MEMORANDUM	Division of Medication Errors and Technical Support Office of Surveillance and Epidemiology HFD-420; White Oak 22, Room 4447 Center for Drug Evaluation and Research

To: Thomas Laughren, MD
Director, Division of Psychiatry Products, HFD-130

Through: Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Richard Abate, R.Ph., MS, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

Date: March 8, 2007

Subject: **DMETS MEDICATION ERROR POSTMARKETING SAFETY REVIEW**
OSE Consult: 2006-879
Cymbalta
Duloxetine Hydrochloride Delayed-release Capsules
20 mg, 30 mg, and 60 mg
NDA: 21-427 & 21-733

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I. EXECUTIVE SUMMARY

During routine post-marketing surveillance of medication errors, DMETS identified a signal involving the opening of Cymbalta capsules prior to administration to achieve a lower dose of the drug. The patient experienced severe nausea and vomiting resulting in an emergency room visit.
This prompted DMETS to investigate all medication error cases from the FDA-AERS database, the USP MedMARX database, Institute of Safe Medication Practices outpatient medication errors, and internet discussion groups. In total, [redacted] cases of medication error were reviewed and classified by the following errors types: wrong strength, wrong technique of opening the capsules, and wrong drug. Significant outcomes associated with these error types include esophageal burning and other GI symptoms, elevated blood pressure, and serotonin syndrome. For each of these error types, we identified contributing factors associated with the container label, carton and insert labeling. To avert further errors of these types, DMETS recommends changes to the labels and labeling to reduce the potential for these errors to continue. The container labels for each strength need editing to decrease the similarity between strengths, such as use of different color for the 20 mg label, the use of better contrast in the display of the 20 mg and 30 mg strengths, and removal of the Cymbalta logo and capsule picture from the primary display panel. In an effort reduce the potential of confusion between Cymbalta and Strattera, we recommend the sponsor alert healthcare providers of this error. In addition, we recommend the additional warnings of opening of the

capsules be added to the labels and labeling. These and other label and labeling recommendations can be found in Section IV of this review.

II. BACKGROUND

PRODUCT INFORMATION

Cymbalta is was initially approved August 4, 2004. It is approved for the following indications: Major Depressive Disorder, Diabetic Peripheral Neuropathic Pain, and, most recently, General Anxiety Disorder. It is available as 20 mg, 30 mg, and 60 mg delayed-release capsules. Oral doses of Cymbalta begin at 20 mg twice daily or 30 mg daily, depending on the indication, and may be increased to 120 mg daily or 60 mg twice daily.

III. INVESTIGATION OF CONTRIBUTING FACTORS TO ERRORS

During routine monitoring of medication errors, DMETS received a case where a patient intentionally opened a Cymbalta capsule to achieve a lower dose. The reporter of this case was the prescriber who stated he reviewed the package insert and did not see a statement indicating not to open the capsules; therefore, he instructed the patient to open the 20 mg capsule to achieve a 10 mg dose of Cymbalta. The patient experienced severe nausea and vomiting resulting in an emergency room visit.

DMETS reviewed the current and historical package insert labeling. We note the "Information for Patient" section does state, "Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating." This information is found in all versions of the package insert labeling since approval. However, neither the carton labeling or label do not explicitly state not to open the capsules.

A. DATABASE SEARCHES

1. FDA Adverse Event Reporting System (AERS)

The FDA Adverse Event Reporting System (AERS) was searched using the MedDRA high level group term (HLGT) "medication error" and the preferred term (PT) "pharmaceutical product complaint" along with the active ingredient name of duloxetine, the trade name Cymbalta and the verbatim names "Cybal%" and "Duloxe%." This search resulted in 299 cases. Of these 299 cases, the following 220 cases were determined not to warrant further action from a medication error perspective:

- Sixty-six (n=66) cases resulted from intentional overdoses.
- Sixty (n=60) cases were results of adverse events without a medication error.
- Fifty-three (n=53) cases resulted from exposure during pregnancy.
- Twenty-three (n=23) cases involved Cymbalta as a secondary or concurrent medication not involved in the error.
- Eight (n=8) cases involved drug-drug interactions for which the product is labeled.
- Eight (n=8) cases were accidental pediatric exposure resulting from children getting access to parent's medication.

