NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	505(b)(2) New Drug Application (NDA)
Application Number(s)	NDA 212516
Priority or Standard	Standard
Submit Date(s)	September 9, 2018
Received Date(s)	September 9, 2018
PDUFA Goal Date	July 19, 2019
Division/Office	Division of Psychiatry Products/ Office of Drug Evaluation I
Review Completion Date	
Established/Proper Name	Duloxetine Delayed-Release Capsules 20 mg, 30 mg, 40 mg, and 60 mg
(Proposed) Trade Name	Drizalma Sprinkle
Pharmacologic Class	Serotonin (5-HT) and Norepinephrine Reuptake Inhibitor
Code name	
Applicant	Sun Pharma Global FZE
Dosage form	Oral Capsules
Applicant proposed Dosing Regimen	Dosing regimen varies by indication. Starting dose 30 mg/day to 60 mg/day; target dose (b) (4) mg/day to 60 mg/day; maximum dose 120 mg/day
Applicant Proposed Indication(s)/Population(s)	Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), Diabetic Peripheral Neuropathic Pain (DPNP), and Chronic Musculoskeletal Pain
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	370143000 Major depressive disorder (disorder) 21897009 Generalized anxiety disorder (disorder) 193184006 Chronic painful diabetic neuropathy (disorder) 762452003 Chronic musculoskeletal pain (finding)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Major Depressive Disorder: Adults Generalized Anxiety: Adults, Elderly, Children and Adolescents (7 to 17 years of age) Diabetic Peripheral Neuropathic Pain: Adults Chronic Musculoskeletal Pain: Adults
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	370143000 Major depressive disorder (disorder) 21897009 Generalized anxiety disorder (disorder) 193184006 Chronic painful diabetic neuropathy (disorder) 762452003 Chronic musculoskeletal pain (finding)
Recommended Dosing Regimen	Dosing regimen varies by indication. Starting dose 30 mg/day to 60 mg/day; target dose (b) (4) mg/day to 60 mg/day; maximum dose 120 mg/day

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Signatures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

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OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1 Executive Summary

1.1. Product Introduction

Sun Pharma Global FZE has submitted a 505(b)(2) application for duloxetine delayed-release capsules (proposed proprietary name Drizalma Sprinkle). Duloxetine is a serotonin and norepinephrine reuptake inhibitor.

Cymbalta (duloxetine delayed-release capsules) (NDA 021427), the listed drug for this application, is currently available in 20 mg, 30 mg, and 60 mg delayed-release capsules that cannot be crushed, chewed, or opened. The Applicant has developed a delayed-release capsule which may be opened and sprinkled over food or given via a nasogastric tube. The Applicant believes that this formulation will be beneficial to patients who have difficulties swallowing capsules. The Applicant has also developed a 40 mg capsule, which would provide more options for dose titration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

This Application relies on the Agency's findings of safety and effectiveness for Cymbalta, the listed drug, as well as a single-dose, crossover, four-treatment, four-sequence bioequivalence study. The submitted bioequivalence study demonstrates that duloxetine delayed-release capsules are bioequivalent to Cymbalta.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The Applicant has demonstrated bioequivalence to the listed drug (Cymbalta). No new safety findings were identified that would indicate a clinically significant difference in the risk-benefit considerations for this form of duloxetine to treat the proposed indications and patients who are unable to swallow pills would have an alternative formulation; therefore, the review team recommends approval of this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), diabetic peripheral neuropathic pain (DPNP), and chronic musculoskeletal pain are associated with psychiatric and physical health co-morbidities and poor functional outcomes. These conditions frequently co-occur.	Effective treatment of MDD, GAD, DPNP, and chronic musculoskeletal pain may reduce distress and disability.
Current Treatment Options	Among the available treatments for MDD, GAD, DPNP, and chronic musculoskeletal pain, medications with serotonergic and noradrenergic effects–namely, serotonin norepinephrine reuptake inhibitors (SNRIs) and tricyclic antidepressants (TCAs)–play an important role for patients who suffer from overlapping symptoms. However, the safety profile of TCAs is unfavorable when compared with SNRIs such as duloxetine. Furthermore, no SNRIs are currently available in a formulation that can be administered to patients who are unable to swallow pills.	The development of a duloxetine formulation that can be administered to patients who are unable to swallow pills addresses an unmet clinical need.
Benefit	The Applicant submitted a single-dose, cross-over, four-treatment, four-period, four-sequence study to assess whether this product is bioequivalent to the listed drug, Cymbalta.	Study results indicate that this product is bioequivalent to the listed drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	Analysis of safety data for this product including vital signs, laboratory assessments, and adverse events did not reveal any unexpected safety signals.	The safety profile of this product is consistent with that of the listed drug, Cymbalta. A medication guide will be included in labeling for this product. No Risk Evaluation and Mitigation Strategy (REMS) is required.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☐	**The patient experience data that were submitted as part of the application include:**			Section of review where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

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2 Therapeutic Context

2.1. Analysis of Condition

Cymbalta, the listed drug, is indicated for the treatment of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), diabetic peripheral neuropathic pain (DPNP), fibromyalgia, and chronic musculoskeletal pain. The Applicant is not seeking a fibromyalgia indication for duloxetine delayed-release capsules due to patent exclusivity limitations.

MDD is the second leading cause of disability worldwide and is associated with increased risk of physical illnesses such as diabetes mellitus, cardiovascular disease, and cancer, as well as increased risk of suicide. In a given year, 6% of the adult population will experience MDD. Lifetime prevalence of MDD in the United States may approach 20%, though estimates vary widely (Otte et al. 2016). GAD has been associated with an increased risk of physical health conditions, problematic use of drugs and alcohol, increased suicide risk, and poor social and occupational functioning (Stein and Sareen 2015). DPNP occurs in 12% to 50% of individuals with diabetes and may lead to significant morbidity, including foot ulcers, skin and bone infections, and amputation. The total annual cost of DPNP in the United States is between $4.6 and $13.7 billion (Gordois et al. 2003). Chronic musculoskeletal pain afflicts between 11% and 24% of the population and affects workforce participation, other functional outcomes, psychological health, and quality of life (Cimmino and Ferrone 2011). MDD, GAD, and chronic pain syndromes are frequently co-morbid, and the presence of one of these disorders may exacerbate the symptoms of any co-occurring disorders.

2.2. Analysis of Current Treatment Options

Current treatment options for Major Depressive Disorder include psychotherapy, antidepressant medications, combined regimens of psychotherapy and medication, and interventional therapies such as electroconvulsive therapy and transcranial magnetic stimulation. Table 1 lists the FDA-approved antidepressant medications that are available for the treatment of MDD and other depressive disorders. Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-norepinephrine reuptake inhibitors (SNRIs) have a more favorable safety profile than tricyclic antidepressants (TCAs) and have replaced TCAs as first-line medications for Major Depressive Disorder (Otte et al. 2016). Monoamine Oxidase Inhibitors (MAOIs) require strict dietary restrictions and also have a less favorable safety profile compared with SSRIs and SNRIs.

In addition to cognitive behavioral therapy and other psychotherapy interventions, antidepressant medications are also used in the treatment of GAD. SSRIs and SNRIs are considered first line treatments for GAD in clinical practice, although only escitalopram, duloxetine, paroxetine, and venlafaxine have FDA-approved indications for treatment of anxiety disorders. Duloxetine is the only FDA-approved medication for treatment of GAD in the pediatric population.

Table 1: FDA-Approved Antidepressant Medications

Pharmacologic Class	Drug Names
Selective Serotonin Reuptake Inhibitors (SSRIs)	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, vilazodone
Serotonin-norepinephrine Reuptake Inhibitors (SNRIs)	desvenlafaxine, duloxetine, levomilnacipran, venlafaxine
Tricyclic Antidepressants (TCAs)	amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, protriptyline, nortriptyline, trimipramine
Monoamine Oxidase Inhibitors (MAOI)	isocarboxazid, phenelzine, selegiline, tranylcypromine
Other Antidepressants	buproprion, mirtazapine, nefazodone, trazodone, vortioxetine

Table 2 lists the FDA-approved antidepressant medications that are available in alternative formulations and that may be prescribed for patients who are unable to swallow pills. FDA-issued Prescribing Information and Medication Guides do not necessarily include guidance about whether oral tablets may be crushed. In clinical practice, antidepressants are frequently crushed and administered with food or through nasogastric tubes (Bostwick and Demehri 2014). However, all currently approved SNRIs appear on the Institute for Safe Medication Practices' list of *Oral Dosage Forms That Should Not Be Crushed* (Institute for Safe Medication Practices 2019).

Table 2: Alternative Formulations of FDA-Approved Antidepressant Medications

Alternative Formulation	Drug Names
Oral solution or concentrate	citalopram (10mg/5ml), doxepin (10mg/ml), escitalopram (5mg/5ml), fluoxetine (20mg/5ml), nortriptyline (10mg/5ml), paroxetine (10mg/5ml), sertraline (20mg/ml)
Topical Patch	selegiline
Orally Disintegrating Tablet	mirtazapine, selegiline

Duloxetine and pregabalin are FDA-approved for treatment of diabetic neuropathic pain. Pregabalin is available as a capsule and as an oral solution (20mg/ml). The label and medication guide for pregabalin do not provide guidance about whether the capsule may be opened.

Available non-pharmacologic treatments for chronic pain syndromes include cognitive behavioral therapy, mindfulness-based stress reduction, exercise therapy, acupuncture, and massage (Kligler et al. 2018). Other available treatments for chronic musculoskeletal pain

include nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, tramadol, and muscle relaxants. Tricyclic antidepressants are also prescribed off-label for chronic pain syndromes. While opioid analgesics are commonly prescribed for chronic musculoskeletal pain, evidence that opioids are effective for this purpose is limited. Opioids are also associated with risk of dependence and overdose (Volkow et al. 2018).

Reviewer Comment: Depression, anxiety, and chronic pain syndromes are conditions that frequency co-occur. Among the available treatments for these conditions, medications with serotonergic and noradrenergic effects–namely, tricyclic antidepressants and SNRIs–play an important role for patients who suffer from overlapping symptoms. Tricyclic antidepressants are associated with a higher risk of cardiovascular adverse effects, may lower the seizure threshold, and are more likely to be lethal in overdose than SSRIs and SNRI. None of the currently available SNRIs are available in formulations that can be administered to patients who are unable to swallow pills. Pregabalin, which is indicated for the treatment of diabetic neuropathic pain, is available in a liquid formulation. However, pregabalin does not have an indication for treatment of MDD or anxiety disorders. Therefore, the development of a duloxetine formulation that can be administered to patients who are unable to swallow pills addresses an unmet clinical need.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cymbalta, the listed drug, first received U.S. marketing approval in 2004.

