

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212516Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABELS
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:	July 16, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 212516
Product Name and Strength:	Drizalma Sprinkle (duloxetine) delayed-release capsules 20 mg, 30 mg, 40 mg, and 60 mg
Applicant/Sponsor Name:	Sun Pharma Global FZE
FDA Received Date:	July 16, 2019
OSE RCM #:	2018-2028-2
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, received on July 16, 2019, for Drizalma Sprinkle. The Division of Psychiatry Products (DPP) requested that we review the revised container labels for Drizalma Sprinkle (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions were made by the Applicant to align the established name presentation on the container labels with the presentation that is in the Prescribing Information.

2 CONCLUSION

We reviewed the revised container labels and find them acceptable from a medication error perspective. We have no additional recommendations at this time.

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/s/

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07/16/2019 04:15:28 PM

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

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

Memorandum

Date: June 20, 2019

To: Martine M. Solages, M.D., Clinical Reviewer
Division of Psychiatry Products (DPP)

Kofi Ansah, PharmD, Regulatory Project Manager, (DPP)

Kimberly Updegraff, PharmD, Associate Director for Labeling, (DPP)

From: Domenic D'Alessandro, PharmD, MBA, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME (duloxetine delayed-release capsules), for oral use

NDA: 212516

In response to DPP consult request dated October 23, 2018, OPDP has reviewed the proposed product labeling (PI), Medication Guide, and carton and container labeling for the original NDA submission for TRADENAME (duloxetine delayed-release capsules), for oral use.

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DPP (Kofi Ansah) on June 7, 2019, and are provided below.

Medication Guide and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU 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 June 14, 2019, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Domenic D'Alessandro at (301) 796-3316 or domenic.dalessandro@fda.hhs.gov.

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/s/

DOMENIC G DALESSANDRO
06/20/2019 01:03:18 PM

**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: June 20, 2019

To: Tiffany Farchione, MD
Acting Director
Division of Psychiatry Products (DPP)

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

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Domenic D'Alessandro, PharmD, MBA, CDE
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (established name): TRADENAME (duloxetine delayed-release capsules)

Dosage Form and Route: for oral use

Application Type/Number: NDA 212516

Applicant: Sun Pharmaceuticals Global FZE

1 INTRODUCTION

On September 19, 2018, Sun Pharmaceuticals Global FZE submitted for the Agency's review an original New Drug Application (NDA 212516) for TRADENAME (duloxetine delayed-release capsules), for oral use. The purpose of the submission is to seek approval of alternative administration options (i.e. capsules can be sprinkled on applesauce or administered through a nasogastric (NG) tube.

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 Psychiatry Products (DPP) on October 23, 2018, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for TRADENAME (duloxetine delayed-release capsules), for oral use.

2 MATERIAL REVIEWED

- Draft TRADENAME (duloxetine delayed-release capsules) MG-IFU received on September 19, 2018 and received by DMPP and OPDP on June 10, 2019.
- Draft TRADENAME (duloxetine delayed-release capsules) Prescribing Information (PI) received on September 19, 2018, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 10, 2019.

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 APhont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial font, size 10 and the IFU document using the Arial font, size 11.

In our collaborative review of the MG-IFU we:

- simplified wording and clarified concepts where possible
- ensured that the MG-IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG-IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG-IFU meets the Regulations as specified in 21 CFR 208.20

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

4 CONCLUSIONS

The MG-IFU 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 MG-IFU 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 MG-IFU.

Please let us know if you have any questions.

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/s/

SHAWNA L HUTCHINS
06/20/2019 12:26:46 PM

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06/20/2019 12:30:23 PM

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06/20/2019 01:24:31 PM

MEMORANDUM
REVIEW OF REVISED LABELS
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 19, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 212516
Product Name and Strength:	Drizalma Sprinkle (duloxetine) delayed-release capsules 20 mg, 30 mg, 40 mg, and 60 mg
Applicant/Sponsor Name:	Sun Pharma Global FZE
FDA Received Date:	June 14, 2019
OSE RCM #:	2018-2028
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels, received on June 14, 2019 for Drizalma Sprinkle. The Division of Psychiatry Products (DPP) requested that we review the revised container labels for Drizalma Sprinkle (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 labels and labeling review^a and in a follow-up emails to DPP on May 15, 2019 and June 5, 2019.

2 CONCLUSION

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

^a Holmes L. Labels and Labeling Review for Drizalma Sprinkle (NDA 212516). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 Apr 03. RCM No.: 2018-2028.