•Two (n=2) cases involved deteriorated capsules which were not used by the patient. The remaining 79 cases are discussed below.

a. Omissions (n=24)

Twenty-four (n=24) cases involved the omission of Cymbalta doses. Of these cases, eight (n=8) resulted from patients who were non-compliant with their medication and simply stopped taking the drug. Seven (n=7) cases involved patients who missed doses of Cymbalta for unknown reasons. Four (n=4) cases involved patients who missed doses because they ran out of medication. Two patients could not afford to purchase the prescription refills. Three (n=3) cases involved patients who were away from home without their medication. The final two (n=2) cases involved patients who never started their Cymbalta therapy.

b. Improper Dose – Resulting in Overdose (n=22)

Twenty-two (n=22) cases involved patients receiving an overdose of Cymbalta. Of these 22 cases, ten (n=10) cases involved the patient taking two or three capsules for a dose rather than the one capsule after a new strength was prescribed. Six (n=6) of the 22 cases involved the patients taking more than the prescribed dose for an unknown reason. The increased dose in these cases was not associated with the intent to harm themselves. Three (n=3) cases involved prescribed doses greater than the labeled 120 mg per day. Two (n=2) cases involved overdoses while the patient was hospitalized. One patient received a overdose as result of a transcription error. The other reporter did not have enough detail to determine a cause. The final (n=1) case involved a patient being weaned off of Cymbalta who chose to continue the 60 mg capsules and take a dose every other day rather than pay for a new prescription.

c. Wrong Technique (n=9)

Nine (n=9) cases involved opening the Cymbalta capsules prior to administration. Of these nine cases, two (n=2) cases involved opening the capsules and dissolving the medication in water to administer it down a feeding tube. Two (n=2) cases involved attempting to start Cymbalta therapy at a low dose. One (n=1) case involved a patient opening the capsules following gastric bypass surgery as she felt the capsules were too large to swallow orally. One (n=1) case involved opening 20 mg capsules while tapering off of Cymbalta to avoid withdrawal effects. One (n=1) case resulted from a patient opening the capsule and sprinkling on yogurt per prescriber instruction to reduce the esophageal burning she experienced while taking Cymbalta. One (n=1) case involved a patient who experienced an arrhythmia after receiving Cymbalta attempting to decrease the risk of this effect by opening the capsules to split the dose and take it twice daily rather than daily as prescribed. The final (n=1) case involved a patient who opened the capsule to take the dose slowly over one hour. The prescriber instructed the patient to open the capsules in two of the aforementioned cases. (See Appendix A)

d. Wrong Strength (n=7)

Seven (n=7) cases involved the wrong strength of Cymbalta being dispensed to or taken by the patient. Of these seven cases, three (n=3) cases involved patients taking the 60 mg capsule at the start of therapy rather than 30 mg for the first week as prescribed. In two of these cases, the patients were given 30 mg and 60 mg capsules as samples to begin Cymbalta therapy. Two (n=2) of the seven cases involved the pharmacy dispensing the wrong strength of Cymbalta to the patient. These cases were reported by the receiving patients, therefore causes were not determined. One (n=1) case involved a pharmacy filling a prescription for 20 mg capsules with 30 mg capsules as the pharmacist was unaware a 20 mg strength capsule existed. The final (n=1) of these cases involved a patient taking a 30 mg capsule of Cymbalta rather than his prescribed 60 mg capsule, but the reporter provided minimal details for DMETS to determine a cause. (See Appendix B)

e. Improper Dose – Extra dose (n=7)

Seven (n=7) cases involved the patient receiving an extra dose of Cymbalta. Of these seven cases, five (n=5) cases resulted from the patient forgetting they had taken their dose for the day and redosing themselves in a few hours. One (n=1) case resulted from the patients prescription being changed from 30 mg twice daily to 60 mg daily. The patient misunderstood the direction for use. The final (n=1) case the patient took Cymbalta 60 mg twice a day instead of the prescribed daily frequency. The case contained minimal details for DMETS to determine a cause. DMETS has no recommendations to possibly reduce these errors.

f. Wrong Drug (n=5)

Five (n=5) cases involved the confusion of Cymbalta with another medication. Of these five cases, two (n=2) cases involved confusion with Symbyax. One case was a report from a pharmacy intern who noted these names sound-like. The other case resulted from a patient whose therapy was switch from Cymbalta to Symbyax. The patient took a capsule of Cymbalta rather than the ordered Symbyax two months after Symbyax therapy was started. One (n=1) case involved confusion of Cymbalta with Strattera. One (n=1) case involved the patient prescribed Duloxetine and received paroxetine. The final (n=1) case involved confusion between Duloxetine and Naproxen. (See Appendix C)

g. Wrong Patient (n=1)

One (n=1) case involved the wrong patient receiving Cymbalta. A patient took one dose of a friend’s prescription of Cymbalta. Minimal details were included for DMETS to determine a cause.

h. Wrong Route of Administration (n=1)

One (n=1) case involved a snorting Cymbalta rather than taking it orally as prescribed. Minimal details were included for DMETS to determine a cause.

i. Others (n=3)

Three (n=3) cases involved no specific error type. Two (n=2) cases provided minimal details by only stating a medication error occurred. One (n=1) case involved a physician raising concerns over the labeling in the Physician's Desk Reference regarding gastric emptying.

