CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-052

PROPRIETARY NAME REVIEW(S)

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(DMETS; WO22, Mail Stop Room 4447)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**OSE REVIEW #:** 2007-545
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July 31, 2006	May 31, 2007	

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Director, Division of Pulmonary and Allergy Products
HFD-570

THROUGH: Linda Kim-Jung, PharmD, Team Leader
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FROM: Kristina C. Arnwine, PharmD, Safety Evaluator
Division of Medication Errors and Technical Support

PRODUCT NAME:
Zyflo XR
(Zileuton Extended-release Tablets)
600 mg

NDA#: 22-052

NDA SPONSOR: Critical Therapeutics

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, Zyflo XR.

2. DMETS anticipates errors between Zyflo and Zyflo XR upon approval of this product because of common prescribing problems noted with drug name suffixes, the product strengths overlap, and the knowledge deficit that will exist upon marketing of this product. Thus, DMETS recommends the sponsor consider revising the strength of Zyflo XR, in addition to instituting an educational program to help practitioners be aware of the presence of the new extended-release product in addition to understanding the differences between the Zyflo product line. Moreover, implement the label and labeling revisions outlined in Section III of this review in order to minimize potential selection errors between Zyflo and Zyflo XR.

3. DDMAC finds the proprietary name, Zyflo XR, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-796-0080.

Division of Medication Errors and Technical Support (DMETS)
White Oak Bldg 22, Mail Stop Room 4447
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

PROPRIETARY NAME AND LABEL/LABELING REVIEW

DATE OF REVIEW: March 20, 2007

NDA#: 22-052

NAME OF DRUG: Zyflo XR (Zileuton Extended-release Tablets), 600 mg

NDA HOLDER: Critical Therapeutics, Inc.

****This document contains proprietary data from USP MEDMARX which cannot be shared outside of the FDA. The provider considers all MEDMARX reports and data to be confidential and therefore can not be disclosed to FOI. Users wanting this information must make such requests in writing via DMETS.****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Pulmonary and Allergy Products (HFD-570), for assessment of the proprietary name, Zyflo XR, regarding potential name confusion with other proprietary or established drug names. Container labels were provided for review and comment.

PRODUCT INFORMATION

Zyflo XR is the extended-release formulation of Zyflo (NDA 20-471, approved December 9, 1996). Zyflo XR is indicated for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. Zyflo XR tablets are triple-layer tablets comprised of an immediate-release layer, a middle barrier layer, and an extended-release layer. Zyflo XR is supplied as 600 mg extended-release tablets. The usual dose of Zyflo XR is two 600 mg tablets taken by mouth twice daily, within one hour after morning and evening meals.

II. RISK ASSESSMENT

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3,4] for existing drug names which sound-alike or look-alike to Zyflo XR to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and

[1] MICROMEDEX Integrated Index, 2007, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-07, and the electronic online version of the FDA Orange Book.
[4] Phonetic and Orthographic Computer Analysis (POCA)

Trademark Office's Text and Image Database was also conducted[5]. The Saegis[6] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

Following completion of these initial steps, an overall risk assessment is conducted that does not evaluate the name alone. The assessment considers the findings from above and more importantly integrates post-marketing experience in assessing the risk of name confusion, product label/labeling, and product packaging. Because it is the product that is inserted into the complex and unpredictable U.S. healthcare environment, all product characteristics of a drug must be considered in the overall safety evaluator risk assessment.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Zyflo XR. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the name, Zyflo XR, acceptable from a promotional perspective.

2. The Expert Panel identified nine proprietary names that were thought to have the potential for confusion with Zyflo XR. They are: Zyban, Cipro XR [redacted] Zyflo, Effexor, Zyflox, and Zyfloxy. The Expert Panel also cited concerns with regard to the modifier 'XR' being used for a product that is dosed twice daily rather than once daily.