3.2. Summary of Presubmission/Submission Regulatory Activity

Pre- NDA Communications

On August 11, 2016, the Division of Psychiatry Products (the Division) provided a written response to pre-IND questions regarding the proposed single-dose (60 mg), crossover, bioavailability study. The Division agreed with the overall study design and provided guidance about the design of dissolution testing and in-use testing for administration with soft foods and nasogastric or gastrostomy tubes. The Division also outlined the conditions under which a biowaiver would be granted for a lower strength formulation. The Division concurred that the Applicant could conduct the study in any geographic location given that similar pharmacokinetics have been observed in different ethnic populations. The Division issued a Study May Proceed letter on March 2, 2017.

Inspections

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) determined in December 2018 that a site inspection was not warranted for this Application as the sites had been recently inspected.

In (b) (4), a routine surveillance inspection of an associated testing lab ((b) (4), FEI (b) (4)) resulted in a change in facility compliance status to Potential Official Action Indicated. The Applicant submitted an amendment to the NDA to withdraw the lab, noting that the lab had not been used for testing of any exhibit batches and would not be used for commercial batches.

Pediatric Requirements

In an email communication dated September 7, 2017, the Division stated that the application would not trigger Pediatric Research Equity Act (PREA) requirements and that an initial pediatric study plan (iPSP) would not be needed. However, upon further review and feedback from Division of Pediatrics and Maternal Health (DPMH), the Division determined that the application would trigger PREA requirements because of the new route of administration (nasogastric tube administration) proposed. The Division issued an advice letter on March 15, 2019, to inform the Applicant of the PREA requirements and to request a pediatric study plan (PSP). On March 21, 2019, the Division clarified that the submission of the PSP would not affect the review clock for the application. The Applicant submitted an initial Pediatric Study Plan (iPSP) on April 11, 2019. The iPSP was reviewed by the Pediatric Review Committee (PeRC) on May 22, 2019.

Labeling Requirements

On March 11, 2019, the Division requested that the Applicant submit additional materials to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential sections of the labeling. In response to the Information Request, the Applicant confirmed that they would submit a review and summary of all available published literature regarding duloxetine use (with references) and a review and summary of relevant cases from the pharmacovigilance database. However, the Applicant noted that a summary of drug utilization rates among females of reproductive potential was not available and reports on pregnancy registries were not applicable. The nonclinical review team and DPMH found the Applicant's approach to the Information Request to be acceptable.

The Division noted adverse event (AE) data in the draft label included data from fibromyalgia studies. However, because of patent limitations, the Applicant is not seeking a fibromyalgia indication. The Division requested that the Applicant resubmit the draft label with fibromyalgia data removed. In response to this information request, the Applicant proposed modifying the draft label by replacing a reference to "FM" (abbreviation for fibromyalgia) in the AE tables with "Another Indication." The Applicant pointed out that this approach was used in approved labeling for generic duloxetine products. The Applicant's proposal was reviewed by the FDA 505(b)(2) committee and was found to be acceptable.

Proprietary Name

On February 14, 2019, the Division of Medication Error Prevention and Analysis (DMEPA) issued a letter to the Applicant indicating that the proposed proprietary name, Drizalma Sprinkle, was conditionally acceptable.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

No clinical site inspections were recommended or conducted for this application.

4.2. Product Quality

Sun Pharmaceutical Industries Limited manufactures the active pharmaceutical ingredient (API), duloxetine hydrochloride USP. The 20 mg dose is supplied as a hard gelatin capsule with a green cap and green body. The 30 mg dose is supplied as a hard gelatin capsule with a blue cap and white body. The 40 mg dose is supplied as a hard gelatin capsule with a white cap and white body. The 60 mg dose is supplied as a hard gelatin capsule with a blue cap and green body. The pellets contained within the capsules are (b) (4) colored. The capsules have at least a (b) (4) shelf-life at room temperature. The Sponsor's Quality Overall Summary states that the expity period for the API is (b) (4) when stored in a (b) (4). The drug product is soluble in methanol and dichloromethane and slightly soluble in water.

4.3. Clinical Microbiology

No new clinical microbiology data were submitted with this application.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

No new nonclinical data were submitted with this application. There are no novel excipients in the duloxetine delayed-release sprinkle capsules. All the excipients in the clinical formulation are listed in the FDA's Inactive Ingredient Database (IID) and the amounts of these excipients are well within the IID limits or within the safe limit reported by different health authorities/agencies or within the safety threshold derived through available safety information. Based on the available data and clinical experience of use of duloxetine, the proposed formulation does not seem to pose any safety concern. Therefore, from a Pharmacology/Toxicology perspective, the nonclinical studies that supported the approval of the innovator product, Cymbalta in combination with published literature are considered adequate to support the current 505(b)(2) application.

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6 Clinical Pharmacology

6.1. Executive Summary

In this submission, one pivotal relative bioequivalence (BE) study, Study DLT_60C_0324_16, was conducted in healthy adult volunteers. The effect of food and applesauce on the PK of the commercial formulation was also evaluated

6.1.1. Recommendations

The Office of Clinical Pharmacology (OCP) has determined that there is sufficient clinical pharmacology and biopharmaceutics information provided in the NDA to support a recommendation of approval of duloxetine delayed-release capsules. Per the recommendation (Appendix 14.4) from the Office of Study Integrity and Surveillance (OSIS), the data from the pivotal BE study is considered acceptable. No inspection of the clinical or analytical site for the pivotal study DLT_60C_0324_16 was deemed necessary, because those sites were recently inspected and no issues were identified. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP?	Comment
Overall	☒ Yes ☐ No ☐ NA	Pending labeling agreements with the sponsor
Evidence of effectiveness	☒ Yes ☐ No ☐ NA	Clinical efficacy and safety information is extended from the listed drug based on PK similarity of duloxetine.
Proposed dose for general patients	☒ Yes ☐ No ☐ NA	Same with the listed drug. Not seeking approval for fibromyalgia indication due to patent exclusivity concern.
Labeling	☐ Yes ☒ No ☐ NA	Pending satisfactory agreement with the sponsor

6.1.2. Post-Marketing Requirements and Commitments

N/A

6.2. Summary of Clinical Pharmacology Assessment

- An adequate bridge has been established between duloxetine delayed-release capsules and Cymbalta through the BE study. The average exposure of duloxetine has been demonstrated to be similar (within BE limits for Cmax, AUC0-t and AUCinf). Hence, the

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efficacy and safety profiles of the duloxetine delayed-release capsules in general population are expected to be similar to those of the listed drug.

- Food and applesauce do not have any impact on bioavailability of duloxetine delayed-release capsules. However, food delays the absorption of duloxetine by approximately 1.7 hours. Duloxetine delayed-release capsules can be administered with or without regard to food. Duloxetine delayed-release capsules can be swallowed whole or can be sprinkled over soft food (i.e., applesauce).

6.2.1. Pharmacology and Clinical Pharmacokinetics

The only pivotal study submitted in this application is a BE study which was to demonstrate the exposure similarity between duloxetine delayed-release capsules and Cymbalta, and to investigate the impact of food and applesauce on bioavailability of test product. The study results showed that the average exposures of duloxetine were similar (within bioequivalence limits for Cmax, AUC0-t and AUCinf) between the two formulations. The average pharmacokinetic profiles from the two formulations are almost superimposable. Food and applesauce do not have any impact on bioavailability of duloxetine delayed-release capsules, although food slightly delays the absorption of duloxetine. Hence, similar pharmacodynamic profiles (i.e., efficacy and safety) are expected between the two duloxetine delayed-release formulations. ADME properties of duloxetine after administration of duloxetine delayed-release capsules are expected to be the same as those after administration of Cymbalta.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

Dosing recommendation will be the same as the listed drug, Cymbalta. However, the Applicant is not seeking approval for fibromyalgia indication due to patent exclusivity concern. The dosing recommendation is summarized in the table below.

Indication	Starting Dose	Target Dose	Maximum Dose
MDD	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 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	60 mg/day	60 mg/day (once daily)	60 mg/day
Chronic Musculoskeletal Pain	30 mg/day	60 mg/day (once daily)	60 mg/day

Therapeutic Individualization

Drizalma Sprinkle can be administered with or without regards to food, and may be swallowed whole or can be sprinkled over soft food. Dosing instructions are expected to the same as the listed drug based on intrinsic factors or extrinsic factors such as drug interactions.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. Overview of the Product and Regulatory Background

Duloxetine is a combined serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI). Reuptake by nerve endings is thought to be a primary mechanism for removing monoamines from the synapse and terminating their effects at pre- and post-synaptic receptors. Therefore, blockade of reuptake may increase synaptic levels of monoamines and enhance monoaminergic neurotransmission. The drug product seeking approval for duloxetine delayed-release sprinkle capsules. The sprinkle capsules would be an alternate dosage form of duloxetine delayed-release capsules for elderly or patients with swallowing difficulties/medication non-compliant patients.

A pre-IND WRO meeting was held in June 2016, during which the Applicant's development plan to submit a 505(b)(2) NDA for their product, study design of the BE study, and pediatric development plans were discussed. If BE to the selected listed drug (Cymbalta) was demonstrated for the proposed product, the Agency agreed that clinical efficacy and safety studies in patients would not be necessary.

6.3.2. General Pharmacology and Pharmacokinetic Characteristics

Refer to section 6.2.1.

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6.3.3. Clinical Pharmacology Questions

Are similar average efficacy and safety profiles expected for duloxetine delayed-release capsules and Cymbalta ?

Yes. Similar average efficacy and safety profiles are expected for duloxetine delayed-release capsules and Cymbalta.

The listed drug, Cymbalta, was shown to be safe and efficacious in the treatment of multiple indications (MDD, GAD, DPNP, FM and Chronic Musculoskeletal Pain) in patients 6 years and older. For duloxetine delayed-release capsules, there are no clinical trials conducted to evaluate its efficacy and safety. However, the efficacy and safety data of duloxetine delayed-release capsules can be extended from the listed drug, Cymbalta, based on the exposure similarity (i.e., Cmax, AUC0-t and AUCinf) demonstrated for duloxetine between the two formulations (Test Product A and Test Product R). The mean pharmacokinetic profiles of duloxetine are almost superimposable between the two formulations.