2. USP MedMARX Search[***]

Upon DMETS request, the US Pharmacopeia searched its MedMARX[***] database to provide DMETS with additional error cases involving Cymbalta. The database was searched for all cases involving Cymbalta. This search provided DMETS with 304 additional medication error cases to evaluate for causality. Four (n=4) of these cases were eliminated as Cymbalta was a secondary medication not involved in the error. A summary of the remaining 300 cases appear below.

a. Seventy (n=70) cases involved the omission of a Cymbalta dose. The causes of these errors relate to the processes within an institution but do not relate specifically to the product.

b. Forty-four (n=44) cases involved the wrong strength of Cymbalta. Thirty-nine of these errors occurred during the dispensing of Cymbalta in both inpatient and outpatient settings. This suggests the packaging, carton labeling or container labels may contribute to these errors.

c. Twenty-six (n=26) cases involved an improper dose resulting in an extra dose of Cymbalta administered to the patient. The causes of these errors relate to the processes within an institution but do not relate specifically to the product.

d. Nineteen (n=19) cases involved the wrong patient receiving the medication. Improper patient identification or patient selection in the computer system were the causes in these cases.

e. Fourteen (n=14) cases involved an improper dose of Cymbalta resulting in under dose. These resulted from dose changes that were missed.

f. Fourteen (n=14) cases involved the patient receiving Cymbalta for the wrong duration of time. These errors resulted from the discontinuation date being incorrectly transcribed either manually or electronically.

g. Thirteen (n=13) cases involved an improper dose of Cymbalta resulting in an overdose. These cases were prescribing and order entry errors. DMETS was unable to determine causes from the data provided.

h. Thirteen (n=13) cases involved the wrong drug. The patient received the wrong drug in ten of these cases. When the patients were ordered Cymbalta, they received Strattera (n=2), Diltiazem (n=1), Geodon (n=1), and Lexapro (n=1). The patients

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received Cymbalta when they were ordered the following medications: Carbidopa (n=1), Celexa (n=1), Fluoxetine (n=1), Geodon (n=1) and Strattera (n=1).

i. Eleven (n=11) cases involved Cymbalta administered at the wrong time. The causes of these errors relate to the processes within an institution but do not relate specifically to the product.

j. Nine (n=9) cases involved drug-drug interactions which were caught prior to patient receiving the medications.

k. Two (n=2) cases involved drug-disease interactions. Pharmacists intercepted orders for Cymbalta on patients with elevated liver enzymes and contacted prescribers to change therapy.

l. Two (n=2) cases involved the wrong dosage form. These cases provided DMETS with no detail to determine a cause.

m. One (n=1) case involved wrong technique. In this case, the patient had a feeding tube, and the capsule was opened and dissolved in water prior to administration.

n. Sixty-two (n=62) cases involved no specific error type and are believed to be errors in the medication use process. Such errors include incomplete orders or prescription, non-formulary medications are handled incorrectly or without all the necessary paper work, or the use of unacceptable abbreviations.

3. Institute of Safe Medciation Practices Outpatient Medication Errors***

Upon DMETS request, the Institute for Safe Medication Practices (ISMP) searched their database for outpatient medication errors involving Cymbalta. The database was searched from July to November 2006. The search provided DMETS with an additional [redacted] cases. These cases did not include narratives but included some causality data. Of these cases, [redacted] involved the wrong strength. [redacted] cases involved wrong drug. The remaining [redacted] cases involved the wrong [redacted].

4. Internet Discussion Groups

DMETS searched the internet for discussion groups for patients relating their experiences with Cymbalta. While the concerns of these discussion groups generally focus on experiences with adverse events, DMETS noted within the www.mytherapy.com discussion for Cymbalta two cases (n=2) of patients opening capsules prior to administration.

*** **The Institute of safe Medication Practices medication errors contains confidential and proprietary data, which cannot be shared outside the FDA.**

B. SAFETY EVALUATOR RISK ASSESSMENT

In review of the cases received from AERS, MedMARX, and INSTITUTE OF SAFE MEDICATION PRACTICES*** databases as well as review of the www.mytherapy.com discussion group, the cases can be categorized as follows: wrong strength (n=), omission (n=94), wrong drug (n=), improper dose resulting in overdose (n=35), improper dose resulting in extra dose (n=33), wrong patient (n=20), drug-drug interactions (n=17), improper dose resulting in an underdose (n=14), wrong duration of therapy (n=14), wrong technique (n=12), wrong time of administration (n=11), and wrong route of administration (n=1). Of these types of errors, the ones the FDA may have some role in minimizing are wrong technique, wrong strength and wrong drug. Although cases involving the opening of capsules have been reported in both the AERS database and the MedMARX databases, the errors involving wrong strength and wrong drug occur frequently and in all three databases.