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Zyflo XR with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 119 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescription were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Zyflo XR (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals

[5] WWW location http://www.uspto.gov/tmdb/index.html.
[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Inpatient Sample: Zyflo XR 600mg 2 tablets by mouth bid	"Zyflo XR 600 mg, dispense number 180. Take two tablets by mouth twice daily."
Requisition #2: Zyflo XR 600mg #180 1 PO BID	

2. Results:

Two respondents in the outpatient written study and two respondents in the inpatient written study misinterpreted the proposed name as Zyflo, without the modifier 'XR'. Zyflo is a currently marketed U.S. drug product. Additionally, one respondent in the verbal study misinterpreted the name as Cyclo XR. Cyclo XR may sound similar to the currently marketed product Cyclopar.

C. FDA ADVERSE EVENT REPORTING SYSTEM (AERS), USP MEDMARX, and PENNSYLVANIA PATIENT SAFETY REPORTING SYSTEM

****This document contains proprietary data from USP MEDMARX and Pennsylvania Patient Safety Reporting System (PA-PSRS) which cannot be shared outside of the FDA. The providers considers all MEDMARX reports and PA-PSRS data to be confidential and therefore can not be disclosed via FOI.****

1. AERS SEARCH

Since Zyflo XR is an addition to the Zyflo product line (NDA 20-471, approved on December 9, 1996), the FDA Adverse Event Reporting System (AERS) was searched for post-marketing safety reports concerning medication errors associated with Zyflo. The search was conducted using the high level terms "maladministrations", "medication monitoring errors", "medication errors due to accidental exposure", and "medication errors NEC" and the preferred terms "overdose", "accidental overdose", "multiple drug overdose", and "multiple drug overdose accidental," as well as the active ingredient "zileuton," the tradename "Zyflo," and the verbatim terms "zileuton%" and "Zyflo%." The search did not identify any medication error cases associated with the use of Zyflo.

2. PENNSYLVANIA PATIENT SAFETY REPORTING SYSTEM (PA-PSRS)

DMETS requested a search of the Pennsylvania Patient Safety Reporting System (PA-PSRS)** for medications errors associated with Zyflo. Similar to the AERS search, the PA-PSRS search did not identify any medication errors associated with the use of Zyflo.

3. USP MEDMARX

D. SAFETY EVALUATOR RISK ASSESSEMENT

To evaluate the potential of medication error with the proposed name of Zyflo XR, DMETS reviewed aspects that commonly lead to error when product extensions are introduced in the marketplace that include: what will happen if the modifier XR is omitted, can the modifier be misinterpreted, is the modifier meaningful, and what is the potential for confusion with the currently marketed Zyflo product line, and what does the addition of the modifier do to the visual presentation or phonetic pronunciation of the name thereby increasing the potential for proprietary name confusion with drug products currently marketed.

1. Examination of the "XR" modifier

When comparing the proposed "XR" modifier, DMETS must not only evaluate the orthographic or phonetic similarity between the currently marketed products and the proposed modifier, but also examine if the meaning of the modifier is consistent with current "XR" products, if "XR" can look like a number, be interpreted as directions for use, is similar to a medical abbreviation or has an appropriate meaning.

a. In analysis of the potential for the "XR" modifier to resemble any numbers, dosing instructions, or medical abbreviation, post-marketing reporting has found that "XR" has been misinterpreted as "x 2." This confusion occurred when the first XR suffix was first approved. However, we have not seen recent confusion and the abbreviation does not appear on the dangerous abbreviations list. Additionally, the modifier "XR" is identified by standard references[7] as extended-release X- linked recessive, X-ray, and Xeroradiography. These interpretations should

[7] http://www.pharma-lexicon.com/, 02May2007.

not result in confusion. Moreover, the "X" of XR is associated with the Roman numeral "ten" and "R" could be misinterpreted as the Roman numeral "L"; thus, XL or "40". However, we have not had such reports of confusion. Despite the potential for the "XR" modifier to look or be defined as above, DMETS does not believe this would prohibit the use of this modifier.

b. When evaluating the appropriateness of the modifier and the intended meaning, we discovered twenty prescription products listed in the Orange Book, drugs@FDA, and DSS that use the "XR" modifier [Adderall XR, Augmentin XR, Cipro XR, Effexor XR, Focalin XR, Glucophage XR, Tegretol XR, Voltaren XR, Xanax XR, Zerit XR (discontinued), Dilacor XR^{+}, Dilt-XR^{+}, Lodrane XR^{+}, Proquin XR^{+}, Tanacof XR^{+}, Tusso-XR^{+}, Avandamet XR***, Mirapex XR***, Sanctura XR***, and Seroquel XR***].