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/s/

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
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PEDIATRIC LABELING REVIEW

From: Carolyn L. Yancey, MD, Medical Officer
Division of Pediatric and Maternal Health (DPMH)

Through: Hari Cheryl Sachs, MD, Pediatric Team Leader, DPMH

John J. Alexander, MD, MPH, Deputy Director, DPMH

NDA Number: 212516

Sponsor: Sun Pharmaceutical Industries, Limited

Drug: Drizalma Sprinkle (duloxetine delayed-release capsule)

Drug Class: Selective serotonin and norepinephrine reuptake inhibitor (SSNRI)

Dosage Form and Route of Administration: Capsule, for oral use

Dosing Regimen: 60 mg once daily

Proposed Indication: For the treatment of:

- Major Depressive Disorder (MDD)
- Generalized Anxiety Disorder (GAD)
- Diabetic Peripheral Neuropathic Pain (DPNP)
- Chronic Musculoskeletal Pain

Consult Request: The Division of Psychiatry Products (DPP) requests the DPMH Pediatric Team review of pediatric labeling for the 505(b)(2), new drug application (NDA) 212516 Drizalma Sprinkle (duloxetine delayed-release capsule) manufactured by Sun Pharmaceutical Industries, Limited (SPIL). DPMH will assist with preparation for the Pediatric Review Committee (PeRC) Meeting discussion on proposed changes to Dosage and Administration (i.e., a sprinkle capsule to be opened and contents sprinkled over (b) (4) or added to water for syringe delivery into a nasogastric tube) trigger the Pediatric Research Equity Act (PREA). The consult is due on June 11, 2019 (consult is dated January 19, 2019).

Background

Duloxetine hydrochloride is a SSNRI. Although the exact mechanism of the antidepressant, central pain inhibitory and anxiolytic actions of duloxetine in humans are unknown, these pharmacologic actions are believed to be related to its potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).¹ Cymbalta (duloxetine hydrochloride (HCl)) capsule, delayed-release pellets, NDA 021427 is indicated for the treatment of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Peripheral Neuropathic Pain (DPNP), Chronic Musculoskeletal Pain, and Fibromyalgia (FM) in adult patients and GAD in pediatric patients 7 years to 17 years of age. Cymbalta is marketed by Eli Lilly and Company as a solid capsule to be taken once daily (60 mg), not be crushed or chewed and not to be opened.

Reviewer Comments:

Of note, pediatric studies for MDD conducted in response to a pediatric Written Request (WR) issued to the innovator June 31, 2006 failed to establish efficacy. The approved indication for GAD is based on a single 10-week, placebo-controlled trial in 272 pediatric patients with GAD in which superiority was demonstrated over placebo measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score. However, under the reference listed drug, Cymbalta, there is a PREA PMR 437-1 for the study of duloxetine delayed-release capsule in pediatric patients 12 years to less than 18 years of age with FM (Final Study Report is due by June 30, 2020).

The labeling under review is for Drizalma Sprinkle (duloxetine delayed-release) capsule, NDA 212516, submitted on September 19, 2018, as a 505(b)(2) submission relying on the listed drug product, Cymbalta. SPIL is seeking the same indications as the innovator except for FM. SPIL carved-out the indication for treatment of FM in this 505(b)(2) NDA submission based on patent protection for management of fibromyalgia for Cymbalta.

Pediatric Research Equity Act Requirements

Under PREA, (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. The new route of administration (e.g., administration via a nasogastric route following dilution with water) prompt PREA requirements for Drizalma Sprinkle.

Incomplete Initial Pediatric Study Plan

Under investigational new drug (IND) 131008 application, SPIL submitted an initial pediatric study plan (iPSP) on May 1, 2017 for Duloxetine Delayed-Release Capsules, 20 mg, 30 mg, 40 mg, and 60 mg for the proposed indications in GAD, MDD, Chronic Musculoskeletal Pain, DPNP, and FM. The applicant proposed plans to request a partial waiver from birth to less than 7 years of age for GAD, an assessment in pediatric patients 7 years to 17 years of age for GAD as well as plans to request a full waiver from birth to 17 years of age in pediatric patients with MDD (because the product would be ineffective or unsafe) as well as for chronic musculoskeletal pain, and DPNP (as studies are “not feasible”). The applicant’s pediatric plan is silent on pediatric patients with FM as the indication for FM is currently under patent protection.

FDA issued an Incomplete Letter to SPIL on June 15, 2017 detailing that the iPSP was submitted prematurely because the BE study against Cymbalta had not been reported to FDA. On July 7, 2017, SPIL submitted response to the Incomplete Letter including a revised iPSP clarifying their intent to submit results of the adult BE study along with a planned NDA submission after June 2018. However, on September 7, 2017, DPP communicated to the sponsor that their planned application will not trigger PREA based on the

¹ NDA 021427 Cymbalta (duloxetine delayed-release capsule) approved FDA-labeling Section 11 and Section 12 Clinical Pharmacology, Subsection 12.1 Mechanism of Action (most recent labeling is dated December 19, 2017).

information submitted and, therefore, an iPSP is not needed. Therefore, the 505(b)(2) NDA was submitted on September 19, 2018 without an Agreed iPSP. DPP noted that the submission included proposal for a new route of administration (via nasogastric tube administration) which triggers PREA. On March 15, 2019, DPP issued an information request to the sponsor to submit a Pediatric Study Plan (PSP) which was successfully negotiated under the current 505(b)(2) NDA 212516 for Drizalma Sprinkle (duloxetine delayed-release) capsule.