1. Opening of capsules prior to administration (n=12)

In total, twelve cases involving the opening of capsules prior to administration of Cymbalta were retrieved. Three cases report the patients had feeding tubes. One case reports a gastric bypass patient who thought the capsule would obstruct her stomach. Four cases report patients attempted to decrease side-effects of Cymbalta. Three cases report patients attempt to take a lower dose than prescribed or available, and the final case describes opening the capsules to slowly take the first dose for an unknown reason.

a. Patients attempting to reduce or avoid adverse effects of Cymbalta (n=7)

Patients may experience adverse events with Cymbalta. Three cases (n=3) reported patients opening the capsule to decrease the adverse effects of Cymbalta they experienced. These adverse effects include arrhythmia, elevated blood pressure, and esophageal burning. In one of these cases, the physician instructed the patient to sprinkle the contents on yogurt to decrease the esophageal pain she was experiencing. Three cases (n=3) reported patients opening the capsules to create a dose of Cymbalta less than 20 mg in an attempt to reduce the adverse events associated with the discontinuation of Cymbalta. In the remaining case (n=1), the prescriber attempted to reduce the potential of an adverse event by instructing a patient “sensitive to antidepressants” to open the capsule and take half the dose.

The package insert labeling states the following in the Information for Patients subsection: “Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the contents be sprinkled on food or mixed with liquids. All of these might affect the enteric coating.” However, this statement does not note that adverse effects could increase if the capsule is opened. The package insert labeling states the potential for adverse events upon discontinuing Cymbalta in the PRECAUTIONS section. One prescriber stated he read the package insert prior to recommending to his patient to open the capsule. This suggests the caution against opening the capsule is not clear and ambiguous to potentially problematic outcomes. A revision to this warning may help strengthen this caution. Additionally, this warning does not appear in the Dosage and Administration section of the labeling or on the

container label or the carton labeling. DMETS' recommendations are outline in Section IV C of this review.

b. Patients with feeding tubes or trouble swallowing (n=4)

It is common practice for medications not available in liquid formulations but available as capsules to be administered via feeding tubes after mixing the content of the capsule with water or some other liquid. This method of administration can be utilized for delayed-release capsules (e.g. Prevacid). Therefore, healthcare providers are accustomed to using this method of administration. We believe this is the main contributing factor to this behavior. DMETS believes the recommendations outlined in Section IV C will provide the needed information to healthcare providers to reduce the potential for this type of error.

2. Wrong strength (n=)

A total of cases involved either selecting, dispensing, or administering the wrong strength of Cymbalta. The common cause identified within the cases is that the package is similar between the commercially available sizes as well as the professional samples.

a. Similarity of container labels (30 and 60 count) (n=50)

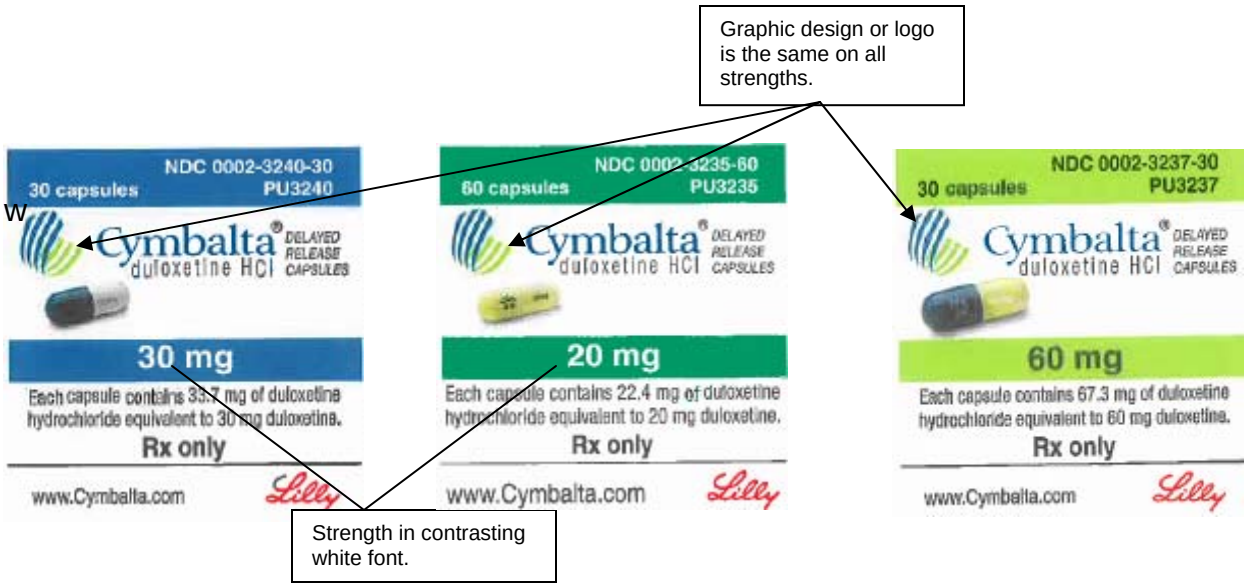
The bottles containing 30 capsules of Cymbalta in 30 mg and 60 mg strengths and 60 capsules in 20 mg strength are the same size and color. The colors used to distinguish strength range from blue to green to light green. The blue color of the 30 mg strength is similar to the darker green of the 20 mg strength. In addition, both the 20 mg and the 60 mg capsules are labeled with different shades of green. The labels appear in Figure 1 on page 9.