Most of the "XR" drugs that represent product line extensions are dosed once daily (n=14) with the remaining five dosed twice daily/three times daily (n=5). Of the five drug products not dosed once daily, three were monograph drug products (Tanacof XR, Tusso-XR, Lodrane XR), and one (Tegretol XR) was approved in 1996 and thus not reviewed by DMETS. The remaining name, Augmentin XR, was reviewed by DMETS and approved by the Agency in 2002. Unfortunately, the name Augmentin XR was reviewed prior to the release of the Institute of Medicine report "Preventing Medication Errors" (2006) [8] or the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) meeting on "Drug Name Suffixes and Medication Errors" (2005) [9] which identified safety concerns with modifiers. Since this, DMETS is addressing these issues in current review practices.

Despite the fact that 5 products have twice-daily or three times daily dosing and use the 'XR' modifier, in DMETS opinion, the XR modifier does not adequately capture the most notable difference between Zyflo XR and the existing Zyflo, which is the dosing interval. As such, DMETS concludes that the 'XR' modifier is not an acceptable choice for the proposed product, and objects to the use of the proprietary name, Zyflo XR.

2. Potential for Product Line Confusion

Post-marketing experience has shown that the introduction of product line extensions result in medication errors especially when there is any overlap in product characteristics and a knowledge deficit with respect to the introduction of the new extended-release formulation. Errors introduced by product line extensions are known to occur at all points in the medication use process. With respect to Zyflo XR, DMETS is concerned with the potential omission of the 'XR' modifier, overlapping strengths, and shelf/computer selection errors between Zyflo & Zyflo XR.

a. Omission of the "XR" modifier

Post-marketing experience has shown that the introduction of product line extensions result in medication errors when the modifier is omitted[10]. In this case, if the XR modifier is omitted it is almost certain that Zyflo will be dispensed because of the overlapping product characteristics. Zyflo XR and Zyflo overlap in established name (zileuton), indication of use (asthma), route of administration (oral), and dosage form (tablet). Additionally, both products are supplied as 600 mg tablets with a total daily dose 2400 mg.

*** Proprietary and confidential information that should not be released to the public.

[8] July 20, 2006, Institute of Medicine (IOM) Report "Preventing Medication Errors" recommendation number four

[9] NCC MERP meeting "Drug Name Suffixes and Medication Errors: Exploring the Relationship and Minimizing the Risk". October 2005.

[10] Lesar TS. Prescribing Errors Involving Medication Dosage Forms. *J Gen Intern Med.* 2002; 17(8): 579-587.

By choosing to develop an extended-release formulation of zileuton tablets that overlaps with the strength of the currently marketed immediate-release formulation (600 mg), the Sponsor has eliminated a potentially valuable error-reduction strategy that has been employed in other product line extensions. DMETS suggests an alternative approach such as the strategy used for the Paxil CR line with strengths of 12.5 mg, 25 mg, 37.5 mg compared to the existing Paxil strengths of 10 mg, 20 mg, 30 mg, and 40 mg. Thus, if the modifier were omitted or overlooked, the difference introduced by the strength offer an opportunity for an error to be caught before it reaches the patient. In the case of Zyflo, there will be nothing to distinguish these products. DMETS acknowledges that the sponsor developed the strengths to "allow patients to titrate to the optimal maintenance dose in the most convenient way." However, the sponsor could and should have chosen a small deviation in strength similar to Paxil CR to lessen confusion.

If Zyflo and Zyflo XR confusion were to occur, the outcome must be considered. The likely cause of this confusion would be due to the omission of the modifier or knowledge deficit that the new formulation exists, which would result in the patient receiving an immediate-release tablet twice daily rather than four times daily. Thus, the patient would not receive the expected total day zileuton coverage with potential fluctuations in blood levels resulting in adverse events.