On May 22, 2019, DPP presented the Drizalma Sprinkle (delayed-release) capsule, 505(b)(2) NDA to PeRC and received PeRC agreement for the assessment in GAD and plan for full waivers for MDD, chronic musculoskeletal pain, and DPNP. PeRC agreed with removal of the indication for the treatment of FM based on the patent protections.

Bioequivalence Study

SPII conducted a single dose, cross-over four-treatment, four-period, four-sequence BE study comparing duloxetine delayed-release capsule, 60 mg, under fasting condition to investigate the impact of food and applesauce on bioavailability in healthy adults.

After review of the bioavailability (BA) and bioequivalence (BE) study, DPP determined that Drizalma Sprinkles are bioequivalent to the approved Cymbalta product, and therefore, the sponsor can rely on the listed product, Cymbalta, for safety and efficacy.

DPMH Pediatric Labeling Recommendations

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population compared with the adult population. For products with pediatric indications, the pediatric information must be placed in the labeling as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric population.

Drizalma Sprinkle (duloxetine delayed-release capsule) proposes one pediatric indication, per the listed product, in GAD in pediatric patients 7 years to 17 years of age. Proposed labeling, submitted in the Pregnancy Lactation and Labeling Rule (PLLR) format, includes a Boxed Warning on the risk of suicidal thoughts and behaviors in pediatric and young adult patients taking antidepressants; other serious Warnings and Precautions are revised for consistency with current class labeling for antidepressants, and indications are revised to be specific in adults with MDD, DPNP, and Chronic Musculoskeletal Pain, and in adults and pediatric patients (7 years to 17 years of age) for GAD.²

DPMH supports revised language in HIGHLIGHTS and Section 2 Dosage and Administration to address the administration instructions. Based on patent protections for management of FM, DPMH supports carving out the indication for FM from Section 1 Indications and Usage from proposed labeling for Drizalma Sprinkle and revising language in Highlights, Dosage and Administration, to address a sprinkle form and a nasogastric route of administration. DPMH recommends retaining the juvenile animal data in subsection 8.4 Pediatric Use supporting the completed study in pediatric patients, 7 years to 17 years of age with GAD as well as the general description of the two failed studies in pediatric patients 7 years to 17 years of age with MDD to discourage off-label use. Once the trade name review is complete, Drizalma Sprinkle, should be inserted in substantially complete proposed labeling where the BE formulation applies as a new product (i.e., Highlights, Indications and Usage, and Dosage and Administration; and in the Full Prescribing Information in Section 1 Indications and Usage and Section 2 Dosage and administration) and

² NDA 212516 Drizalma Sprinkle, substantially complete proposed labeling (most recent version dated June 5, 2019)

in language on instructions for use.

This review focuses on labeling sections and revisions that directly address pediatric use. These recommendations are based on the DPP substantially complete proposed DRIZALMA SPRINKLE labeling (dated June 5, 2019). DPMH's recommended information to be added to the labeling is underlined. Information to be deleted has a ~~strike through~~. Comments and rationale for DPMH's recommendations to the labeling are in *italics*.

The Maternal Health Team will complete a separate review with updates to safety risks during pregnancy and lactation (subsections 8.1, 8.2, 8.3, and Section 17) incorporated in Cymbalta labeling that are included in proposed labeling for Drizalma Sprinkle as a 505(b)(2) NDA submission.

HIGHLIGHTS OF PRESCRIBING INFORMATION

DULOXETINE delayed-release capsules, for oral use.

Initial U.S. Approval: 2004

BOXED WARNING

WARNING: RISK OF SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- Increased risk of suicidal thinking and behavior in pediatric and young (b) (4) -
adult patients taking antidepressants (5.1)
- Closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors (5.1)

INDICATIONS AND USAGE

DRIZALMA SPRINKLE is a serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for:

- Major Depressive Disorder (MDD) in adults (1)
- Generalized Anxiety Disorder (GAD) in adults and pediatric patients ages 7 years to 17 years old (1)
- Diabetic Peripheral Neuropathic Pain (DPNP) in adults (1)
- Chronic Musculoskeletal Pain in adults (1)

DOSAGE AND ADMINISTRATION

Note: A Table appears at the beginning of the section, Dosage and Administration, detailing the Indications, Starting Dose, Target Dose, and Maximum Dose for Drizalma Sprinkle.