Not only are the colors very similar, but the strength presentation on both the 20 mg and 30 mg strengths appear in a contrasting white font which provides additional similarity between the packaging. In addition, the graphic design next to the proprietary names is identical on all strengths thus, providing additional similarity between the different strengths.

Pictures of the capsules are displayed on the labels to provide an additional means of identifying the strength. While the 20 mg capsule is a single color, the 30 mg and 60 mg strengths are dual color capsules, but they are also similar because the same color scheme is used for all capsules. For example, the 20 mg capsule is yellow, the 30 mg capsule is blue and white and the 60 mg capsule is blue and yellow. The contrasting colors (white and yellow) of the 30 mg and 60 mg capsules look similar which also contributes to the potential for selecting the wrong strength as pharmacy personnel may look at the capsule on the label rather than reading the strength.

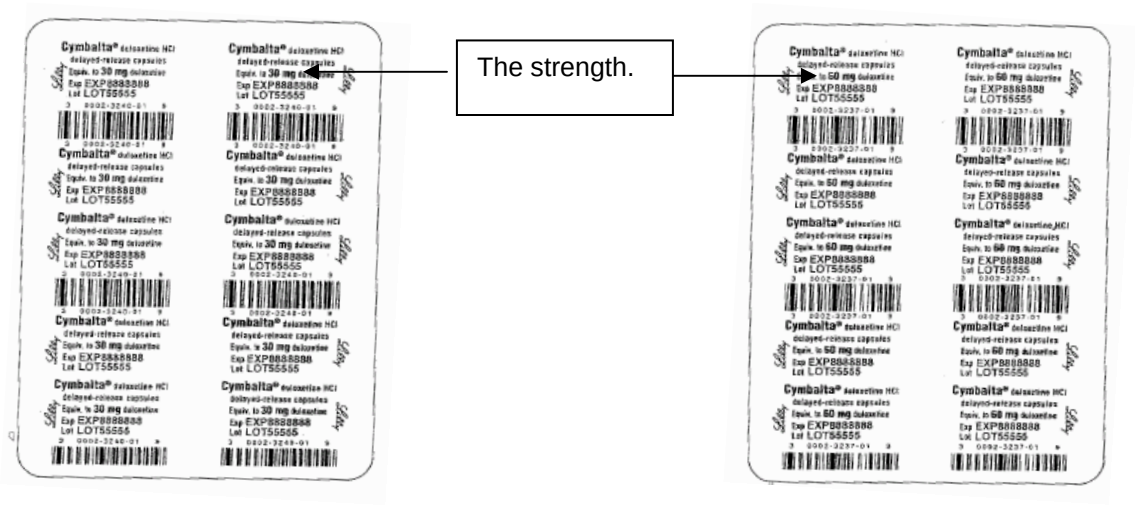
DMETS believes the pictures on the main display panel create a potential for confusing the strengths more than providing confirmation of identity. DMETS recommends revising the labels and labeling as outlined in Section IV B to minimize this type of error..

Figure 1. Container labels for Cymbalta



Cymbalta 30 mg capsules **Cymbalta 20 mg capsules** **Cymbalta 60 mg capsules**

Figure 2. Identi-Dose® unit-dose container labels for Cymbalta



Cymbalta 30 mg capsules **Cymbalta 60 mg capsules**

b. Similarity of unit-dose capsules container labels (n=23)

The Identi-dose® unit-dose labels are nearly identical (see Figure 2 above.) The only difference found on these labels is the strength and the barcode. The problem arises for institutions using these products that do not utilize barcode scanners in selecting or administering medications to patients. It is very difficult to distinguish the strength on these labels when comparing these labels side by side. This indistinction has resulted in the wrong strength being placed or returned to the incorrect medication bin in the pharmacy or automated dispensing cabinet compartments. In order to avert this type

of error, DMETS recommends revising the labels and labeling as outlined in section IV A.

c. Similarity of professional sample labeling (n=2)

Prescribers provide patients with samples for both the 30 mg and 60 mg strengths so that the patient can gradually titrate to the desired goal dose of 60 mg. The prescriber intends for the patient to take the 30 mg capsules for one week followed by the 60 mg capsules. The titration is generally achieved over seven to 14 days. Physician samples contain seven capsules which equates to a week's supply of medication. In the two case reports, patients took the 60 mg capsules first when given both of these professional samples at the start of therapy.