Thus, we believe this confusion will occur based on the possibility of omission of the suffix, product characteristic overlap, and a knowledge deficit of the new product. Education alone will not fully address this confusion and we strongly recommend the sponsor revise the product strengths so that they do not overlap.

b. Shelf and Computer Selection Errors

Typically, pharmaceutical products are organized alphabetically by proprietary name, established name, or sorted by manufacturer. Since these attributes are identical with the currently marketed Zyflo product line and the proposed Zyflo XR, it is likely that the products will be stored near one another in virtually any organization carrying both product lines. Thus, this proximity could lead to selection errors, especially if the container labels look the same. Additionally, due to the shared root name of "Zyflo", there is a possibility for computer selection errors. In order to minimize this potential source of confusion, differentiation in the packaging and labeling of Zyflo and Zyflo XR is essential.

Overall, DMETS believes that labeling and packaging differentiation will help to minimize the potential for product selection errors, but will not be able to fully avoid confusion between Zyflo and Zyflo XR. Thus, DMETS believes that it is imperative that healthcare practitioners are educated about the existence of this extended-release formulation to avoid overdosing (and subsequent adverse events). In addition, to avoid ambiguity over the dosing regimen, it is imperative that the "Twice Daily Dosing" statement be prominently presented on all Zyflo XR labels and labeling, and as well as any related marketing material, in order to prevent confusion.

3. Look-Alike/Sound-Alike Concerns

In reviewing the proprietary name Zyflo XR, the names identified to have visual and phonetic similarity to Zyflo XR are: Zyflo, Zyban, Cipro XR, [redacted]*, Effexor, Zyflox, Zyfloxy, and Zyvox.

In the initial analysis of these 10 names it was determined that the following eight names: Zyban, Cipro XR, [redacted], Effexor, Zyflox, and Zyfloxy would not be considered further for the following reasons.

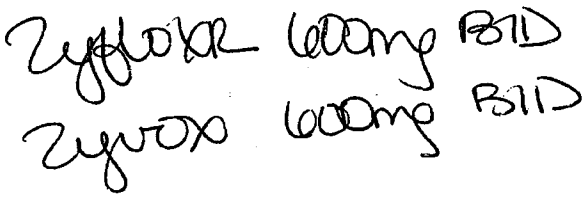
***Name pending approval. Not FOI releasable.**

- Lack of significant orthographic and or phonetic similarities
- Zyban, Cipro XR, [redacted], and Effexor do not share product commonalities such as dosage form, route of administration, product strength, usual dose, and/or indication of use.
- Zyflox is a foreign product (Philippines) that does not share product commonalities such as product strength, usual dose, and/or indication of use with Zyflo XR.
- The names [redacted] and [redacted] were proposed names for separate products that are/were the subject new drug applications, however, neither name was used.
- Zyfloxy, available in Thailand, was cited in Thomson & Thomson as an antibiotic with sales last recorded in 2004.

The remaining name, Zyvox, is reviewed in detail below. For analysis of name confusion within the Zyflo product line see section II-D-2.

Zyvox was identified as a name that sounds and looks similar to Zyflo. Zyvox is indicated for treatment of susceptible strains of Vancomycin-resistant Enterococcus, nosocomial pneumonia, in addition to skin and skin structure infections.

The postmarketing searches revealed existing confusion between Zyflo and Zyvox. Given this existing confusion and overlapping product characteristics, DMETS believes that it is possible that confusion may occur between Zyvox and Zyflo XR, despite the addition of the modifier. In fact, the addition of the modifier "XR' may cause Zyflo XR to look more similar to Zyvox than the root name Zyflo alone, since it causes the name Zyflo to have the letter 'x' presented toward the end of the name similar to Zyvox. This is especially true if the modifier is scripted in close proximity to the root name so that it appears as a single name
(i.e. ZyfloXR, see below).



ZyfloXR and Zyvox are both oral tablets available in 600 mg tablets. DMETS notes that confusion occurred despite the fact that Zyflo is dosed four times daily unlike Zyvox which is dosed twice daily. With the introduction of Zyflo XR, the potential for confusion may be increased since Zyflo XR is dosed twice daily similar to Zyvox. Additionally, the errors revealed in the MEDMARX search demonstrate that the name similarity between Zyflo and Zyvox has the potential to cause error during the transcription and drug selection phases of the medication use process.

