 27, 2019. This resubmission includes a revised product label and updated safety information. The current resubmission includes no new clinical pharmacology data and thus the clinical pharmacology review team focused on the labeling recommendation in this review cycle.

The NDA is still approvable from the clinical pharmacology standpoint provided that the CMC review team determines that CMC deficiencies have been resolved and an agreement on the language in the package insert is reached between the Applicant and the Agency.

2. SUMMARY OF LABELING RECOMMENDATON

The Office of Clinical Pharmacology provides the following recommendations on the labeling information:

- Dosing administration information in HIGHLIGHTS and Section 2 DOSAGE AND ADMINISTRATION and 17 PATIENT COUNSELING INFORMATION should include instruction regarding water or milk intake after taking the suspension.
- Each subsection under Section 7 DRUG INTERACTIONS should be revised to include clinically relevant mechanisms, findings and management/mitigation strategies in relation to drug interaction. A subsection can be deleted or relocated unless it provides concrete supporting data and actionable mitigation strategies. Accordingly, DRUG INTERACTIONS in HIGHLIGHTS should be modified to be consistent with the revised contents in Section 7.
- Information described for patients with renal impairment (8.6) or hepatic impairment (8.7) in Section 8 USE IN SPECIFIC POPULATIONS should be revised to include key findings associated with organ impairments and dosage recommendation. (b) (4) (b) (4).

3. SUMMARY OF THE PRIOR OCP'S REVIEW

The Applicant proposed daily doses (i.e. starting and maximum doses) of solifenacin succinate oral suspension based on body weight for pediatric patients aged 2 years and older with NDO. In support of this NDA, the Applicant conducted 3 clinical studies (one phase 1 study and two phase 3 studies) in pediatric patients with NDO for evaluation of PK, efficacy, and safety of the proposed drug. In addition, the

Applicant performed two PK studies in healthy adults to compare the relative bioavailability between suspension and tablet formulations.

The Applicant developed population PK and physiologically based pharmacokinetics (PBPK) models by leveraging clinical information collected in the studies conducted in pediatric patients with NDO or OAB. The developed final model was verified by comparing the PBPK-predicted and observed or estimated exposure in pediatric patients with NDO. The Applicant proposed weight-range adjusted doses for pediatric patients with NDO to achieve plasma exposure equivalent to those following administration of the currently approved doses, 5 mg (staring dose) and 10 mg (maximum dose), of the oral tablet formulation of solifenacin succinate (VESIcare®) in adults with OAB. The Applicant proposed the following dosing table was established based on solifenacin exposure values (area under the plasma concentration-time curve, AUC) estimated by the PBPK model for pediatric patients with NDO (Table 1).

Table 1. Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

	Recommended doses by weight range	
Weight range (kg)	Starting dose (mL)	Maximum dose (mL)
9 to 15	2	4
> 15 to 30	3	5
> 30 to 45	3	6
> 45	4	8

Solifenacin succinate oral suspension is provided as a 1 mg/mL oral suspension

The OCP review team concluded that the established PBPK model adequately described the exposure of solifenacin in pediatric population aged 2 year and older. However, considering that the pediatric dosing is intended to achieve plasma exposures equivalent to those in adults at the approved doses of 5 mg and 10 mg and some pediatric patients have body weight similar to adults, the OCP review team recommended that the dosing table include an additional dosage of 5 mg starting dose and 10 mg maximal dose for patients with body weight > 60 kg (Table 2). This recommendation was accepted by the Applicant during the previous review cycle and was reflected in the prescribing information submitted in this review cycle.

Table 2. Recommended doses by weight range for pediatric patients with NDO aged 2 years to less than 18 years

	Recommended doses by weight range	
Weight range (kg)	Starting dose (mL)	Maximum dose (mL)
9 to 15	2	4
> 15 to 30	3	5
> 30 to 45	3	6
> 45 to 60	4	8
> 60	5	10

Solifenacin succinate oral suspension is provided as a 1 mg/mL oral suspension

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/s/

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05/01/2020 03:59:57 PM

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