Reviewer Comment: DPMH recommends and agrees with revisions in Highlights to the Boxed Warning, removal of FM (because of patent protection) from the list of approved indications, the addition of specific pediatric ages for GAD, and DPP revisions to Dosage and Administration adding language on two new routes of administration based on a sprinkle form of duloxetine delayed-release capsule. DPMH did not add any language to Dosage and Administration in Highlights. DPMH defers to DPP Clinical Pharmacology on final language in Highlights and the Full Prescribing Information to reflect the new Trade Name (DRIZALMA SPRINKLE) under this 505(b)(2) NDA labeling and new administration instructions.

FULL PRESCRIBING INFORMATION

WARNING: SUICIDAL THOUGHTS AND BEHAVIORS

Antidepressants increased the risk of suicidal thoughts and behavior in pediatric (b) (4) and young adults patients in short-term studies. (b) (4)

(b) (4) Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. (b) (4)

Reviewer Comment: DPMH agrees with revisions to the Boxed Warning on suicidal thoughts and behaviors in pediatric and young adult patients to reflect current class labeling.

1 INDICATIONS AND USAGE

(b) (4) DRIZALMA SPRINKLE is (b) (4) indicated for the treatment of:

- Major Depressive Disorder in adults [see Clinical Studies (14.1)]
- Generalized Anxiety Disorder in adults and pediatric patients 7 years to 17 years old [see Clinical Studies (14.2)]
- Diabetic Peripheral Neuropathy in adults [see Clinical Studies (14.3)]
- Chronic Musculoskeletal Pain in adults [see Clinical Studies (14.5)]

Reviewer Comment: DPMH recommends revisions to Indications and Usage clarifying the specific pediatric age group approved for treatment of GAD and noting the remaining indications are in adults.

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions

Administer DRIZALMA SPRINKLE (b) (4) -with or without food. Swallow

(b) (4) -DRIZALMA SPRINKLE whole, do not chew or crush. (b) (4)

For patients unable to swallow an intact capsule, refer to the alternative administration (b) (4) instructions below. (b) (4)

Directions for use with (b) (4) *(applesauce)*

For patients with swallowing difficulty, DRIZALMA SPRINKLE; (b) (4) can be opened and contents can be sprinkled over (b) (4) applesauce. The contents of the capsules should be swallowed along with a small amount (b) (4) applesauce. The drug/food mixture should be swallowed immediately (b) (4) -and not stored for future use. (b) (4)

Nasogastric tube administration

Open and add contents of a (b) (4) -capsule to an all plastic (b) (4) tip syringe and add 50 mL of water. Gently shake the syringe for approximately 10 seconds. Promptly deliver through a 12 French or larger nasogastric tube. Ensure no (b) (4) are left in the syringe. Rinse with additional water (about 15 mL) if needed.

Reviewer Comments: As stated above, DPMH recommends updating language in Section 2, Dosage and Administration, to include the new administration instructions. DPMH defers to DPP and Clinical Pharmacology on the final wording. DPMH recommends use of the new trade name, DRIZALMA SPRINKLE, for language on instructions on use, if it is approved.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Thoughts and Behaviors in (b) (4) Adolescents, and Young Adults

It is unknown whether the risk of suicidal (b) (4) thoughts and behaviors in children, adolescents, and young adults (b) (4) extends to longer-term use, i.e., beyond four (b) (4) months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with (b) (4)-MDD that (b) (4) antidepressants (b) (4)-delay the recurrence of depression and that depression itself is a risk factor for suicidal thoughts and behaviors.

(b) (4)

Note: All previous Cymbalta labeling language in Warnings and Precautions (5.1) is removed between the above paragraph and a new paragraph below.

Monitor all antidepressant-treated patients for any indication for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy, and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing duloxetine delayed-release capsules, in patients whose depression is persistently worse, or who are experiencing emergent suicidal thoughts or behaviors.

Reviewer Comments: DPMH agrees with revisions to Warnings and Precautions (5.1) to be consistent with updated class warnings, where applicable. See updates to the substantially complete proposed labeling for Drizalma Sprinkle (most recent version dated June 5, 2019).

8 USE IN SPECIAL POPULATIONS

8.4 Pediatric Use

Generalized Anxiety Disorder - In pediatric patients aged 7 to 17 years, efficacy was demonstrated in one 10-week, placebo-controlled trial. The study included 272 pediatric patients with GAD of which 47% were 7 to 11 years of age. Duloxetine delayed-release capsules demonstrated superiority over placebo as measured by greater improvement in the Pediatric Anxiety Rating Scale (PARS) for GAD severity score [see Clinical Studies (14.2)]. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

Major Depressive Disorder - Efficacy was not demonstrated in two 10-week, placebo-controlled trials with 800 pediatric patients with MDD, age 7 to 17. Neither duloxetine delayed-release capsules nor an active control (indicated for treatment of pediatric depression) was superior to placebo. The safety and effectiveness in pediatric patients less than 7 years of age have not been established.