These errors stem from the similarity of the capsule on the principal display panel in addition to the fact the products are supplied in separate containers. The container label and carton labeling appear in Figure 3 below. The information on the main panel appears in a similar location for both strengths. The colors of blue and light green contrast the differences of the strengths. However, the capsules displayed on the main panel look very similar as noted in section III B 2 a. If the patient uses the picture of the capsule rather than the stated strength to select a dose, there is a potential to confuse these strengths. If the professional samples were only available in the 30 mg strength, the potential for these errors to occur would be eliminated.

Figure 3. Professional sample carton labeling and container labels for Cymbalta

Cymbalta 30 mg **Cymbalta 60 mg**

3. Wrong Drug (n=)

A total of cases involved the wrong drug. Two cases report confusion between Symbyax and Cymbalta. One case stated the potential for confusion between these names, and the remaining case stems from the patient's therapy change and her impaired judgment related to drug abuse. (See Appendix C) This potential confusion was discussed in OSE consults #01-0167-1 dated June 20, 2003, #01-0167-3 dated March 3, 2004 and

01-0167-4 dated June 30, 2004. DMETS determined this potential sound-alike confusion could be address and avoided if education was completed at launch of Cymbalta. We are unaware if this education was ever provided to healthcare providers. These cases occurred October 7, 2004 and April 6, 2006. Therefore, DMETS believes the sound-alike similarities between Symbyax and Cymbalta are not currently contributing added risk for medication errors.

Ten cases (n=10) report confusion between Cymbalta and Strattera. These cases were derived from every source and involve selecting and dispensing the wrong medication to the patient. While the source of the prescription were identified in 6 of these cases (written n=3; verbal n=2, and computer generated n=1.) Five of these six cases provide enough detail to see these as a drug selection error. In addition, the reporters list the similarity in packaging as a cause for these errors. DMETS review of the current labels of Cymbalta and Strattera revealed that these products have the same sponsor and therefore similar packaging. In addition, the container labels appear to share a similar color blue. However, the label design and layout do not appear similar. Examples of container labels for Strattera and Cymbalta appear below in Figure 4.

The container labels share similar colors when comparing Cymbalta 30 mg with Strattera 40 mg and 60 mg which may contribute to the confusion. The products share a similar strength, 60 mg, however the container labels share little similarity. Therefore, DMETS believes education of pharmacy and other healthcare professionals may to minimize the potential for this confusion to continue.

Figure 4. Container Labels for Strattera 40 mg and 60 mg and Cymbalta 30 mg and 60 mg.

Strattera 40 mg **Cymbalta 30 mg** **Strattera 60 mg** **Cymbalta 60 mg**

Of the remaining drugs involved in this type of error only one case of each has been reported except Geodon which has two cases. The drugs involved in confusion include other medications produced by Lilly or other antidepressant or psychoactive medications. Upon review of these cases, DMETS does not believe any additional changes are warranted at this time. However, we will continue to monitor these events.

IV. RECOMMENDATIONS TO PREVENT FURTHER ERROR:

In order to minimize the following types of post-marketing errors we have experienced with Cymbalta, we recommend the following:

A. MINIMIZATION OF SIMILAR APPEARANCE OF CONTAINER LABELS/CARTON LABELING

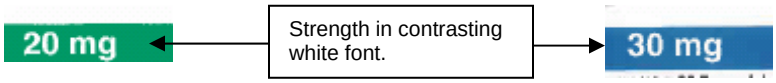
1. Blister Labels (20 mg, 30 mg, and 60 mg Identi-dose®)

   The strengths on the Identi-dose labels are indistinguishable. Use of contrasting colors (e.g., similar to the container label displays), boxing, bolding or some other method to distinguish each strength of Cymbalta is needed. Revise the labels so that when compared side-by-side there is some distinguishing feature.

2. Container labels, 20 mg, 30 mg, and 60 mg (30, 90, and 1000 capsules)

   a. The dark green color used on the labels and labeling for Cymbalta 20 mg is similar to the blue used for the 30 mg strength as well as the light green used for the 60 mg strength. This similarity in color contributes to the selection errors relating to wrong strength. We recommend using a different color for the Cymbalta 20 mg that provides better color contrast when compared to the other two strengths.

   b. The contrast of the white text used for the strength on the blue or dark green background makes differentiating the 20 mg from the 30 mg strength difficult (see sample below.) We recommend another method to contrast the 20 mg strength to provides more distinguishable strengths, such as the use of another contrasting color, boxing or some other means.



   c. DMETS recommends removing the curved-line logo adjacent to the proprietary name as it provides additional similarity between the label strengths. Furthermore, it also distracts from prominence of the proprietary name.

   d. DMETS recommends removing the picture of the capsule from the main display panel. While the capsule picture is likely intended to assist end users to confirm the strength of the capsules inside the carton or container is correct, the similar appearance of the 30 mg and 60 mg capsules may have contributed to the wrong strengths being dispensed. If the sponsor intends to keep the capsule picture as part of the labeling, consider reducing its prominence by placing it on a side panel for reference.

