Cross-Discipline Team Leader (CDTL) Brief Memo Update

Date	May 26, 2020
From	Mark S. Hirsch, M.D.
Subject	Cross-Discipline Team Leader Brief Update
NDA/BLA# /Supplement#	209529
Applicant	Eli Lilly & Company
Date of Submission	November 27, 2019
PDUFA Goal Date	May 27, 2020
Proprietary Name / Established (USAN) names	VESIcare LS solifenacin succinate
Dosage forms / Strengths	2 mg, 3 mg, 4 mg, 5 mg, 6 mg, 8 mg, 10 mg oral suspension
Indication(s)	Treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Recommended:	***Approval***

The purpose of this CDTL Brief Memo Update is:

1) To confirm my agreement with the review team's recommendation for Approval of this application, which is a resubmission in response to the August 28, 2017, Complete Response Letter describing Chemistry, Manufacturing, and Controls (CMC) deficiencies,

2) To provide brief summaries of the recently completed discipline-specific and consultative FDA reviews, and

3) To confirm my agreement with the final labeling for this NDA.

1. Confirm CDTL Recommendation for Approval

CDTL Note: For full CDTL conclusions on benefits and risks of VESIcare LS for the indication, the reader is referred to the final Clinical Review dated May 18, 2020, under "Benefit-Risk Assessment" (Section 1.3) and to my August 28, 2017, CDTL review of the February 28, 2017, original NDA. Herein, I briefly summarize conclusions on the product's benefits and risks, and I confirm my agreement with the team's regulatory decision.

In brief, VESIcare LS (solifenacin) oral suspension will be indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients. NDO is defined as detrusor overactivity that develops as a result of a neurologic lesion. An oral suspension will facilitate dosing in young children and will allow for accurate dose titration. The goal of treatment is to preserve renal function by increasing bladder capacity and bladder compliance, and to minimize the negative consequences of NDO by improving voiding indices such as reducing the number of incontinence episodes.

The efficacy of VESIcare LS oral suspension was demonstrated in two adequate and well-controlled studies (Studies 905-CL-074 and 905-CL-047) through clinically meaningful increases in maximum cystometric capacity (MCC) and was supported by 1) improvements in other urodynamic parameters, such as bladder compliance and number of overactive detrusor contractions, and 2) improvements in voiding diary measurements, such as maximum catheterized urine volume and incontinence episode frequency. The magnitude of the treatment effect was similar across age groups.

The safety of VESicare LS oral suspension was assessed in 95 pediatric patients with NDO in the two pivotal Phase 3 studies and their long-term extensions. The safety profile of VESicare LS in pediatric patients with NDO was shown to be consistent with the known safety profile of VESIcare tablets for the treatment of overactive bladder (OAB) in adults. As expected, the most commonly reported adverse reactions to VESIcare LS in pediatric NDO patients were constipation, dry mouth and urinary tract infection (UTI). Aside from one report of somnolence, there were no CNS adverse effects observed in the pediatric clinical studies of VESIcare LS.

Based on the benefits and risks reported in the pediatric NDO clinical studies, I confirm my agreement with the review team that the prior CMC deficiencies have been resolved and this application for VESIcare LS for the treatment of NDO in patients 2 years of age and older may now be Approved.

2. Brief Summaries of the Recently Completed Discipline-Specific and Consultative FDA Reviews

CDTL Note: For details on the discipline-specific and consultative reviews completed for this NDA through May 18,2020, the reader is referred to the final Clinical Review dated May 18, 2020, under "Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety" and to my August 28, 2017, CDTL review of the February 28, 2017, original NDA. The reader is also referred to the final discipline-specific reviews themselves. Herein, I briefly summarize the recently completed discipline-specific and consultative reviews.

2.1 Chemistry

In their final Integrated Quality Assessment #2 (IQA), conveyed by email on May 25, 2020, the Chemistry (OPQ) team of Mark Seggel and Moo Jong Rhee had the following Quality Assessment Team Recommendation and Conclusion:

"Astellas Pharma's resubmission of 505(b)(1) New Drug Application 209529, for VESIcare LS (solifenacin succinate) oral suspension, 1 mg/mL, is recommended for APPROVAL from the OPQ perspective.

Sufficient chemistry, manufacturing and controls information and supporting data have been provided in accordance with 21 CFR 314.50 to ensure the identity, strength, quality,

purity, and bioavailability of the drug product. The previously identified product quality microbiology issues have been adequately resolved. To ensure that the requisite product viscosity is maintained throughout the shelf life and in-use period, the acceptance tests for Carbomer Homopolymer, NF (Type B) have been revised (b) (4) (b) (4)

The drug product labels (container / carton) as submitted on May 15, 2020, and the labeling (prescribing information, PPI) as submitted on May 19, 2020, is accurate, complete and complies with the requirements under 21 CFR 201.

The drug substance manufacturing, packaging and testing facility has acceptable CGMP status. The (b) (4) *drug product manufacturing site, which was cited as deficient in the August 28, 2017 Complete Response Letter, was recently found acceptable via the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. The associated product packaging and testing facilities also have acceptable drug CGMP status. An overall manufacturing inspection recommendation of APPROVE was issued on May 8, 2020.*

An expiration dating period of 24 months for product packaged in amber PET bottles and stored at 20°C to 25°C is granted.

The claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(b) is acceptable."

2.1.1 Chemistry: Biopharmaceutics

In their final review dated April 1, 2020, the ***Biopharmaceutics*** review team of Assadollah Noory and Vidula Kolhatkar had the following Conclusion:

"*Approval of this NDA is recommended by the Division of Biopharmaceutics*."

The original NDA received a Complete Response due to three Chemistry deficiencies. The first Chemistry deficiency was related to an inspection finding that the product viscosity for two batches intended for marketing (commercial batches) was below the specification limit. (b) (4) was thought to be a result of changes in the manufacturing process of the excipient carbomer homopolymer Type B by its supplier. (b) (4) (b) (4) (b) (4) the Chemistry review team noted that the original application could not be approved without the establishment of adequate controls for carbomer homopolymer type B and demonstration that the Sponsor could consistently manufacture drug product of the requisite quality.

In their review of this resubmission, the Biopharmaceutics review team noted that the Sponsor addressed this deficiency (b) (4) (b) (4) in the to-be-marketed product. To demonstrate comparability of the commercial and clinical trial formulations, the Sponsor provided FDA-requested in vitro dissolution data from multi-point profiles using multiple, physiologic pH media that showed similar release profiles from the two formulations.

2.1.2 Chemistry: Manufacturing

In a May 9, 2020, email, Mark Seggel stated:

> "***OPMA*** *and* ***ORA*** *have completed their 'paper' inspection of the* (b) (4) *drug product manufacturing site conducted under Sec. 704 (a)(4) (FDASIA Sec. 706). After several rounds of requests for documentation and review, OPMA and ORA are now recommending APPROVAL for this site*".

The May 25, 2020, OPQ IQA concluded:

- "*As described in the attached Integrated Manufacturing Assessment (Chapter V), a "paper' inspection (of the* (b) (4) *site) was conducted in accordance with the Sec. 704 (a)(4) (FDASIA Sec. 706) Records Request process. Documents were requested and reviewed by ORA and OPMA. After three rounds of this inspection process, ORA and OPMA now recommend approval of the* (b) (4) *site".*

- *An overall manufacturing inspection recommendation of APPROVE was issued on May 8, 2020*".

The May 25, 2020, OPQ IQA also stated that the Applicant had successfully demonstrated that (b) (4) (b) (4) finished product that meets the previously established viscosity requirements. In this regard, the IQA concluded:

- "*The Applicant has demonstrated that the drug product with the requisite quality can be manufactured consistently*".

2.1.3 Chemistry: Product Quality Microbiology

At the milestone review team meetings for this resubmission, the ***Product Quality Microbiology*** review team of Andrew Brown and Nandini Bhattacharya stated that the prior deficiency related to inadequate manufacturing controls to ensure the absence of (b) (4) (b) (4) in the drug product had been successfully resolved.

Concerning the (b) (4) NDA deficiency, the May 25, 2020, OPQ IQA concluded:

> "*Although the drug product contains a* (b) (4) (b) (4) *because this is an aqueous formulation it is susceptible to contamination* (b) (4) (b) (4). *As documented in the November 27, 2019 NDA resubmission and the January 12, 2020 resubmission amendment, controls for ensuring that the absence of* (b) (4) *have been established. The Applicant has added a test and suitably validated analytical procedure for confirming the absence of the* (b) (4) *in the finished product to the regulatory specification. The Microbiology deficiencies identified in the Complete Response letter have been adequately resolved*".

2.2 Division of Biometrics III (DB3)

In their final ***Statistical*** review dated May 19, 2020, Jia Guo and Mahboob Sobhan had the following Conclusion:

> "*…This submission did not contain new efficacy data. For efficacy evaluation from statistical perspective, please refer to the Statistical review dated 18 August 2017 for the original submission, which concluded that both studies demonstrated that there is clinical benefit of solifenacin succinate in treatment of neurogenic detrusor overactivity (NDO) in pediatric patients".*

2.3 Clinical

In our final ***Clinical*** review dated May 18, 2020, Elena Boley and I had the following Conclusion:

> "*At this time, the Clinical review team recommends that this NDA should be APPROVED".*

In regard to efficacy, safety and benefit-risk analysis, the Clinical team concluded:

- "*From the Clinical perspective, the evidence presented in the original submission for this NDA is adequate to support the effectiveness of this product in the treatment of pediatric patients with NDO. No new clinical data to support efficacy was provided in this resubmission."*

- "*The safety profile of solifenacin oral suspension is consistent with the known risks of solifenacin tablets for the treatment of OAB in adults and of anticholinergics in general*".

- "*Solifenacin oral suspension provides an alternative treatment to the single approved option, is efficacious, and has a similar side effect profile. Additionally, solifenacin oral suspension offers a more convenient once daily dosing regimen and data to support safety and efficacy for pediatric patients as young as 2 years old*".