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Table 3: Summary of Pharmacokinetic Parameters for Duloxetine

Product/Statistics	Cmax* (ng/mL)	AUC0-t* (ng.h/mL)	AUC0-inf* (ng.h/mL)
Test Product A (Under Fasting Condition)			
Geometric Mean	50.1583	758.8185	789.6574
CV(%)	41.01	52.98	52.41
N	57	57	57
Test Product B (Under Fed Condition)			
Geometric Mean	49.8663	857.2361	887.1042
CV(%)	47.14	48.97	49.00
N	56	56	56
Test Product C (Under Fasting with Applesauce)			
Geometric Mean	50.9218	748.1728	793.6328
CV(%)	43.50	61.71	61.12
N	55	55	53
Reference Product R (Under Fasting Condition)			
Geometric Mean	51.2915	789.3683	801.7941
CV(%)	43.20	52.08	49.74
N	56	56	55
Least squares mean			
A	49.9291	753.9644	784.7514
B	49.5721	854.3575	884.3826
C	50.9866	752.9041	788.5707
R	51.9073	795.5450	822.3786
Ratio of least squares mean			
(A/R)%	96.18	94.77	95.42
(B/A)%	99.28	113.31	112.69
(C/A)%	102.11	99.85	100.48
90% Confidence Intervals (A/R)			
Lower Limit:	88.97	88.59	89.35
Upper Limit:	103.99	101.38	101.91
90% Confidence Intervals (B/A)			
Lower Limit:	91.83	105.92	105.56
Upper Limit:	107.34	121.22	120.30
90% Confidence Intervals (C/A)			
Lower Limit:	94.40	93.30	94.00
Upper Limit:	110.46	106.87	107.40
p-value[ANOVA]			
Formulation	0.7617	0.0065	0.0105
Period	0.0020	<.0001	0.0001
Sequence	0.9697	0.9357	0.9151
Power (%)	99.64	99.97	99.98
Intra-subject CV(%)	25.39	21.87	21.17

* Log-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported

The mean Tmax value for duloxetine was 5.0360 hours for Reference product (R).
The mean Tmax value for duloxetine was 5.0529 hours for Test product (A).
The mean Tmax value for duloxetine was 6.7423 hours for Test product (B).
The mean Tmax value for duloxetine was 5.1730 hours for Test product (C).

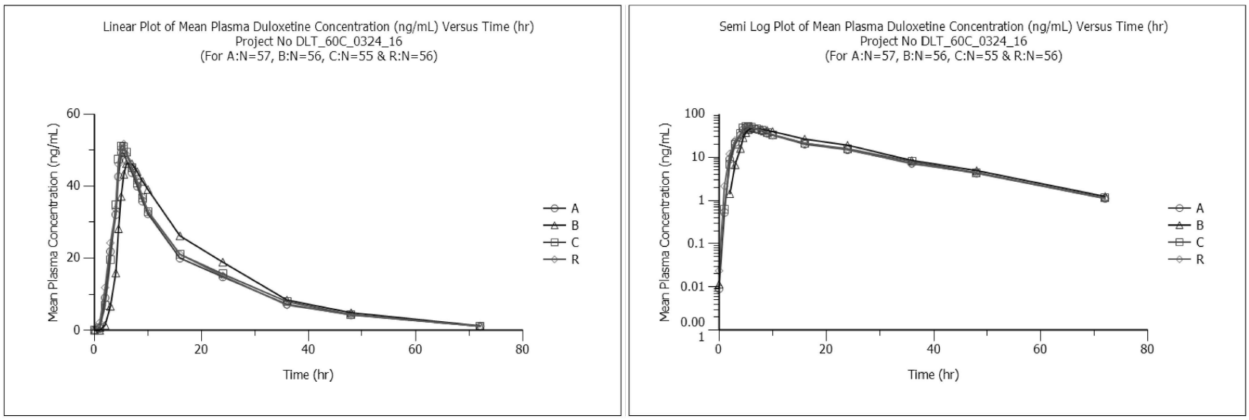
Table 4: Ratios of LSM for Log-transformed Pharmacokinetic Parameters [Cmax, AUC0-t and AUC0-inf] for Duloxetine (90% Confidence Interval)

Parameter	Test (A) vs Reference (R)
C_{max}	96.18 % (88.97 % – 103.99%)
AUC_{0-t}	94.77 % (88.59 % – 101.38 %)
$AUC_{0-\infty}$	95.42 % (89.35 % – 101.91%)

Parameter	Test (B) vs Test (A)
C_{max}	99.28 % (91.83% – 107.34%)
AUC_{0-t}	113.31 % (105.92% – 121.22 %)
$AUC_{0-\infty}$	112.69 % (105.56% – 120.30%)

Parameter	Test (C) vs Test (A)
C_{max}	102.11 % (94.40 % – 110.46%)
AUC_{0-t}	99.85 % (93.30% – 106.87%)
$AUC_{0-\infty}$	100.48 % (94.00 % – 107.40%)

Figure 1 Linear and Semi-log Plot or Mean Plasma Duloxetine Concentration (ng/ml) Versus Time (hr)



What are the PK properties of duloxetine after single dose administration of duloxetine delayed-release capsules?

Following a single dose administration of 60 mg duloxetine delayed-release capsules to healthy volunteers under fasting conditions, duloxetine reached Cmax approximately 5 hours post dose, with a mean terminal half-life ~ 12.4 hours (range 7.8 to 22.2 hour). With once daily dosing of duloxetine delayed-release capsules, about 35% accumulation of duloxetine is expected.

Does food affect the bioavailability of duloxetine delayed-release capsules?

Food has no meaningful effect on the bioavailability of duloxetine delayed-release capsules. However, food delays the absorption of duloxetine by approximately 1.7 hours. The change of Tmax is expected to have a minimal effect on the efficacy or safety profile of the product. Duloxetine delayed-release capsules can be administered with or without regard to food.

Does sprinkle over soft food (i.e., applesauce) affect the bioavailability of duloxetine delayed-release capsules?

Sprinkling over applesauce does not have meaningful impact on the bioavailability of duloxetine delayed-release capsules. The bioavailability of duloxetine was considered comparable (i.e., met bioequivalence criteria). Therefore, duloxetine delayed-release capsules can be swallowed whole or can be sprinkled over soft food (i.e., applesauce).

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7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 5: Listing of Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	No. of patients enrolled	Study Population	No. of Centers and Countries
DLT_60C-0324_16	Single-dose, crossover, randomized, four-treatment, four-period, four-sequence study	Four treatment conditions: Treatment R – reference, fasting condition Treatment A – fasting condition Treatment B – fed condition Treatment C – dose given with applesauce, fasting condition	PK parameters Safety parameters: vital signs, ECGs, CXR, physical exam, medical and medication history, laboratory tests	64 patients enrolled 54 patients completed	Healthy, male, Asian volunteers	Single site (Hamdard University, New Delhi, India)

*ECG=electrocardiogram
*CXR=Chest X-ray

7.2. Review Strategy

As noted above, the Applicant will rely on the Agency's findings of safety and effectiveness from the listed drug and did not conduct any efficacy studies. This review focuses on the safety record of the submitted bioequivalence Study DLT_60C-0324_16. The safety review included evaluation of adverse events, vital sign parameters, laboratory assessments, and use of concomitant medications in the BE study.

Table 6: Material Reviewed

Material Submitted	eCDT Sequence Number	Submission Date
NDA 212516	0001	SEP 18, 2018
Proprietary Name/Request for Review	0002	NOV 16, 2018
IND 131008	0002	JAN 13, 2018
IND 131008	0003	JAN 31, 2017

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. [DLT_60C-0324_16]

Trial Design

The only clinical trial submitted with this NDA was intended to establish BE between Cymbalta and duloxetine delayed-release capsules. No additional efficacy studies were submitted. Study DLT_60C-0324_16 was conducted with a randomized, single-dose, crossover, four-treatment, four-sequence BE design to compare duloxetine delayed-release capsules to Cymbalta under both fasting and fed conditions. The study also assessed the impact of food (applesauce) on bioavailability. The study was designed to expose all participants to each of the four treatment conditions—duloxetine delayed-release capsules in the fasted condition (Treatment A), duloxetine delayed-release capsules in the fed condition (Treatment B), duloxetine delayed-release capsules given with applesauce (Treatment C), and Cymbalta (Treatment R, reference, in the fasted condition). Participants were assigned to a treatment sequence using a SAS-generated randomization schedule. Laboratory analysts did not have access to the randomization scheme. Participants served as their own controls in the study. The dose administered in each treatment condition was 60 mg orally once daily. Participants were admitted to the Clinical Pharmacology Unit at Hakeem Abdul Centenary Hospital (Hamdard University, New Delhi, India) during each treatment period. A 6-day washout period was required between treatments.

Healthy, non-vegetarian volunteers aged 18 to 45 years who had unremarkable screening

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medical histories, physical examinations, and results on screening parameters were eligible to participate in the study. Participants were required to have a body weight that was within normal range as defined by the Life Insurance Corporation of India height/weight chart for non-medical cases. Exclusion criteria included:

- Hemoglobin < 12 g/dL
- Abnormal urinalysis
- Any evidence of organ dysfunction
- History of serious physical illness
- History of chronic headache, tremor, sleep disturbance, sensory disturbance, anxiety, agitation, dizziness, excessive sweating, dry mouth, bleeding events, seizure disorder, or narrow angle glaucoma or visual disorders
- Diarrhea, vomiting, or nausea within 1-week of study enrollment
- History of suicidality or significant suicidal ideation at time of enrollment
- History of regular tobacco use, habitual alcohol use, other drug dependence, positive alcohol breath test at screening, or use of alcohol within 48 hours of study enrollment
- Use of any medication within 30 days of enrollment, consumption of grapefruit juice within 48 hours of enrollment, donation of > 350 mL of blood within 90 days of enrollment, or participation in any clinical trial within 90 days of enrollment

Screening assessments are outlined in Table 7.

Participants could be withdrawn from the study if they experienced vomiting post-dose, if they required medications that would affect the pharmacokinetics of the study medication, or in the case of a positive breath alcohol or urine toxicology screen.

Study Endpoints

Pharmacokinetic endpoints included the area under the plasma concentration curve (AUC) from time zero to the last measurable concentration and from time zero to infinity; percentage of extrapolated area under the plasma concentration curve from the last measurable concentration to infinity; maximum plasma concentration (C_{max}); time to maximum plasma concentration (T_{max}); first order terminal elimination rate constant (K_{el}); and the first order terminal elimination half-life ($T_{1/2}$).

Safety assessments at the end of the study included vital signs, medical history, medication history, physical examination, adverse event monitoring, ALT, AST, BUN, creatinine, complete blood count, and UA. A schedule of study assessments is outlined in Table 7.

Table 7: Schedule of Study Assessments - Study DLT_60C-0324_16

	Screening	Study Days in Period I, II, III and IV			End of Study Safety Assessment
Activity		Day 0	Day 1	Day 2	
Clinical examination	x	x		x	
Vital Signs Recording	x	x	x	x	
Chest X-ray	x				
Electrocardiogram	x				
Hematology	x				x
Biochemistry[1, 2]	x				x
HIV[3], Hepatitis B, Hepatitis C, and RPR[4]	x				
Urinalysis					x
Urine drug screen for drugs of abuse	x				
Breath alcohol test	x				
Adverse event Monitoring		x	x	x	

1. Biochemistry assessments at screening included: serum glucose, blood urea nitrogen (BUN), creatinine, total bilirubin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and cholesterol.
2. Biochemistry assessments at the end of the study included: ALT, AST, BUN, and creatinine.
2. HIV - Human Immunodeficiency Virus serology
3. RPR - rapid plasma reagin

Statistical Analysis Plan

Statistical analysis was performed using the SAS system. To evaluate the pharmacokinetic endpoints, the Sponsor conducted an analysis of variance (ANOVA) using Type III sum of squares. No interim analyses were performed on the data. No subgroup analyses were performed.