3. Carton Labeling

   See Container label comments B2a through B2d.

B. MINIMIZATION OF CONFUSION BETWEEN STRENGTHS OF PROFESSIONAL SAMPLES

DMETS believes the prescriber providing patients with both strengths (30 mg and 60 mg) of Cymbalta is the root cause of this type of error. We believe prescribers can achieve the same therapy with 30 mg capsules alone when the patient is titrated up to a 60 mg dose. Prescribers could communicate the need to take one capsule daily for the first week followed by two capsules daily beginning the second week. While communication between the prescriber and patient is important to reduce medication errors with professional samples,

DMETS recommends eliminating the potential for confusion of strength by providing professional sample of Cymbalta in only the 30 mg strength.

C. MINIMIZE CONFUSION BETWEEN CYMBALTA AND STRATTERA

It is unclear if the sponsor provided education to healthcare providers as suggested in our pre-marketing reviews. DMETS requests any information on what, if any, education was provided and how it was disseminated. If no education was provided, DMETS recommends the sponsor alert healthcare providers, especially pharmacy personnel, of the potential for confusion between Cymbalta and Strattera as well as the potential confusion between Cymbalta and Symbyax.

D. MINIMIZATION OF OPENING OF CYMBALTA CAPSULES PRIOR TO ADMINISTRATION

1. Container Labels

   If the package insert labeling is discarded, the current labels and labeling provide no warning regarding opening the capsule and its potential to result in an adverse event. DMETS recommends the statement “Cymbalta should be swallowed whole. Do not chew, crush or open capsules prior to administration.” be added to the principal display panel of the container.

2. Carton labels

   See Container Label comment above.

3. Package Insert Labeling

   DMETS recommends specifying the capsules should not be opened in “Information for Patients” section of the insert labeling. Revise the current warning to include the words “capsule be opened and its” so that the statement reads as follows: “Cymbalta should be swallowed whole and should not be chewed or crushed, nor should the capsule be opened and its contents sprinkled on food or mixed with liquids. All of these might affect the enteric coating.” In addition, DMETS recommends adding this warning to the DOSAGE AND ADMINISTRATION section of the package insert labeling.

DMETS would appreciate feedback regarding the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. If you have any questions concerning this memorandum, please contact the project manager, Angela Robinson, at 301-796-2284.

APPENDIX A: Wrong Technique Errors Summary

ISR #/Date	Error type	Contributing factors	Summary of Narrative
4599733-6 12/18/2004	Wrong technique	Lack of knowledge regarding the formulation.	A 35 year old woman was to start Cymbalta at 30 mg daily for 2 weeks then increase to 60 mg daily. The patient decided she did not need the full 30 mg dose and felt she was not "tolerating" this dose. She opened the capsule and poured some of its content out prior to taking it.
4687167-5 2/09/2005	Wrong technique	Lack of discussion with healthcare provider	A 51 year old woman was to start Cymbalta 30 mg per day. She took her first dose by opening the capsule and taking the content over one hour for unknown reason. The patient experienced elevated blood pressure.
4876286-6 10/02/2005	Wrong technique	Lack of knowledge regarding the formulation.	The patient was experiencing esophogeal burning after her Cymbalta dose. After speaking with her neurologist, she was instructed to open the capsule and mix the contents with yogurt and take at lunchtime. The patient was sent to the emergency room for treatment of esophageal burning.
5011285-5 12/2005	Wrong technique	Withdrawal effects. Lack of discussion with healthcare provider.	An 18 year old woman was attempting taper off of Cymbalta after more than 15 months of receiving 60 mg daily. She was having withdrawal symptoms. Without speaking to her physician, she decreased the dose by taking part of a 20 mg capsule.
5067303-5 4/25/2006	Wrong technique	Lack of knowledge regarding the formulation. Unable to find needed information in package insert.	The physician wanted to start a twenty year old woman on Cymbalta who was sensitive to antidepressants. He wanted to start with a low dose. He checked the package insert of a sample. He saw that the pellets were enteric coated. He told the patient to take ½ of a 20 mg capsule by opening capsule and mixing half of its content with water. The patient took dose as directed and began experiencing severe nausea and continuous vomiting. She was taken to the emergency and diagnosed with gastritis.