The most frequently observed adverse reactions in the clinical trials included nausea, headache, decreased weight, and abdominal pain. Decreased appetite and weight loss have been observed in association with the use of SSRIs and SNRIs. Perform regular monitoring of weight and growth in children and adolescents treated with an SNRI such as duloxetine [see Adverse Reactions (6.11)]. Use of duloxetine delayed-release capsules in a

child or adolescent must balance the potential risks with the clinical need [see Boxed Warning and Warnings and Precautions (5.1)].

Animal Data - Duloxetine administration to young rats from post-natal day 21 (weaning) through post-natal day 90 (adult) resulted in decreased body weights that persisted into adulthood, but recovered when drug treatment was discontinued; slightly delayed (~1.5 days) sexual maturation in females, without any effect on fertility; and a delay in learning a complex task in adulthood, which was not observed after drug treatment was discontinued. These effects were observed at the high dose of 45 mg/kg/day (2 times the MRHD, for a child); the no-effect-level was 20 mg/kg/day (~1 time the MRHD, for a child).

Reviewer Comments: DPMH recommends that the findings from study with the innovator, Cymbalta (duloxetine delayed-release capsules), e.g., positive trial for GAD, negative trials for MDD, should remain in Section 8.4 as described. The juvenile animal data should also remain as written because these studies are relevant to the pediatric GAD indication and supported initiating clinical pediatric studies in MDD.

DPMH Actions and Labeling Recommendations

DPMH reviewed the applicant's proposed labeling for Drizalma Sprinkle (duloxetine delayed-release) capsule and participated in meetings with the DPP Clinical Team from February 14, 2019 to June 3, 2019. The most recent proposed labeling revisions per DPMH are dated June 5, 2019. DPMH labeling recommendations were provided in track changes for DPP consideration to revise the Drizalma Sprinkle labeling to conform to the *Draft Guidance for Industry and Review Staff on Pediatric Labeling*.³ DPMH's input will be reflected in the final labeling and the action letter from DPP. Should this product be approved, final labeling will be negotiated with the applicant, and may differ from recommendations in this DPMH labeling review.

³ *Draft Guidance for Industry and Review Staff - Pediatric Information Incorporated into Human Prescription Drug and Biological Products Labeling*, February 2013

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/s/

CAROLYN L YANCEY

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NDA 212516 DRIZALMA SPRINKLE (duloxetine delayed-release capsule) DPMH Labeling Review
dated 12Jun2019

JOHN J ALEXANDER

06/12/2019 07:06:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Office of New Drugs
Center for Drug Evaluation and Research
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PLLR Labeling Memorandum

Date: 6/5/2019 **Date consulted:** 3/5/2019

From: Catherine Roca, M.D., Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Miriam Dinatale, D.O., Team Leader
Division of Pediatric and Maternal Health

To: Division of Psychiatry Products (DPP)

Drug: Duloxetine Delayed-Release Capsules

NDA : 212516

Applicant: Sun Pharma Global FZE

Subject: Pregnancy and Lactation Labeling Rule (PLLR) Conversion

Indication(s): Major Depressive Disorder (MDD)
Generalized Anxiety Disorder (GAD)
Diabetic Peripheral Neuropathy Pain
Chronic Musculo-skeletal Pain

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for NDA 021427
- DPMH consult request dated January 29, 2019, DARRTS Reference ID 4382762
- DPMH review of CYMBALTA (duloxetine), NDA 21427, Catherine Roca, M.D., May 31, 2019. DARRTS Reference ID #4441290

Consult Question: “DPP is consulting the MHT for the review of this NDA to assist with updating the proposed label so that it conforms to the PLLR format.”

BACKGROUND

On September 19, 2018, Sun Pharmaceuticals Global FZE submitted a New Drug Application (NDA) 505(b)(2) for Duloxetine Delayed-Release Capsules for the following indications: 1) Major Depressive Disorder (DPP), 2) Generalized Anxiety Disorder (GAD, 3) Diabetic Peripheral Neuropathic Pain, and 4) Chronic Musculoskeletal Pain. DPP consulted DPMH on March 5, 2019 to assist with the Pregnancy and Lactation subsections of labeling for NDA.