Protocol Amendments

The Applicant submitted the original study protocol on January 13, 2017. On January 31, 2017, the Applicant submitted an amendment which reduced the minimum blood sample volume to 2 ml (based on advice from the Agency), reduced the total blood volume to 260 ml, and updated sampling and storage procedures.

8.1.2. Study Results

Compliance with Good Clinical Practices

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The principal investigator has submitted a letter of certification that the clinical study for this application was conducted in compliance with all requirements of good clinical practice.

Financial Disclosure

Was a list of clinical investigators provided: Yes ☒ No ☐

Total number of investigators identified: 1

Number of investigators who are Applicant employees (including both full-time and part-time employees): 1

Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A
- Significant payments of other sorts: N/A
- Proprietary interest in the product tested held by investigator: N/A
- Significant equity interest held by investigator in sponsor of covered study: N/A

Is an attachment provided with details of the disclosable financial interests/ arrangements: Yes ☐ No ☐ N/A ☒

Is a description of the steps taken to minimize potential bias provided: Yes ☐ No ☐ N/A ☒

Number of investigators with certification of due diligence (FDA 3454, box 3) 0

Is an attachment provided with the reason: Yes ☐ No ☐ N/A ☒

Patient Disposition

A total of 65 volunteers consented to participate in the trial; 64 volunteers met the inclusion and exclusion criteria and were enrolled. Ten participants dropped out of the study or were withdrawn. Table 8 shows the number of patients who were exposed to each treatment condition during the four treatment periods.

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Table 8: Number of Patients Exposed to Duloxetine Delayed-Release per Treatment Period

Treatment Condition	Period I	Period II	Period III	Period IV	Total
Treatment A	16	16	15	13	60
Treatment B	16	14	15	15	60
Treatment C	16	13	13	14	56
Treatment R	16	15	13	12	56

Protocol Violations/Deviations

The protocol specified that laboratory investigations including aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea nitrogen (BUN), creatinine, urinalysis, and hematology should be repeated at the end of the study. However, participants (b) (6) and (b) (6) did not report for post-treatment laboratory testing.

Table of Demographic Characteristics

The study was conducted at a university hospital in India and the study population was comprised entirely of Asian males aged 18 to 43 years (Table 9).

Reviewer Comment: A published pharmacokinetic study did not detect statistically significant differences in C_{max}, AUC, or $T_{1/2}$ in Japanese and Caucasian populations (Chan et al. 2006). Another study demonstrated shorter T_{max} in Caucasian volunteers as compared with Japanese and Chinese volunteers, but pharmacokinetic parameters were otherwise comparable in these populations (Tianmei et al. 2007). During the pre-IND stage, the Division advised that because pharmacokinetics are similar across different ethnic populations, the study could be conducted in any geographic location. The study protocol did allow for enrollment of both male and female participants; however only males ultimately participated in the study. Duloxetine's half-life is similar in males and females and gender-based dose adjustments are not recommended for the listed drug. Therefore, the absence of female participants is not likely to affect the applicability of these study results.

Table 9: Study DLT_60C_0324_16 - Demographics

Demographic Parameters	Total(N= 64)
Sex	
Male	64 (100 %)
Age	
Mean years (SD)	28.72 (6.5)
Median (years)	29
Min, max (years)	18, 43
Age Group	
< 65 years	64 (100 %)
Race	
Asian	64 (100%)_
Ethnicity	
Not Hispanic or Latino	(100 %)
Region (optional)	
Asia	64 (100 %)

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Prescription medications, over the counter medications, vitamins, and herbal supplements were prohibited within 30 days of study enrollment.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Participants experiencing adverse events during the study could receive medications for symptomatic relief. Sixteen participants received rescue medications during the study, primarily for treatment of gastrointestinal symptoms and rash. Two patients who required rescue medications (DLT_60C_0324_16-SUN-11 and DLT_60C_0324_16-SUN-37) dropped out of the study. The pattern of rescue medication use under all treatment conditions was similar (Table 10).

Table 10: Rescue Medication Use

Treatment Condition	Number Participants	Rescue Medications
Treatment A	8	acetaminophen, ciprofloxacin, domperidone, lactic acid bacillus, levocetirizine, ORS
Treatment B	9	acetaminophen, domperidone, Lactic acid bacillus, ondansetron, ORS, pantoprazole, pheniramine,
Treatment C	4	acetaminophen, drotaverine, ondansetron
Treatment R	5	acetaminophen, domperidone, lactic acid bacillus, ORS

Data Quality and Integrity

The application was submitted in the Electronic Common Technical Document (eCTD) format. All required datasets were included with the submission and were sufficiently well-organized to allow for an efficient review.

8.2. Review of Safety

8.2.1. Safety Review Approach

The safety review included evaluation of adverse events occurring under all treatment conditions as well as an assessment of changes in vital sign parameters and laboratory assessments following exposure to the drug. The review also examined the use of concomitant medications to ameliorate symptoms associated with adverse events. I also referred to safety information contained in the label for the listed drug.

8.2.2. Review of the Safety Database

Overall Exposure

In this four-treatment, four-sequence crossover study, all patients who completed the study were exposed to all the treatment conditions. 64 patients were enrolled in the study and 54 patients completed the study.

Table 11: Safety Population, Size and Denominators

Safety Database for the Study Drug (duloxetine delayed-release capsules)[1] Individuals exposed to the study drug in this development program for the indication under review N=64 (N is the sum of all available numbers from the columns below)			
Clinical Trial Groups	Duloxetine delayed-release capsules (n=64)	Cymbalta (n=64)	Placebo (n=0)
Controlled trials conducted for this indication[2]	64	64	0

[1] *study drug* means the drug being considered for approval.
[2] to be used in product's labeling

Adequacy of the safety database:

The safety population included all participants who received a dose of study medication. As noted above, the demographic characteristics of enrolled participants do not reflect the general U.S. population. However, significant pharmacokinetic differences between ethnic groups are not expected. The dose and duration of exposure are considered adequate to obtain accurate assessment of bioequivalence and to assess safety.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The application was submitted in the Electronic Common Technical Document (eCTD) format. All required datasets were included with the submission and were sufficiently well-organized to allow for an efficient review.

Categorization of Adverse Events

The Applicant categorized adverse events using MedDRA version 19.1. Adverse events were examined by system organ class (SOC) as well as by preferred terms Routine Clinical Tests

Routine clinical tests were performed as per the schedule of study assessments described in Table 7.

8.2.4. Safety Results

Deaths

No deaths occurred during the clinical study.

Serious Adverse Events

No serious adverse events occurred during the clinical study.

Dropouts and/or Discontinuations Due to Adverse Effects

Table 12 summarizes the dropouts and discontinuations during the study. Two participants withdrew due to adverse events (vomiting).

Table 12: Dropouts or Discontinuations

Study	Subject	Discontinuation Reason
DLT_60C_0324_16	DLT_60C_0324_16-SUN (b) (6)	Dropped out in Period 2 (did not arrive for admission)
	DLT_60C_0324_16-SUN	Withdrawn in Period 2 (vomiting)
	DLT_60C_0324_16-SUN	Dropped out in Period 1 (personal reasons)
	DLT_60C_0324_16-SUN	Withdrawn in Period 1 (vomiting)
	DLT_60C_0324_16-SUN	Dropped out in Period 4 (personal reasons)
	DLT_60C_0324_16-SUN	Dropped out (did not arrive for Period 2 admission)
	DLT_60C_0324_16-SUN	Withdrawn in Period 2 (positive toxicology screen)
	DLT_60C_0324_16-SUN	Dropped out (did not arrive for Period 2 admission)
	DLT_60C_0324_16-SUN	Withdrawn in Period 3 (positive toxicology screen)
	DLT_60C_0324_16-SUN	Dropped out in Period 4 (did not arrive for admission)

Significant Adverse Events

No significant adverse events occurred during the study.

Treatment Emergent Adverse Events and Adverse Reactions

A total of 30 treatment-emergent adverse events in 19 participants, including one laboratory abnormality (increased urine red blood cells), occurred in the study. The adverse events that occurred in this study appeared to be consistent with the known safety profile of Cymbalta. Adverse events that occurred in ≥ 5% of patients in Cymbalta clinical trials for approved indications (and more frequently than placebo) included: nausea, headache, dry mouth, somnolence, fatigue, insomnia, constipation, dizziness, diarrhea, decreased appetite, hyperhidrosis, and abdominal pain (Table 13).

Table 13: Adverse Events By Treatment Condition

Adverse Event By Treatment Condition								
Treatment Condition	Treatment R	%	Treatment A	%	Treatment B	%	Treatment C	%
Nausea	2	3.6%	3	5.0%	4	6.7%	1	1.8%
Vomiting	0	0.0%	1	1.7%	1	1.7%	0	0.0%
Diarrhea	0	0.0%	1	1.7%	1	1.7%	0	0.0%
Dyspepsia	0	0.0%	0	0.0%	1	1.7%	0	0.0%
Abdominal Pain	0	0.0%	0	0.0%	0	0.0%	1	1.8%
Headache	1	1.8%	2	3.3%	2	3.3%	1	1.8%
Rash	0	0.0%	1	1.7%	1	1.7%	0	0.0%
Urticaria	0	0.0%	0	0.0%	1	1.7%	0	0.0%
Pyrexia	0	0.0%	0	0.0%	0	0.0%	1	1.8%
Increased Urine RBC	0	0.0%	0	0.0%	0	0.0%	1	1.8%

Laboratory Findings

As per the schedule of assessments above, laboratory assessments were conducted at screening and during post-study follow up. Post-study assessments included BUN, creatinine, complete blood count, urinalysis, and liver function tests. The laboratory values for clinical significance were examined and no pattern of laboratory changes that represented a new safety signal was found. The reference ranges for laboratory assessments are shown in Table 14. No BUN or creatinine elevations were observed in the study. The lowest post-study hemoglobin value was 11.3 g/dL. The lowest post-study leukocyte value was 3400 cells per mm^3 and the highest value was 11,500 cells per mm^3. No platelet abnormalities were observed. Glycosuria was detected in one patient in the post-study urinalysis.