2.4 Division of Medical Policy Program (DMPP)

In their final ***Patient Labeling*** review dated May 8, 2020, Kelly Jackson, Elvy Varghese and LaShawn Griffiths had the following Conclusion:

> "*…The PPI is acceptable with our recommended changes."*

All of the PPI changes recommended by DMPP were successfully instituted.

2.5 Office of Prescription Drug Promotion (OPDP)

In their final ***OPDP*** review dated May 4, 2020, Elvy Varghese and Matthew Falter stated:

> *"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."

All of OPDP's labeling comments were successfully addressed, either through internal discussion or by instituting labeling changes.

2.6 Office of Clinical Pharmacology (OCP)

In their final ***Clinical Pharmacology*** review dated May 1, 2020, Jihong Shon and Yanhui Lu of had the following Conclusions:

"(For the original application)….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 the Division of Pharmacometrics…concluded that the application was acceptable and recommended approval from the clinical pharmacology standpoint (refer to) the original Clinical Pharmacology review for NDA 209529 dated August 8, 2017)…. 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".

The CMC review team determined that the CMC deficiencies have been resolved and agreement has been reached between the Sponsor and the Agency on all labeling.

2.7 Pharmacology/Toxicology

In their final ***Pharmacology/Toxicology*** review dated April 27, 2020, Laurie McLeod-Flynn and Kim Hatfield had the following Conclusion:

"*No additional nonclinical studies were submitted with the 27 November 2019 resubmission. Reference is made to the Pharmacology/Toxicology review submitted to DARRTS for NDA 209529 on 28 July 2017 by Laurie McLeod-Flynn, which recommended approval of this product from a nonclinical perspective…. At this time, there is no impediment to Approval of this drug from a Pharmacology/Toxicology perspective".*

2.8 Division of Medication Errors Prevention and Analysis (DMEPA

In their final ***DMEPA*** labeling reviews dated April 9, 2020, March 23, 2020 and March 2, 2020, Justine Kalonia and Briana Rider had the following Conclusions:

In regard to carton and container labeling

"*The Applicant submitted revised carton labeling received on April 6, 2020 for VESIcare LS…The (Applicant's) revisions are in response to recommendations that we made during a previous labeling review… The Applicant implemented all of our recommendations and we have no additional recommendations at this time*".

In regard to the Prescribing Information labeling

"*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".

All of DMEPA's recommendations for changes to the PI and container and carton labeling were successfully instituted.

In their final ***DMEPA*** tradename review dated February 21, 2020, Denise Baugh and Briana Rider had the following Conclusion:

"We have completed our review of the proposed proprietary name, Vesicare LS, and have concluded that this name is acceptable".

3. Confirm CDTL Agreement with Final Labeling

3.1 VESIcare LS Labeling

Labeling discussions were held with the entire FDA review team on April 23, 2020, April 28,2020 and April 30, 2020.

The Division's edits to the PI were conveyed to the Sponsor on May 1, 2020. The Sponsor accepted all of the Division edits and returned the PI with minor revisions on May 8, 2020. Several additional minor Division edits to the PI were conveyed to the Sponsor on May 12, 2020 and May 18, 2020. A final, agreed-upon PI was received from Sponsor on May 19, 2020.

For the PPI, the Division's edits were conveyed to the Sponsor on May 12, 2020. The Sponsor accepted all of the Division edits and returned the PPI with minor revisions on May 15, 2020. Several additional minor Division edits to the PPI were conveyed to the Sponsor on May 18, 2020. A final, agreed-upon PPI was received on May 19, 2020.

I confirm that I agree with the final agreed-upon VESIcare LS PI and PPI received from Sponsor on May 19, 2020.

3.2 VESicare Tablets Labeling

In parallel with labelling for VESicare LS oral suspension under NDA 209529, the Sponsor also submitted prior approval supplement (PAS) 017 to NDA 021518 for VESIcare Tablets to update the Pediatric Use section of that label. In addition to changes to the Pediatric Use section, SLR017 included:

- Updated content in Section 8 related to Pregnancy and Lactation to comply with the Pregnancy and Lactation Labeling Rule (PLLR).
- Additions to Section 6.2 Post-Marketing Experience, of the following adverse event terms: "dizziness", "urinary retention", and "vomiting".
- Minor changes in other sections for document maintenance and internal consistency.

To support the addition of the three new postmarketing event terms, the Sponsor provided a link to a post marketing safety report index showing, through December 2016, a total of 799 cumulative reports of urinary retention, 136 cumulative reports of vomiting, and 921 cumulative reports of dizziness.

Labeling discussions for SLR017 were held with the entire review team on May 4, 2020 and May 6, 2020. The FDA-edited labeling for SLR017 was conveyed to the Sponsor on May 7, 2020. The Sponsor accepted all of the Division edits and returned the label with minor revisions on May 13, 2020. Several minor edits were returned to Sponsor on May 18, 2019 and the final agreed-upon PI and PPI for VESIcare Tablets was received on May 19, 2020.

I confirm that I agree with the final agreed-upon VESIcare Tablets PI and PPI received from Sponsor on May 19, 2020.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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