Duloxetine DR Drug Characteristics¹

Drug Class	Serotonin and norepinephrine reuptake inhibitor
Mechanism of action	The exact mechanism of action is unknown but is believed to be related to its potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS).
Molecular weight	333.88 Daltons
Half-life	Mean terminal half-life was 12.4 hours (range: 7.8 – 22.2 hours)
Protein Binding	>90%
Oral Bioavailability	Percent oral bioavailability was not reported. Orally administered duloxetine is well-absorbed.
Serious Adverse Reactions	• Hepatotoxicity • Orthostatic hypotension • Serotonin syndrome • (b) (4) bleeding • Severe skin reactions, including Stevens-Johnson syndrome • Discontinuation symptoms • Activation of mania or hypomania • Angle-closure glaucoma • Seizures • Hyponatremia • Blood pressure – monitor blood pressure prior to initiating treatment and throughout treatment • Inhibitors of CYP1A2 or thioridazine should not be administered with duloxetine delayed-release capsules • Glucose control is worsened in some patients with diabetes, including small increases in fasting blood sugar • Conditions that slow gastric emptying – use cautiously in these patients • Urinary hesitation and retention

REVIEW

DPMH has completed a review of CYMBALTA (duloxetine).² See this review for background on MDD, GAD, diabetic neuropathic pain and chronic musculoskeletal

¹ Duloxetine Delayed-Release Capsules proposed package insert

pain and pregnancy, nonclinical information, and details regarding the use of duloxetine during pregnancy and lactation, and the effects of duloxetine on fertility.

RECOMMENDATIONS

DPMH revised subsections 8.1, 8.2, and 17 in labeling for compliance with the PLLR (see below). DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

HIGHLIGHTS OF PRESCRIBING INFORMATION

-----USE IN SPECIFIC POPULATIONS-----

- Pregnancy: Third trimester use may increase risk for symptoms of poor adaptation (respiratory distress, temperature instability, feeding difficulty, hypotonia, tremor, irritability) in the neonate. (8.1)

FULL PRESCRIBING INFORMATION

5 Warnings and Precautions

5.5 (b) (4) Bleeding

(b) (4) including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this risk. Case reports and epidemiologic studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding (b) (4). Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. (b) (4) about the risk of bleeding associated with the concomitant use of (b) (4) and NSAIDs, aspirin, or other drugs that affect coagulation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antidepressants during pregnancy. Healthcare providers are encouraged to register patients by calling the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visiting online at <https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/antidepressants/>

Risk Summary

Data from (b) (4) studies with duloxetine use in pregnant women have not identified a clear drug-associated risk of major birth defects or (b) (4). There are risks associated with untreated depression in pregnancy, and with exposure to

² DPMH review of CYMBALTA (duloxetine), NDA 21427, Catherine Roca, M.D., May 31, 2019.
DARRTS Reference ID #4441290

SNRIs and SSRIs, including duloxetine delayed-release capsules, during pregnancy (*see Clinical Considerations*).

In (b) (4) fetal weights were decreased but there was no evidence of (b) (4) the maximum recommended human dose (MRHD) of 120 mg/day, (b) (4) When duloxetine was administered orally to pregnant rats throughout gestation and lactation, pup weights at birth and pup survival to 1 day postpartum were decreased at a dose 2 times the MRHD. At this dose, pup behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity were observed. Post-weaning growth was not adversely affected.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Women who discontinued antidepressants during pregnancy are more likely to experience a relapse of major depression than women who continued antidepressants. This finding is from a prospective, longitudinal study that followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

(b) (4)

Fetal/Neonatal adverse reactions

Neonates exposed to duloxetine and other SNRIs (b) (4) SSRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These findings are consistent with either direct toxic effect of SSRIs and SNRIs or possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.4)*].

Data

(b) (4)

(b) (4)

Animal Data

In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of

(b) (4)

However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day approximately equal to the MRHD in rats.

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (2 times the MRHD); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

8.2 Lactation

Risk Summary

Data from the published literature report the presence of duloxetine in human milk (*see Data*).

(b) (4)

There are no data on the effect of duloxetine on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for duloxetine delayed-release capsules and any potential adverse effects on the breastfed child from duloxetine delayed-release capsules or from the underlying maternal condition.

(b) (4)

Data

Disposition of duloxetine was studied in 6 lactating women who were at least 12 weeks postpartum and had elected to wean their infants. The women were given 40 mg of duloxetine twice daily for 3.5 days. The peak concentration measured in breast milk occurred at a median of 3 hours after the dose. The amount of duloxetine in breast milk was approximately 7 mcg/day while on that dose; the estimated

(b) (4)

daily infant dose was approximately 2 mcg/kg/day, which is less than 1% of the maternal dose. The presence of duloxetine metabolites in breast milk was not examined.