Table 14: Reference Ranges for Laboratory Assessments

Parameter	Reference Range	Units
Neutrophils	40-75	%
Lymphocytes	20-45	%
Monocytes	0-8	%
Eosinophils	0-6	%
Basophils	0-1	%
Platelets	150000-450000	per mm3
Total Leukocyte Count (TLC)	4000-10000	per mm3
Hemoglobin	13-17	g/dL
Total Cholesterol	<200	mg/dl
Total Bilirubin	0.2-1.3	mg/dl
Creatinine	0.66-1.25	mg/dl
Glucose, Fasting	74-106	mg/dl
Glucose, Random	70-140	mg/dl
ALP	38-126	U/L
BUN	20-Sep	mg/dl
ALT	13-69	U/L
AST	15-46	U/L

Source: Study Report, Protocol DLT_60C_0324_16, page 237

Seven participants experienced elevations in liver function enzymes above the upper limit of normal (Table 15). However, liver function enzyme values greater than three times the upper limit of normal were not observed. Serum bilirubin was obtained only at screening; no data about whether any participants experienced associated bilirubin elevations is available. As outlined in the label, Cymbalta, the listed drug, also increased the risk of elevation of serum transaminase levels in clinical trials.

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Table 15: Elevations in Liver Function Tests

Subject/Liver Function Test	Screening	Follow Up #1	Follow Up #2
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	97 (day -14), 82 (day -9)	80 (day 22)	x
AST	64 (day -14), 41 (day -9)	48 (day 22)	x
Alkaline phosphatase	107 (day -14), 116 (day -9)	x	x
Total Bilirubin	0.6 (day -14), 0.64 (day -9)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	74 (day -9)	100 (day 22)	91 (day 29)
AST	44 (day -9)	74 (day 22)	53 (day 29)
Alkaline phosphatase	85 (day -9)	x	x
Total Bilirubin	0.46 (day -9)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	38 (day -9)	57 (day 22)	x
AST	25 (day -9)	53 (day 22)	x
Alkaline phosphatase	54 (day -9)	x	x
Total Bilirubin	1.21 (day -9)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	44 (day -14)	69 (day 22)	x
AST	35 (day -14)	49 (day 22)	x
Alkaline phosphatase	100 (day -14)	x	x
Total Bilirubin	0.65 (day -14)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	56 (day -14)	133 (day 22)	69 (day 29)
AST	47 (day -14)	114 (day 22)	54 (day 29)
Alkaline phosphatase	68 (day -14)	x	x
Total Bilirubin	0.3 (day -14)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	67 (day -11)	96 (day 22)	72 (day 34)
AST	42 (day -11)	54 (day 22)	41 (day 34)
Alkaline phosphatase	66 (day -11)	x	x
Total Bilirubin	1.14 (day -11)	x	x
DLT_60C_0324_16-SUN[(b) (6)]			
ALT	38 (day -13)	70 (day 22)	41 (day 43)
AST	41 (day -13)	84 (day 22)	35 (day 43)
Alkaline phosphatase	98 (day -13)	x	x
Total Bilirubin	0.57 (day -13)	x	x

Reference ID: 4463875

Vital Signs

Vital sign parameters for participants in the study fell within the normal range, with few exceptions. No clinically significant pattern of vital sign changes was observed. The lowest heart rate observed in the study was 54 beats per minute (bpm) and the highest heart rate observed was 96 bpm. Twenty participants (Table 16) did experience a change in heart rate ≥ 20 beats per minute from baseline. However, these changes did not appear to be clinically significant and did not appear to vary based on treatment condition. Systolic blood pressures ranged from 90 to 136 mmHg (Figure 2); diastolic blood pressures ranged from 60 to 90 (Figure 3Figure 3). No clinically significant blood pressure changes were observed. Mean blood pressures were similar across treatment conditions.

Table 16: Participants Experiencing Change in Heart Rate ≥ 20 Beats per Minute from Baseline

Subject	Screening	Reference	Treatment A	Treatment B	Treatment C
DLT_60C_0324_16-SUN-(b)(6)	62	70 -80	68 – 80	68 - 88	68 - 72
DLT_60C_0324_16-SUN-(b)(6)	88	70 – 86	74 – 88	68 - 88	74 - 80
DLT_60C_0324_16-SUN-(b)(6)	84	70 – 82	66 – 78	64 - 78	70 - 74
DLT_60C_0324_16-SUN-(b)(6)	66	no data	64 – 84	72 - 96	no data
DLT_60C_0324_16-SUN-(b)(6)	60	62 – 80	66 – 82	62 - 78	64 – 78
DLT_60C_0324_16-SUN-(b)(6)	84	70 – 82	68 – 72	64 - 78	64 – 76
DLT_60C_0324_16-SUN-(b)(6)	86	66 – 76	66 – 86	68 - 76	64 – 84
DLT_60C_0324_16-SUN(b)(6)	56	no data	no data	no data	68 – 80
DLT_60C_0324_16-SUN(b)(6)	88	74 – 88	74 – 84	72 - 88	68 – 88
DLT_60C_0324_16-SUN(b)(6)	86	62 – 74	68 – 86	66 - 76	62 – 76
DLT_60C_0324_16-SUN(b)(6)	66	64 – 76	68 – 76	72 - 86	no data
DLT_60C_0324_16-SUN(b)(6)	64	64 – 76	64 – 78	72 - 84	62 – 78
DLT_60C_0324_16-SUN(b)(6)	66	64 – 76	66 – 74	70 - 86	68 – 76
DLT_60C_0324_16-SUN(b)(6)	54	60 – 76	62 – 70	60 - 64	56 – 74
DLT_60C_0324_16-SUN(b)(6)	60	62 – 68	66 – 74	64 - 78	66 – 80
DLT_60C_0324_16-SUN-(b)(6)	94	no data	64 – 78	no data	no data
DLT_60C_0324_16-SUN(b)(6)	96	no data	no data	66 - 70	no data

DLT_60C_0324_16-SUN-(b) (6)	90	no data	68 – 82	66 - 84	70 – 80
DLT_60C_0324_16-SUN-(b) (6)	62	74 – 84	68 – 80	80 - 94	80 – 88
DLT_60C_0324_16-SUN-(b) (6)	56	70 – 80	68 – 78	64 - 80	64 – 86

Figure 2: Systolic Blood Pressure by Treatment Condition

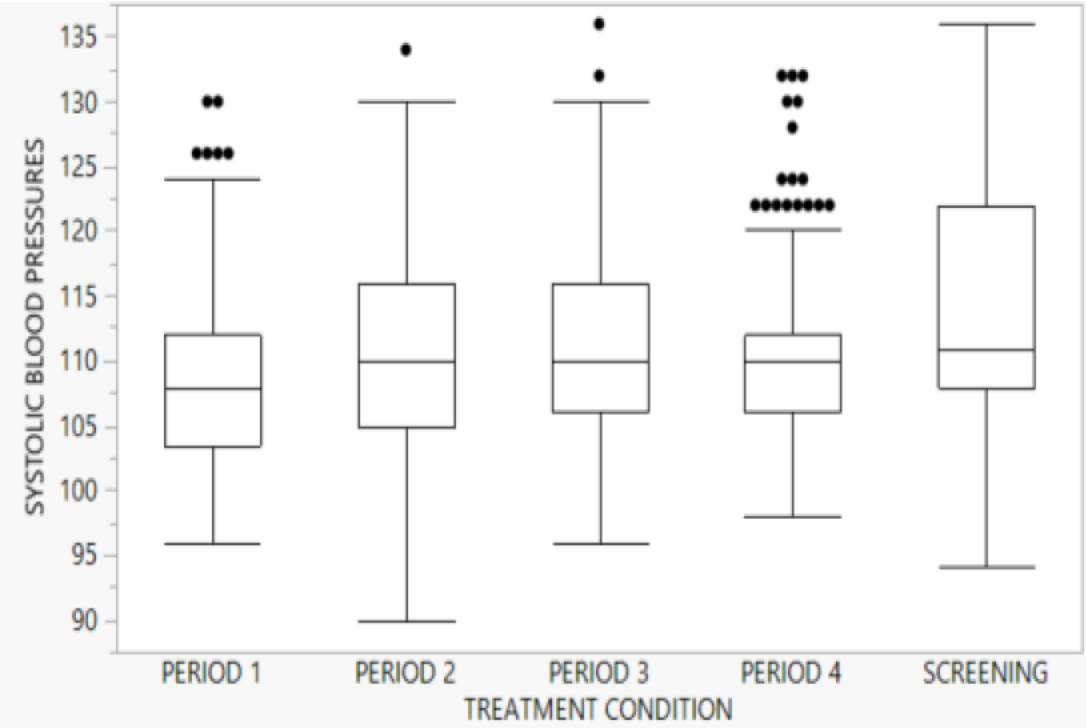
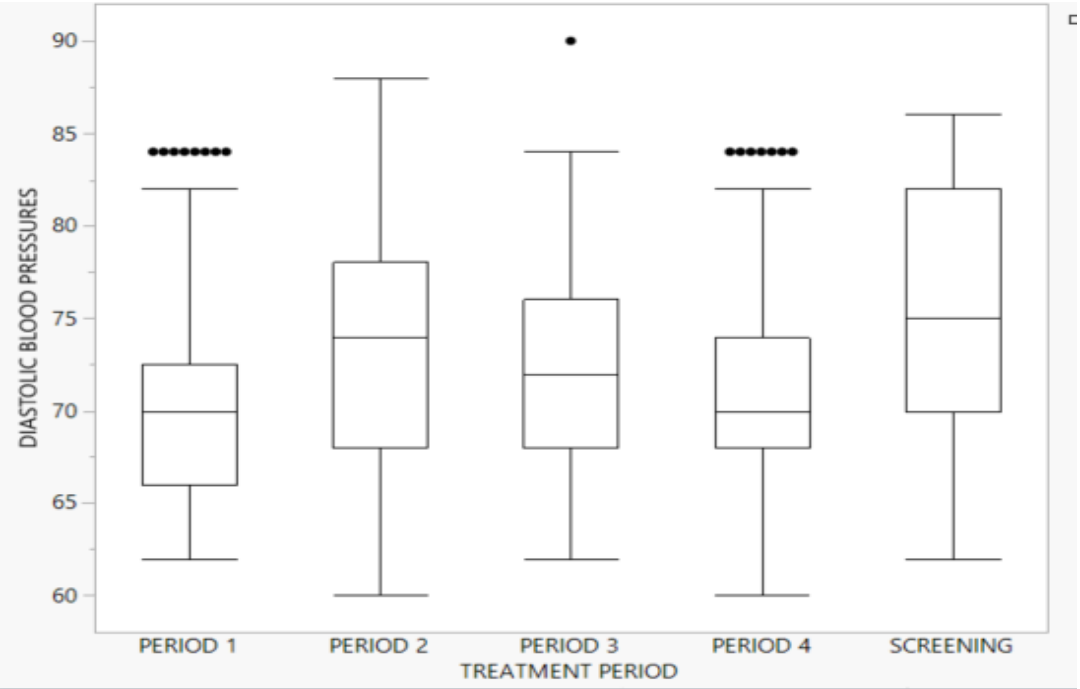


Figure 3: Diastolic Blood Pressures by Treatment Condition



Electrocardiograms (ECGs)

ECGs performed at screening were within normal limits. ECGs were not conducted at the end of the study.