5132657-3 4/27/2006	Wrong technique/ Improper dose - resulting in overdose	Patient with a feeding tube. Lack of knowledge regarding the drug and formulation. Drug-drug interaction.	The physician ordered 150 mg twice a day to begin on a 51 year old woman with a jejunal feeding tube. The patient also receiving Imitrex. The drug given against patient and patient's advocate concerns. The patient experienced serotonin syndrome.
5105026-0 7/2006	Wrong technique	Lack of knowledge regarding the formulation.	A 51 year old woman experienced arrhythmia at night, high blood pressure and stomach upset after receiving Cymbalta. The patient for arrhythmia and high blood pressure. She restarted Cymbalta and split the 30 mg capsule and tool ½ twice a day to decrease the side effects. She continued to have stomach upset.
5113148-3 08/2006	Wrong technique	Lack of knowledge regarding the formulation. Patient with gastric bypass surgery.	A 39 you old woman taking Cymbalta underwent gastric bypass surgery. the capsules were "too big" to take. Patient was opening capsules and putting pellets in applesauce.
5235343-5 12/1/2006	Wrong technique	Patient with a feeding tube. Lack of knowledge regarding the drug and formulation.	Nurses were administering Cymbalta through a feeding tube after first dissolving it in water. Patient had been sedated in ICU. Patient pointed out error to nursing staff after sedation was stopped.

Appendix B: Wrong Strength Errors Summary

ISR #/Date	Error type	Contributing factors	Summary of Narrative
4653550-7 01/2005	Wrong strength	Drug new to the market.	A pharmacy filled a prescription for 20 mg Cymbalta with 30 mg capsules. Pharmacy was unaware Cymbalta was available in a 20 mg strength. The patient experienced diarrhea and therapy was discontinued.
4654119-0 3/16/2005	Wrong strength	Lack of understanding of directions from healthcare provider.	A 45 year old man was prescribed 60 mg Cymbalta daily. He was to start his first week of therapy taking 30 mg daily. The patient took a 60 mg capsule his first day and experienced a nosebleed, dizziness, headache, nausea and diarrhea. The Cymbalta therapy was discontinued.
4877176-5 10/04/2005	Wrong strength	The use of samples. Lack of understanding of directions from healthcare provider.	A female patient received 30 mg and 60 mg samples from her physician with directions to start 30 mg daily for one week then increase to 60 mg. The patient took 60 mg capsule for the first dose of therapy in error. No adverse events were reported.
4876586-X 10/17/2005	Wrong strength	The use of samples. Lack of understanding of directions from healthcare provider.	A 62 year old woman received 30 mg and 60 mg samples from her physician with directions to start 30 mg daily for one week then increase to 60 mg. The patient took 60 mg capsules for the first 4 days of therapy. No adverse events were reported.
4877025-5 11/4/2005	Wrong strength	Undetermined	A 60 year old man receiving 60 mg Cymbalta experienced nausea. He dropped his dose to 30 mg for unknown reasons. Patient experienced tachycardia and dizziness. No further outcomes were reported.
5008355-4 01/2006	Wrong strength	Undetermined	A 32 year old woman taking 20 mg of Cymbalta three times daily received a bottle containing 60 mg capsules. The pharmacy label read 20 mg three capsules daily. The label was on a bottle from the manufacturer of 60 mg capsules. The patient experienced stomach cramps, flu-like symptoms, could not urinate, headache and sweating. Duloxetine therapy was discontinued.

5043841-2 5/23/2006	Wrong strength	Undetermined	A patient was prescribed 30 mg Cymbalta twice daily. The pharmacy filled the prescription with 60 mg capsules with the directions to take one daily. No outcome or cause were reported.

Appendix C: Wrong Drug Errors Summary

ISR #/Date	Error type	Contributing factors	Summary of Narrative
4459303-7 09/20/2004	Wrong drug	Cymbalta new to the market.	The patient was prescribed duloxetine but received paroxetine from the pharmacy. The reporter stated these names are too similar.
4473184-7 10/7/2004	Wrong drug	Cymbalta new to the market.	The reporting pharmacy Intern noted the sound-alike similarity between Cymbalta and Symbyax.
5011597-5 10/31/2005	Wrong drug	Patient had a cold at the time of the error.	A 37 year old woman had been taking Cymbalta 60 mg each day at 5 pm for several months. The patient developed a chest cold in October and took Naproxen 500 mg rather than her Cymbalta. The patient was taking natural oil of oregano for her chest cold.
4876297-0 11/04/2005	Wrong drug		A nine year old was prescribed Strattera 60 mg and had been taking for several months. The patient received Cymbalta from the pharmacy in error and took for two or three days. The prescriber noted she generates prescriptions through the computer.
503661-9 4/03/2006	Wrong drug	Patient switched from Cymbalta to Symbyax. Patient urine screen was positive for barbiturates, cocaine, and marijuana the day of the error.	A 32 year old woman was taking Cymbalta. The patient switched to Symbyax 6/25 mg in February of 2006. The patient took a dose of Cymbalta rather than Symbyax on April 3, 2006, The patient had a positive urine dug test the next day.