17 PATIENT COUNSELING INFORMATION

- Advise (b) (4) to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with (b) (4)
- Advise patients that (b) (4) use late in pregnancy (b) (4) may increase the risk of neonatal complications requiring prolonged hospitalization, respiratory support, tube feeding.
- Advise women that there is a risk of relapse with discontinuation of antidepressants.
- Advise patient that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to (b) (4) during pregnancy [see *Use in Specific Populations (8.1)*]

(b) (4)

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/s/

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06/05/2019 10:51:40 AM

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06/05/2019 10:55:32 AM

LABELS 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:	April 3, 2019
Requesting Office or Division:	Division of Psychiatry Products (DPP)
Application Type and Number:	NDA 212516
Product Name and Strength:	Drizalma Sprinkle (duloxetine) delayed-release capsules 20 mg, 30 mg, 40 mg, and 60 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharma Global FZE
FDA Received Date:	September 19, 2018
OSE RCM #:	2018-2028
DMEPA Safety Evaluator:	Loretta Holmes, BSN, PharmD
DMEPA Team Leader:	Sevan Kolejian, PharmD, MBA

1 PURPOSE OF REVIEW

As part of the approval process for Drizalma Sprinkle (duloxetine) delayed-release capsules, 20 mg, 30 mg, 40 mg, and 60 mg, the Division of Psychiatry Products (DPP) requested that we review the proposed labels and labeling for areas that may lead to medication errors. DPP requested this review as part of their evaluation of the 505(b)(2) submission for Drizalma Sprinkle. The listed drug product (Cymbalta, NDA 021427) was approved on August 3, 2004.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Labels and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B (N/A)
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

3 FINDINGS AND RECOMMENDATIONS

We note that Drizalma Sprinkle will be available in a 40 mg strength whereas the referenced drug, Cymbalta, is not available in a 40 mg strength. However, the proposed Drizalma Sprinkle 40 mg strength is consistent with the recommended dosage of the product (see Appendix A). Therefore, we have no concern with introducing the new 40 mg strength to the market.

Table 2 below includes the identified medication error issues with the submitted labels, DMEPA's rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2: Identified Issues and Recommendations for Sun Pharma (entire table to be conveyed to Applicant)

Container Labels			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The proposed proprietary name “Drizalma Sprinkle” is not on the container labels.	The currently proposed labels do not represent the “to-be-marketed” presentation of the container labels.	Submit your proposed “to-be-marketed” container labels which include the proposed proprietary name “Drizalma Sprinkle” for our review.
2.	The statement of strength is difficult to see due to its lack of prominence.	The lack of prominence of the statement of strength may lead to product selection or wrong strength medication errors.	Increase the size of the statement of strength.
3.	The “Rx only” statement and net quantity statement are too prominent due to the bold font.	The bold font draws attention away from important product identifying information such as the established name and Medication Guide (MG) statement.	Debold the “Rx only” and net quantity statements.
4.	The dispense Medication Guide (MG) statement lacks prominence because it is not in bold font.	Due to its lack of prominence, the product may be dispensed without the MG.	Increase the prominence of the dispense Medication Guide (MG) statement. You may achieve this by using a bold font for the MG statement.

5.	The proposed expiration date format is not indicated on the labels.	We are unable to evaluate the expiration date format because it is not indicated on the labels. It is important that the expiration date formatting is clearly presented in order to help minimize confusion and reduce the risk of deteriorated drug medication errors.	We recommend the human-readable expiration date on the drug package label include a year, month, and non-zero day. We recommend 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. We recommend that a hyphen or a space be used to separate the portions of the expiration date.
6.	The labels have an area containing vertical lines with "FPO" superimposed over the lines. However, it is not clear what will be placed in that location.	We are unable to assess the FPO area of the labels.	Clarify the information that will be placed in the FPO area of the labels.

7.	The labels do not contain a 2D data matrix barcode.	A 2D data matrix barcode is used for tracking and tracing purposes.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.¹ The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. ¹The draft guidance is available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
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4 CONCLUSION

Our evaluation of the proposed labels and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for Sun Pharma Global FZE. We ask that the Division convey Table 2 in its entirety to Sun Pharma Global FZE so that the recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Drizalma Sprinkle that Sun Pharma Global FZE submitted on September 19, 2018, and the listed drug (LD), Cymbalta^a.