QT

No QT/QTc elevations were noted at baseline. ECGs were not conducted at the end of the study.

8.2.5. Analysis of Submission-Specific Safety Issues

No submission specific safety issues were considered, as the primary focus was assessment of bioequivalence.

8.2.6. Specific Safety Studies/Clinical Trials

No specific safety studies were submitted to this application.

8.2.7. Safety in the Postmarket Setting

Expectations on Safety in the Postmarket Setting

The Applicant has demonstrated that duloxetine delayed-release capsules are bioequivalent to the listed drug, Cymbalta. Duloxetine delayed-release capsules are expected to have a similar

postmarket safety profile as Cymbalta. General Disorders and Administration Site Conditions, Nervous System Disorders, Psychiatric Disorders, and Gastrointestinal Disorders are the classes of adverse events most frequently reported in the FDA Adverse Events Reporting System (FAERS) database for Cymbalta.

8.3. Conclusions and Recommendations

Results of the submitted study indicate that duloxetine delayed-release capsules is bioequivalent to the listed drug, Cymbalta. The safety profile of duloxetine delayed-release capsules is also consistent with that of Cymbalta. Therefore, we recommend approval of this application.

Reference ID: 4463875

9 Advisory Committee Meeting and Other External Consultations

This 505(b)(2) application relies on the findings of safety and efficacy of the listed drug. There were no questions for an Advisory Committee. No external consultations were needed for review of this application.

Reference ID: 4463875

10 Pediatrics

No new pediatric data was submitted with this application; this application relies on the Agency's findings of safety and effectiveness for the listed drug, Cymbalta. This application triggered PREA because of the proposed new route of administration (nasogastric tube administration) proposed. The Applicant's iPSP was reviewed by the Pediatric Review Committee in May 2019.

Clinical trials evaluating Cymbalta for treatment of pediatric MDD failed to demonstrate effectiveness. Pediatric trials for DPNP and chronic musculoskeletal pain have been waived because these conditions do not typically affect the pediatric population. Cymbalta has a pediatric indication for the treatment of GAD in patients aged 7 to 17 years. No additional pediatric trials will be required for this formulation; pediatric labeling will match that of Cymbalta.

Reference ID: 4463875

11 Labeling Recommendations

11.1. Prescription Drug Labeling

Labeling for duloxetine delayed-release capsules is generally consistent with that of Cymbalta. The label has been updated to conform to the Pregnancy and Lactation Labeling Rule (PLLR) format, dosage and administration guidelines have been expanded to account for new modes of administration, current class language has been included to describe warnings and precautions when appropriate, and references to the fibromyalgia indication have been removed. Pertinent differences between the duloxetine delayed-release capsules and Cymbalta labels are described below.

HIGHLIGHTS

The boxed warning has been updated to align with the more recent Suicidal Thoughts and Behaviors warning. The boxed warning indicates that there is increased risk of suicidal thinking and behavior in pediatric and young adult patients taking antidepressants and advises healthcare professionals to closely monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors.

1 INDICATIONS AND USAGE

Duloxetine delayed-release capsules are indicated for the treatment of Major Depressive Disorder in adults, Generalized Anxiety Disorder in adults and pediatric patients 7 years to 17 years old, Diabetic Peripheral Neuropathy in adults, and Chronic Musculoskeletal Pain in adults. Due to patent exclusivity limitations, the Applicant did not seek an indication for the management of fibromyalgia.

2 DOSAGE AND ADMINISTRATION

Dosage and administration guidelines differ from guidelines in Cymbalta labeling because they provide instructions for use by patients who will open the capsule and administer duloxetine delayed-release capsules in applesauce or via nasogastric tube.

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

The contents of the capsule may be added to an all plastic catheter tip syringe with 50 mL of water, shaken for approximately 10 seconds, and delivered via a 12-French or larger nasogastric tube. No granules should be left in the syringe.

Reference ID: 4463875

5 WARNINGS AND PRECAUTIONS

Warnings and precautions regarding suicidal thoughts and behaviors in adolescents and young adults, serotonin syndrome, discontinuation syndrome, activation of mania/hypomania, angle-closure glaucoma, and elevated blood pressure have been revised to include class language.

6 ADVERSE REACTIONS

Adverse event data presented in Section 6 are unchanged from those presented in the Cymbalta label. However, references to fibromyalgia have been replaced with the term “other indication.”

8 USE IN SPECIFIC POPULATIONS

Section 8 (Use in Specific Populations) has been revised to conform to PLLR format.

14 CLINICAL STUDIES

Clinical studies that evaluated the efficacy of duloxetine for management of fibromyalgia have been removed from labeling.

12 Risk Evaluation and Mitigation Strategies (REMS)

No specific risk evaluation and mitigation strategies (REMS) are recommended as the safety profile of duloxetine delayed-release capsules does not differ from the listed drug.

Reference ID: 4463875

13 Postmarketing Requirements and Commitment

No postmarketing requirements or commitments are recommended.

Reference ID: 4463875

14 Appendices

14.1. References

1. Bostwick, JR and A Demehri, 2014, Pills to Powder: A Clinician's Reference for Crushable Psychotropic Medications, Curr Psychiatr, 13(5): e1-e4.

2. Chan, C, KP Yeo, AX Pan, M Lim, MP Knadler, DS Small, 2006, Duloxetine Pharmacokinetics Are Similar in Japanese and Caucasian Subjects, Br J Clin Pharmacol, 63(3): 310-314.

3. Cimmino, MA and C Ferrone, 2011, Epidemiology of Chronic Musculoskeletal Pain, Best Pract Res Clin Rheumatol, 25:173-183.

4. A Gordois, P Scuffham, A Shearer, A Oglesby, JA Tobia, 2003, The Health Care Costs of Diabetic Peripheral Neuropathy in the U.S, Diabetes Care, 26:1790-1795.

5. Institute for Safe Medication Practices, Oral Dosage Forms That Should Not Be Crushed, accessed April 5, 2019, https://www.ismp.org/recommendations/do-not-crush.

6. Kligler, B, MJ Bair, RB Banerjea, L DeBar, S Ezeji-Okoye, A Lisi, JL Murphy, F Sandbrink, DC Cherkin, 2018, Clinical Policy Recommendations from the Veterans Health Administration State-of-the-Art Conference on Non-Pharmacological Approaches to Chronic Musculoskeletal Pain, J Gen Intern Med, 33(Suppl 1):S16-S23.

7. Otte, C, SM Gold, BW Penninx, CM Pariante, A Etkin, M Fava, DC Mohr, AF Schatzberg, 2016, Major Depressive Disorder, Nat Rev, 2:1-20.

8. Stein, MB and J Sareen, 2015, Generalized Anxiety Disorder, N Engl J M, 373(21):2059-2068.

9. Tianmei, S, MP Knadler, MT Lim, KP Yeo, L Teng, S Liang, AX Pan, ED Lobo, 2007, Pharmacokinetics and Tolerability of Duloxetine Following Oral Administration to Healthy Chinese Subjects, Clin Pharmacokinet 46(9):767-775.

10. Volkow, N, H Benveniste, AT McLellan, 2018, Use and Misuse of Opioids in Chronic Pain, Annu Rev Med, 69:451-65.

14.2. Financial Disclosure

The Applicant has submitted signed financial disclosure forms for the clinical investigator.

Covered Clinical Study (Name and/or Number): Study DLT_60C_0324_16

Was a list of clinical investigators provided:	Yes ☒	No ☐
Total number of investigators identified: 1		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in sponsor of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/ arrangements:	Yes ☐	No ☐ N/A ☒
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ N/A ☒
Number of investigators with certification of due diligence (FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ N/A ☒

14.3. Nonclinical Pharmacology/Toxicology

N/A

14.4. OCP Appendices (Technical documents supporting OCP recommendations)

14.4.1. OSIS Memo

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 12/18/2018

TO: Division of Psychiatry Products
Office of Drug Evaluation I

FROM: Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 212516

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the sites listed below. The rationale for this decision is noted below.

Rationale

The clinical site was inspected in March 2017 and the analytical site was inpected in January 2018, which fall within the surveillance interval. The inspections were conducted under the following submissions: (b) (4)

The final classification for the inspections was No Action Indicated (NAI).

Therefore, based on the outcome of the previous inspections and the rationale described above, an inspection is not warranted at this time.

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Sun Pharmaceutical Industries, Ltd., Clinical Pharmacology Unit	Hakeem Abdul Hameed Centenary Hospital 2nd Floor, Jamia Hamdard a.k.a. Hamdard University, Hamdard Nagar, New Delhi, India
Analytical	Sun Pharmaceutical Industries, Ltd., Clinical Pharmacology & Pharmacokinetics	Plot No. GP-5, Sector 18, Udyog Vihar, Industrial Area, HSIDC, Old Delhi – Gurugram Road, Gurugram, Haryana, India

Reference ID: 4463875

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/

ANGEL S JOHNSON
12/18/2018

14.4.2. Individual Study Review

BE Study

Report # DLT_60C_0324_16 Study Period: 12/26/2017-1/17/2018
Title: Single dose crossover four-treatment, four-period, four-sequence bioequivalence study on Duloxetine delayed release capsules 60 mg under fasting condition and to investigate the impact of food and applesauce on bioavailability in healthy, adult, human subjects.

- Objective:
  - To assess the bioequivalence between test product and reference product under fasting condition and to investigate the impact of food and applesauce on bioavailability of test product in healthy, adult, human subjects.
  - To assess the safety of test product and reference product in healthy, adult, human subjects.

- Study Design:

The study was conducted as an open label, balanced, randomized, four-treatment, four-period, four-sequence, single dose crossover bioequivalence study comparing Cymbalta® (Duloxetine) Delayed Release Capsules 60 mg, marketed by Lilly USA with Duloxetine Delayed Release Capsules USP 60 mg of Sun Pharmaceutical Ind. Ltd. under fasting condition and to investigate the impact of food and applesauce on bioavailability in healthy, adult, human subjects. Subjects served as their own control in this study. Sixty-four (64) healthy, adult, human subjects who met all the inclusion and none of the exclusion criteria as described in the protocol were enrolled into the study. Fifty-four (54) subjects completed the study.

Subjects were admitted and housed in the Clinical Pharmacology Unit well in time so as to ensure that at least 10 hours fasting requirement before dose administration is met and were discharged approximately 24 hours after administration of either of the test or reference product during each period of the study. Subjects were made three ambulatory visits, at 36, 48 and 72 hours post dose in each period. Washout period between all four periods was 6 days.