Computer selection errors have also been identified as an etiology for confusion between Zyflo and Zyflo XR. From the perspective of the leading "Zyf" on selection from a list, this modifier will provide no difference as the "XR" will likely make it last in the selection line (after Zyflo). Additionally, the quick codes assigned to a drug product to allow for keystroke entry (thus, avoiding drop-down selection) may or may not alleviate confusion, depending on how assigned. For example, an assignment of ZyfX600 or ZyfXR600 could help, but Zyf600X could result in proliferation of the confusion. Lastly, if any of the drug names known to result in confusion were to add a modifier (e.g. Zyvox), this would likely lead to confusion.

In light of the history of medication errors with Zyflo and Zyvox, and now potentially overlapping product characteristics between Zyvox and Zyflo XR, DMETS does not recommend the use of the name Zyflo XR because it increases the similarity to Zyvox. Although, the errors between Zyvox and Zyflo do not reach the threshold for a name change at this time; it is important for the sponsor to consider the potential impact their proposed modifier will have on existing confusion when choosing an alternate modifier to "XR."

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels of Zyflo XR, DMETS has focused on safety issues relating to medication errors. DMETS has identified the following areas of improvement, which will minimize potential user error.

A. General Comments

1. Relocate the net quantity so that it is not presented in close proximity to the product strength (see below). Postmarketing evidence demonstrates that confusion between net quantity and product strength may occur if they are presented in close proximity to one another.

2. Revise the presentation of the proprietary name so that the entire name is presented in the same font color (see below). As currently presented, the root name (Zyflo) is presented with more prominence than the modifier (XR), which may lead to the modifier being missed.

3. Revise the "Usual adult dose" statement to read "Usual Dosage: See package insert".

B. Container Label (Sample, 20 tablets)

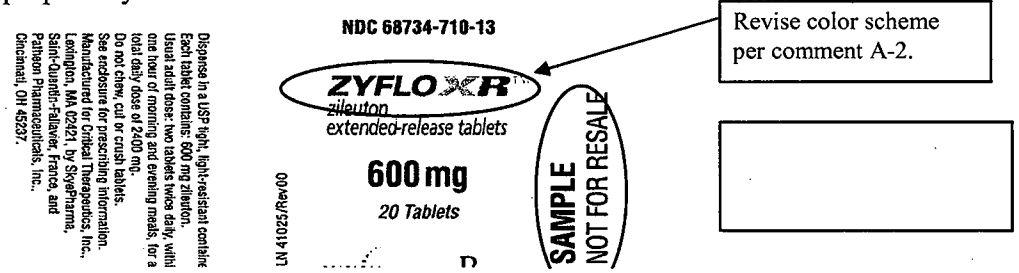
1. See General Comments.

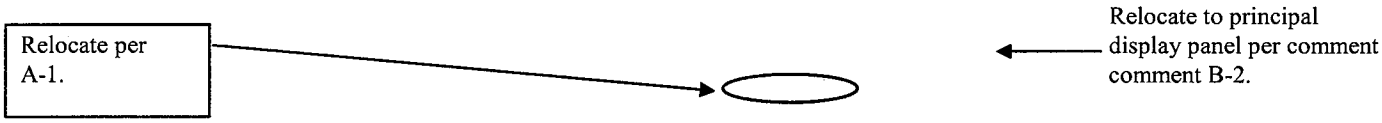
2. Relocate the "Sample. Not for Resale" statement to the principal display panel (see below).

C. Container Label (Trade, 120 Tablets)

1. See General Comments.

2. Per CFR 21 201.10(g)(2), increase the prominence of the established name so that it is at least ½ the size of the proprietary name.





Zyflo XR 600 mg Sample Container

APPEARS THIS WAY
ON ORIGINAL

Attachment 1

Verbal	Inpatient Written	Outpatient Written
Cyclo XR	Zyflo	Zyflo
Xyclo XR	Zyflo	Zyflo
Zyclo XR	Zyflo XR	Zyflo XR
Zyflo XR	ZYFLO XR	Zyflo XR
Zyflo XR	Zyflo XR	Zyflo XR
Zyflo XR	Zyflo XR	Zyflo XR
Zyflo XR	Zyflo XR	Zyflo XR
Zyflow xr	Zyflo XR	Zyflo XR
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