Table 4. Relevant Product Information for Listed Drug (Cymbalta) and Drizalma Sprinkle																																																																				
Product Name	Cymbalta			Drizalma Sprinkle																																																																
Initial Approval Date	August 3, 2004			N/A																																																																
Active Ingredient	duloxetine			duloxetine																																																																
Indication	- Major Depressive Disorder (MDD) - Generalized Anxiety Disorder (GAD) - Diabetic Peripheral Neuropathic Pain (DPNP) - Fibromyalgia (FM) - Chronic Musculoskeletal Pain			- Major Depressive Disorder (MDD) - Generalized Anxiety Disorder (GAD) - Diabetic Peripheral Neuropathic Pain (DPNP) - Chronic Musculoskeletal Pain																																																																
Route of Administration	Oral			Oral																																																																
Dosage Form	Delayed-release capsules			Delayed-release capsules																																																																
Strengths	20 mg, 30 mg, and 60 mg			20 mg, 30 mg, 40 mg and 60 mg																																																																
Dose and Frequency	<table><tr><th>Indication</th><th>Starting Dose</th><th>Target Dose</th><th>Maximum Dose</th></tr><tr><td>MDD (2.1)</td><td>40 mg/day to 60 mg/day</td><td>Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day</td><td>120 mg/day</td></tr><tr><td>GAD (2.2)</td><td></td><td></td><td></td></tr><tr><td>Adults</td><td>60 mg/day</td><td>60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>Elderly</td><td>30 mg/day</td><td>60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>Children and Adolescents (7 to 17 years of age)</td><td>30 mg/day</td><td>30 to 60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>DPNP (2.3)</td><td>60 mg/day</td><td>60 mg/day (once daily)</td><td>60 mg/day</td></tr><tr><td>FM (2.4)</td><td>30 mg/day</td><td>60 mg/day (once daily)</td><td>60 mg/day</td></tr><tr><td>Chronic Musculoskeletal Pain (2.5)</td><td>30 mg/day</td><td>60 mg/day (once daily)</td><td>60 mg/day</td></tr></table>			Indication	Starting Dose	Target Dose	Maximum Dose	MDD (2.1)	40 mg/day to 60 mg/day	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day	120 mg/day	GAD (2.2)				Adults	60 mg/day	60 mg/day (once daily)	120 mg/day	Elderly	30 mg/day	60 mg/day (once daily)	120 mg/day	Children and Adolescents (7 to 17 years of age)	30 mg/day	30 to 60 mg/day (once daily)	120 mg/day	DPNP (2.3)	60 mg/day	60 mg/day (once daily)	60 mg/day	FM (2.4)	30 mg/day	60 mg/day (once daily)	60 mg/day	Chronic Musculoskeletal Pain (2.5)	30 mg/day	60 mg/day (once daily)	60 mg/day	<table><tr><th>Indication</th><th>Starting Dose</th><th>Target Dose</th><th>Maximum Dose</th></tr><tr><td>MDD (2.1)</td><td>40 mg/day to 60 mg/day</td><td>Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day</td><td>120 mg/day</td></tr><tr><td>GAD (2.2) Adults</td><td>60 mg/day</td><td>60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>Elderly</td><td>30 mg/day</td><td>60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>Children and Adolescents (7 to 17 years of age)</td><td>30 mg/day</td><td>30 to 60 mg/day (once daily)</td><td>120 mg/day</td></tr><tr><td>DPNP (2.3)</td><td>60 mg/day</td><td>60 mg/day (once daily)</td><td>60 mg/day</td></tr><tr><td>Chronic Musculoskeletal Pain (2.5)</td><td>30 mg/day</td><td>60 mg/day (once daily)</td><td>60 mg/day</td></tr></table>	Indication	Starting Dose	Target Dose	Maximum Dose	MDD (2.1)	40 mg/day to 60 mg/day	Acute Treatment: 40 mg/day (20 mg twice daily) to 60 mg/day (once daily or as 30 mg twice daily); Maintenance Treatment: 60 mg/day	120 mg/day	GAD (2.2) Adults	60 mg/day	60 mg/day (once daily)	120 mg/day	Elderly	30 mg/day	60 mg/day (once daily)	120 mg/day	Children and Adolescents (7 to 17 years of age)	30 mg/day	30 to 60 mg/day (once daily)	120 mg/day	DPNP (2.3)	60 mg/day	60 mg/day (once daily)	60 mg/day	Chronic Musculoskeletal Pain (2.5)	30 mg/day	60 mg/day (once daily)	60 mg/day
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Chronic Musculoskeletal Pain (2.5)	30 mg/day	60 mg/day (once daily)	60 mg/day																																																																	
How Supplied	30, 60, 90, and 1,000-count bottles			30, 60, 90, and 1,000-count bottles																																																																

^a Cymbalta prescribing information obtained online at DailyMed, available via this link: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=2f7d4d67-10c1-4bf4-a7f2-c185fbad64ba>. Accessed on March 27, 2019.

Storage	Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].	Store at 20°C to 25°C (68°F to 77°F) [See USP Controlled Room Temperature.] Dispense in a tightly closed container.
Container Closure	Info not available	30, 60, and 90-count bottles have child-resistant closures.

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,^b along with postmarket medication error data, we reviewed the following Drizalma Sprinkle labels and labeling submitted by Sun Pharma Global FZE on September 19, 2018.

- Container labels received on September 19, 2018.
- Prescribing Information (image not shown) received on September 19, 2018 (available in EDR via this link: <\\cdsesub1\evsprod\nda212516\0001\m1\us\draft-labeling-text.pdf>).

F.2 Container Labels (not to scale)



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

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