Treatments:
Test Product under fasting condition (Treatment A) and Reference product under fasting

condition (Treatment R):

A single oral dose of either Reference or Test formulation was administered with 240 mL of drinking water at an ambient temperature, after an overnight fasting of at least 10 hours under supervision of trained study personnel in each period of the study.

Test product under fed condition (Treatment B):

After an overnight fast of at least 10 hours, a single oral dose of test product (Treatment B) was administered with 240 mL of drinking water at an ambient temperature, 30 minutes after start of high fat & high calorie breakfast under supervision of trained study personnel during each period of the study.

Test product under fasting with Applesauce (Treatment C):

A single oral dose of test product (Treatment C) was opened and contents were sprinkled on one tablespoon full applesauce. Approximately 15 mL of applesauce was used. That was swallowed by the subject along with 240 mL (milliliter) of drinking water, at an ambient temperature after an overnight fasting of at least 10 hours under supervision of trained study personnel in each period of the study.

Sixty-four (64) subjects fulfilled the inclusion and exclusion criteria in the protocol and were enrolled into the study. Both test and reference products were administered once to 54 study subjects except subject numbers (b) (6) these 10 subjects either dropped out or withdrawn from the study.

• Subject no (b) (6) was dosed with Treatment B in Period I.
• Subject no was dosed with Treatment A and Treatment B in Period I and II respectively.
• Subject no was dosed with Treatment C in period I.
• Subject no was dosed with treatment A in period I.
• Subject no was dosed with Treatment R, Treatment A and Treatment B in Period I, II and III respectively
• Subject no was dosed with Treatment B in period I.
• Subject no was dosed with treatment A in period I.
• Subject no was dosed with treatment B in period I.
• Subject no was dosed with Treatment R and Treatment A in period I and II respectively.
• Subject no was dosed with Treatment A, Treatment B and Treatment C in Period I, II and III respectively.

Meal used meets the FDA Guidance Recommendations: Yes ☑ No ☐

- Blood Sampling Times:

Pharmacokinetics: pre-dose (-1.5) and at 1, 2, 3, 4, 4.5, 5, 5.5, 6, 7, 8, 9, 10, 16, 24, 36, 48 and 72 hours post dose in each period of the study.

- Analytical Method:

Analyte		Duloxetine
Method		LC-MS/MS
Matrix		Plasma
Calibration	Range	0.503 – 159.090 ng/mL
	#Conc	8
	%CV	1.74 – 3.54
	%Bias	-
	R2	0.9984 – 1.0000
Quality Control	Range	0.504 – 269.989 ng/mL
	#Conc	6
	%CV	2.24 – 3.49
	%Bias	-
Performance		Acceptable

- Results:

Study Population

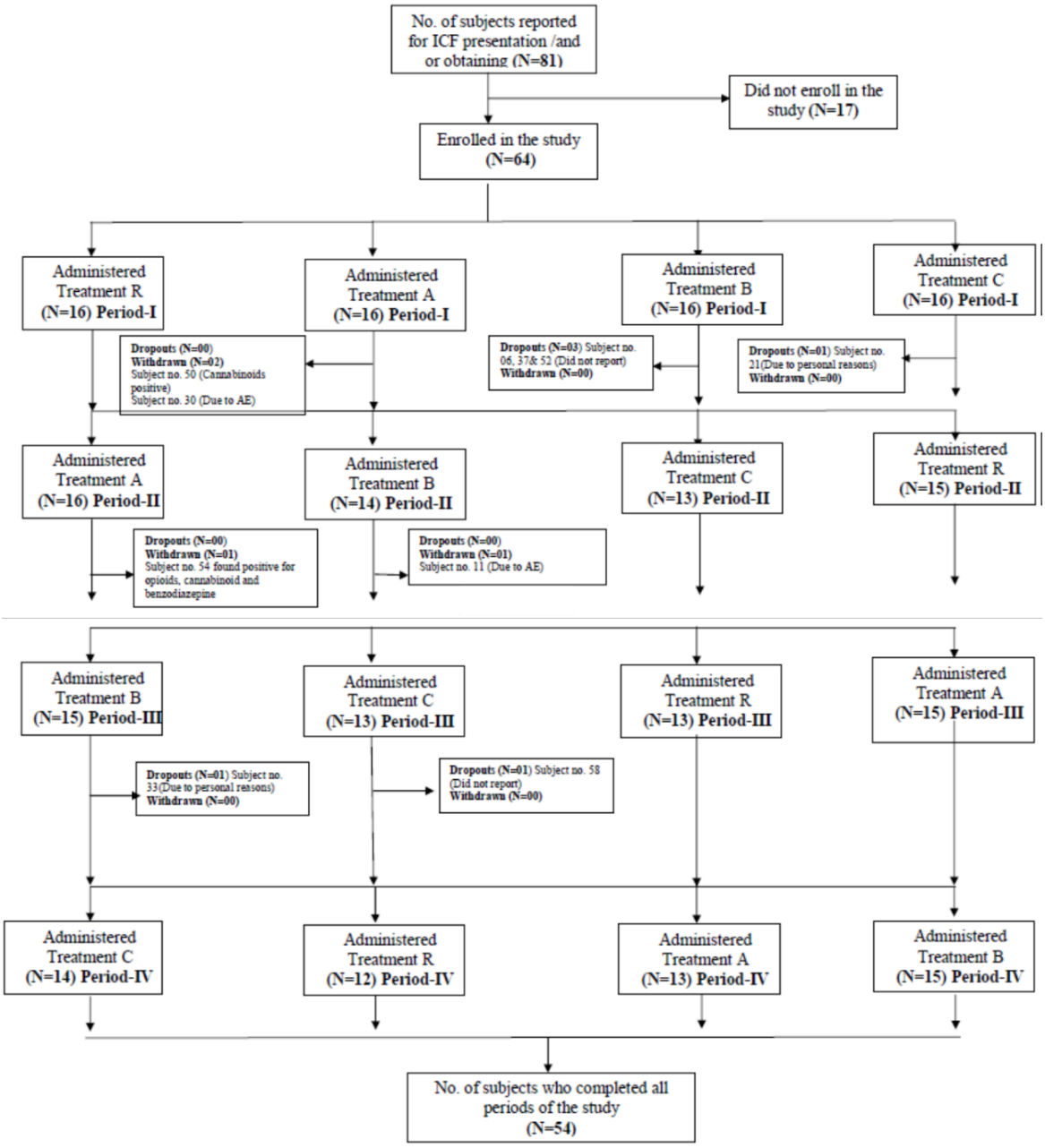
Table 17 Summary of Subject Demographic (Left) and Subjects Completing the Bioequivalence Study (Right)

Reference ID: 4463875

	Subjects enrolled in the study (N = 64)
Age (years)	
Mean ± SD	28.72 ± 6.55
Range	18 - 43
Groups	
< 18	0 %
18 – 40	61 (95.31%)
41 – 64	03 (4.69%)
65 – 75	0 %
> 75	0 %
Sex	
Female	0 %
Male	64 (100 %)
Race	
Asian	64 (100 %)
Black	0 %
Caucasian	0 %
Hispanic	0%
Others	0 %
Height (cm)	
Mean ± SD	166.43 ± 5.61
Range	154.4 –180.0
Weight (kg)	
Mean ± SD	61.54 ± 8.01
Range	47.5 – 85.2
Smokers	
Yes	05 (7.81%)
No	59 (92.19%)

	Subjects who completed the study (N = 54)
Age (years)	
Mean ± SD	28.93 ± 6.58
Range	18 - 43
Groups	
< 18	0 %
18 – 40	52 (96.30 %)
41 – 64	02 (3.70 %)
65 – 75	0 %
> 75	0 %
Sex	
Female	0 %
Male	54 (100 %)
Race	
Asian	54 (100 %)
Black	0 %
Caucasian	0 %
Hispanic	0%
Others	0 %
Height (cm)	
Mean ± SD	166.87 ± 5.75
Range	154.4 –180.0
Weight (kg)	
Mean ± SD	62.48 ± 8.05
Range	47.5 – 85.2
Smokers	
Yes	04 (7.41%)
No	50 (92.59%)

Figure 4 Subject Enrollment and Disposition by Treatment Sequence



Pharmacokinetics

Bio-analysis of samples from completed subjects (N=54) were performed. Subject no(s) (b) (6) did not complete clinical phase of the study. Samples from these subjects were also analyzed as per study protocol of this bio-study. Subject (b) (6) were considered during pharmacokinetic evaluation as these subjects completed at least two periods of the study (as defined in study protocol). Therefore, pharmacokinetic and statistical evaluation was performed on datasets from fifty-seven (57) subjects. The results are summarized below.

Table 18 Summary of Pharmacokinetic Parameters for Duloxetine

Product/Statistics	Cmax* (ng/mL)	AUC0-t* (ng.h/mL)	AUC0-inf* (ng.h/mL)
Test Product A (Under Fasting Condition)			
Geometric Mean	50.1583	758.8185	789.6574
CV(%)	41.01	52.98	52.41
N	57	57	57
Test Product B (Under Fed Condition)			
Geometric Mean	49.8663	857.2361	887.1042
CV(%)	47.14	48.97	49.00
N	56	56	56
Test Product C (Under Fasting with Applesauce)			
Geometric Mean	50.9218	748.1728	793.6328
CV(%)	43.50	61.71	61.12
N	55	55	53
Reference Product R (Under Fasting Condition)			
Geometric Mean	51.2915	789.3683	801.7941
CV(%)	43.20	52.08	49.74
N	56	56	55
Least squares mean			
A	49.9291	753.9644	784.7514
B	49.5721	854.3575	884.3826
C	50.9866	752.9041	788.5707
R	51.9073	795.5450	822.3786
Ratio of least squares mean			
(A/R)%	96.18	94.77	95.42
(B/A)%	99.28	113.31	112.69
(C/A)%	102.11	99.85	100.48
90% Confidence Intervals (A/R)			
Lower Limit:	88.97	88.59	89.35
Upper Limit:	103.99	101.38	101.91
90% Confidence Intervals (B/A)			
Lower Limit:	91.83	105.92	105.56
Upper Limit:	107.34	121.22	120.30
90% Confidence Intervals (C/A)			
Lower Limit:	94.40	93.30	94.00
Upper Limit:	110.46	106.87	107.40
p-value[ANOVA]			
Formulation	0.7617	0.0065	0.0105
Period	0.0020	<.0001	0.0001
Sequence	0.9697	0.9357	0.9151
Power (%)	99.64	99.97	99.98
Intra-subject CV(%)	25.39	21.87	21.17

* Log-transformed parameters, the antilog of the mean (i.e. the geometric mean) is reported

Table 19 Ratios of LSM for log-transformed pharmacokinetic parameters [Cmax, AUC0-t and AUC0-∞] for Duloxetine (90% Confidence Interval)

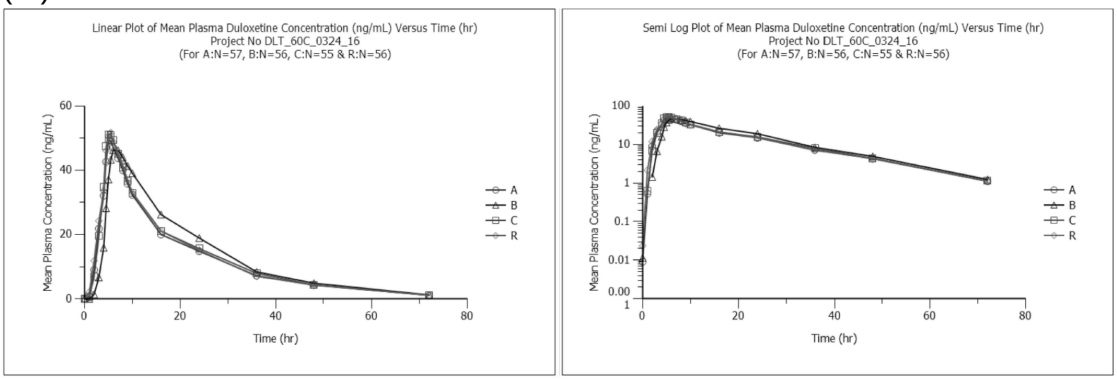
Parameter	Test (A) vs Reference (R)
C_{max}	96.18 % (88.97 % – 103.99%)
AUC_{0-t}	94.77 % (88.59 % – 101.38 %)
$AUC_{0-\infty}$	95.42 % (89.35 % – 101.91%)

Parameter	Test (B) vs Test (A)
C_{max}	99.28 % (91.83% – 107.34%)
AUC_{0-t}	113.31 % (105.92% – 121.22 %)
$AUC_{0-\infty}$	112.69 % (105.56% – 120.30%)

Parameter	Test (C) vs Test (A)
C_{max}	102.11 % (94.40 % – 110.46%)
AUC_{0-t}	99.85 % (93.30% – 106.87%)
$AUC_{0-\infty}$	100.48 % (94.00 % – 107.40%)

The mean Tmax value for Duloxetine was 5.0360 hours for Reference product (R).
The mean Tmax value for Duloxetine was 5.0529 hours for Test product (A).
The mean Tmax value for Duloxetine was 6.7423 hours for Test product (B).
The mean Tmax value for Duloxetine was 5.1730 hours for Test product (C).

Figure 5 linear and Semi-log Plot or Mean Plasma Duloxetine Concentration (ng/ml) Versus Time (hr)



- Safety: Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Thirty (30) adverse events including one (01) laboratory abnormality adverse events were reported in the study. The adverse events were mild to moderate in severity and not serious in nature

- Conclusion:

Fasting Bioequivalence:

The 90% confidence interval for the ratio of the test (Treatment A) to reference (R) product average (least squares means) for pharmacokinetic parameters (Cmax, AUC0-t and AUC0-∞) was within 80-125% for log-transformed data.

Based on these results, single oral dose of Duloxetine Delayed Release Capsules USP 60 mg manufactured by Sun Pharmaceutical Industries. Ltd with Cymbalta® (Duloxetine) Delayed Release Capsules 60 mg, marketed by Lilly USA are bioequivalent in healthy adult human male subjects under fasting condition.

Impact of food and apple Sauce on Bioavailability:
The 90% confidence interval for the ratio of the test (Treatment B) to test (Treatment A) and test (Treatment C) to test (Treatment A) product average (least squares means) for pharmacokinetic parameters (Cmax, AUC0-t and AUC0-∞) was within 80-125% for log transformed data.

Based on these results, Food and Applesauce does not have any impact on bioavailability of Duloxetine Delayed Release Capsules USP 60 mg manufactured by Sun Pharmaceutical Industries. The ratio and 90% CIs for rate and extent of absorption were within the range of 80-125%, when administered either with apple sauce or with a high fat meal in healthy adult human subjects.

The Test (Treatment A, Treatment B and Treatment C) and Reference (R) products were well tolerated by the study subjects. Thirty (30) adverse events including one (01) laboratory abnormality adverse events were reported in the study. The adverse events were mild to moderate in severity and not serious in nature.

Reviewer's comments

Design elements:

- Dose: the study was conducted at 60mg for the delayed-release capsules. As 60mg is the highest to-be-marketed strength of the capsule, it meets guidance recommendation.

- Food: high fat, high calorie breakfast provided after an overnight fast of at least 10 hours in the study. This meets Guidance recommendation.

- Water: water should be restricted from 1 hour prior to drug administration until 1 hr postdose (except the water administered with the drug). The sponsor did not mention if water was restricted during the study. However, according to the protocol, subjects will be restricted from drinking water from 1 hour pre-dose to 2 hours post-dose, no protocol violations were reported regarding water restriction. This follows Guidance recommendation.

- Design: the study deployed a randomized, four-period, four-treatment, four-sequence, crossover design. Although there are more treatment arms than a standard two-period crossover, it is considered a valid design for the study objectives.

Reference ID: 4463875

- Washout period: the washout period between all four periods were 6 days. It is considered adequate to avoid any potential carryover effect, considering the half-life of duloxetine is about 12 hours.

- Subjects: healthy subjects were enrolled in the study, prior and concomitant medication use were restricted from 30 days prior to the onset of the study until the completion of the study. This avoided potential confounding effects that might affect the PK of duloxetine. However, in this study, only Asian male subjects were included. According to Cymbalta clinical pharmacology review (Dated: 8/23/02), women have 2-fold higher exposures than men on average, with possible lower expression of CYP1A2. In addition, previous studies have found that exposures in Asian populations are approximately half of those in Caucasians, Blacks and Hispanics with single dose administration whereas multiple dosing exposures are similar. This is probably because CYP2D6 PMs are found in 6-10% of the Caucasian population, ~2% of Blacks and ~1% of Asian. There also appears to be a common allelic variant in Asians that results in higher clearances and lower exposures on average. Overall, considering the study objectives, subject selection in this study appears to be acceptable.

- PK sampling scheme: blood samples were collected 72 hrs post dose and the sampling frequency was considered reasonable. It is adequate to capture the PK profile for duloxetine, and for accurate PK parameter estimation, considering the half-life of duloxetine is about 12 hours.

Study Conduct (protocol deviation):
PK related protocol deviations in each period are summarized in the table below. The deviations included either missed PK samples or delayed PK sampling. Missed PK samples are all around 36, 48 or 72 hours, considering that these are the last three PK samples during each period, the overall PK shape and parameter estimates are not considered to be significantly impacted. For delayed PK sampling, the delay ranges from 3 mins to 101 mins, and most of delay occurs at 48 and 72 h time points, therefore, the overall PK shape and parameter estimates are not considered to be significantly compromised.

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Subject Number	Time Point (Hours post dose)	Deviations		Comments
		Minutes	Late/Early	
Period - I				
(b) (6)	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	72.000	-	-	Did not report for sample
	72.000	-	-	Did not report for sample
	48.000	+94	Late	Subject arrived late
	48.000	+76	Late	Subject arrived late

Subject Number	Time Point (Hours post dose)	Deviations		Comments
		Minutes	Late/Early	
Period - II				
(b) (6)	5.500	+03	Late	Subject arrived late
	16.000	+03	Late	Difficulty with veins
	2.000	+03	Late	Difficulty with veins
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	72.000	-	-	Did not report for sample
	72.000	-	-	Did not report for sample
	72.000	+76	Late	Subject arrived late
	48.000	+73	Late	Subject arrived late
	48.000	+79	Late	Subject arrived late
	48.000	+77	Late	Subject arrived late
	48.000	+79	Late	Subject arrived late
	72.000	+73	Late	Subject arrived late
	48.000	+70	Late	Subject arrived late

Subject Number	Time Point (Hours post dose)	Deviations		Comments
		Minutes	Late/Early	
Period - III				
(b) (6)	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	72.000	-	-	Did not report for sample
	6.000	+03	Late	Difficulty with veins
	36.000	-	-	Did not report for sample
	48.000	+80	Late	Subject arrived late
	48.000	+71	Late	Subject arrived late
Period - IV				
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	36.000	-	-	Did not report for sample
	48.000	-	-	Did not report for sample
	8.000	+03	Late	Difficulty with veins
	48.000	+87	Late	Subject arrived late
	72.000	+101	Late	Subject arrived late

Data Analysis

- Treatment compliance: Sixty-four (64) subjects fulfilled the inclusion and exclusion criteria in the protocol and were enrolled into the study. Both test and reference products were administered once to 54 study subjects except subject numbers (b) (6) these 10 subjects either dropped out or withdrawn from the study. Subject (b) (6) were considered during pharmacokinetic evaluation as these subjects completed at least two periods of the study (as defined in study protocol). Therefore, pharmacokinetic and statistical evaluation was performed on datasets from fifty-seven (57) subjects.

- Missed PK samples: In each period, several subjects did not report PK samples at around 36, 48 or 72 hours. Considering that these are the last three PK samples during each period, and AUC0-36 accounts for 3 half-lives for duloxetine, the missed PK samples are not considered to have significant impact on the PK profiles of duloxetine.

- Measurable predose concentrations: predose levels of duloxetine were measurable in several occasions as shown in the table below. However, a calculation of the ratio to Cmax is less than 5%. Therefore, it is acceptable to include the subjects in the PK analysis.

S. NO.	Subject (b) (6)	Period	Treatment
1		IV	B
2		II	R
3		III	R

- BE metrics: Traditional BE metrics (i.e., Cmax, AUC0-t and AUCinf) were included in the analysis. This meets recommendations from the general BE guidance.

PK results:

- Extrapolation: mean extrapolation from AUCt to AUCinf was less than 6% for each treatment, indicating reliable estimation of PK parameters.

- For duloxetine, the average PK parameters (Cmax, AUCt and AUCinf) meet bioequivalence criteria, suggesting similar average pharmacological effects after administration of Duloxetine Delayed Release Capsules USP 60 mg manufactured by Sun Pharmaceutical Industries. Ltd and Cymbalta® (Duloxetine) Delayed Release Capsules 60 mg, marketed by Lilly USA. In addition, food and applesauce does not have any impact on bioavailability of Duloxetine Delayed Release Capsules USP 60 mg manufactured by Sun Pharmaceutical Industries.

Overall Comments:

A linkage between Duloxetine Delayed Release Capsules USP 60 mg manufactured by Sun Pharmaceutical Industries. Ltd and Cymbalta® (Duloxetine) Delayed release capsules 60 mg, marketed by Lilly USA has been established through the bioequivalence study. Food is not considered to have a clinically significant effect. This capsule can be administered with or without food. The capsule can be sprinkled on applesauce for administration.

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/s/

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