CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-204

OTHER REVIEW(S)

MEMORANDUM

To: **Jeannie Roule**
Division of Reproductive and Urologic Products

From: **Iris Masucci, PharmD, BCPS**
Division of Drug Marketing, Advertising, and Communications
for the Study Endpoints and Label Development (SEALD) Team, OND

Date: **January 6, 2009**

Re: **Comments on draft labeling for Gelnique (oxybutynin chloride) gel**
NDA 22-204

We have reviewed the proposed label for Gelnique (FDA version received 12/30/08) and offer the following comments. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, labeling Guidances, and FDA recommendations to provide for labeling quality and consistency across review divisions. We recognize that final labeling decisions rest with the review division after a full review of the submitted data.

HIGHLIGHTS

- When the text of Highlights is finalized, please reformat to make the lengths of the two columns approximately equal.

- *"GELNIQUE (oxybutynin chloride) 10% gel"*

  All text on this line should be in bolded type. Please revise.

  In general, product strengths should not appear on the title line. The regulations require four items here: tradename, established name, route of administration, and dosage form. As such, we recommend revising this line to:

  GELNIQUE (oxybutynin chloride) topical gel

  There should be no hard return (white space) after this line. The U.S. approval line should appear directly underneath it.

Indications and Usage

- *"GELNIQUE, 10% oxybutynin chloride gel, is an* (b) (4) *agent indicated for:…"*

The phrase “10% oxybutynin chloride gel” should be removed from this line. It should read, “GELNIQUE is an…”

- Is (b) (4) the agreed-upon pharmacologic class for oxybutynin? The SEALD records of proposed pharmacologic classes say “muscarinic antagonist” for oxybutynin and other drugs in the class. Please confirm and revise accordingly if necessary.

- Because this product has only one indication, the bullet within the indication could be deleted, e.g.,

(b) (4)

Dosage and Administration

- For ease of reading, we suggest revising this section to use bullets instead of a paragraph of text. We propose:

  - Apply contents of one sachet of GELNIQUE once daily to dry, intact skin on abdomen, upper arms/shoulders, or thighs. (2)
  - Rotate application sites, avoiding use of the same site on consecutive days. (2)
  - GELNIQUE is for topical application only and should not be ingested. (2)

Dosage Forms and Strengths

- *“Sachet: 1 gram unit dose (1.14 mL) 100 mg/g oxybutynin chloride gel. (3)”*

  To avoid confusion, we suggest using “10%” instead of “100 mg/g” here, especially if “10%” is deleted from the product title line. We propose:

  Sachets: Each containing 1 gram (1.14 mL) of 10% oxybutynin chloride gel. (3)

Contraindications

- We suggest left-justifying the bullets in this section, rather than indenting them.

- *“Known hypersensitivity to* (b) (4) *Gelnique (4)”*

(b) (4)

Warnings and Precautions

- We recommend using bullets to separate each topic in this section instead of bolding the "title" of each.
- [redacted] (b) (4)

  Please revise this sentence to use active voice, e.g., Discontinue GELNIQUE in patients with…
- [redacted] (b) (4)

  We suggest streamlining the language somewhat in this bullet for ease of reading. We propose:

  [redacted] (b) (4)

  [redacted] (b) (4)
- *"Flammable Gel: Alcohol based gels are flammable. Avoid open fir or smoking until the gel has dried. (5.5)"*

  As above, we recommend revising this bullet. We suggest:

  > Flammable Gel: Contains alcohol-based gel. Avoid open fire or smoking until gel has dried. (5.5)

Adverse Reactions

- We suggest revising this section to the following:

  The most common adverse reactions (incidence > 5% and > placebo) were dry mouth and application site reactions. (6)
- We recommend deleting [redacted] (b) (4)

Drug Interactions

- As in "Warnings and Precautions," we recommend using a bullet instead of bolded titles for this section.

(b) (4)

We recommend revising this sentence slightly to:

> Concomitant use with other anticholinergic agents may increase the frequency and/or severity of dry mouth, constipation, blurred vision, and other anticholinergic pharmacological effects.

(b) (4)

Revision Date

- The revision date should be right-justified in the column.

CONTENTS

- Once the FPI has been finalized, the Contents must be updated to ensure accuracy of the numbering and section titles. Then, any corresponding changes should be made to the Highlights and cross-references throughout the label.
- All text in the "Contents" section should be bolded.
- The page numbers, along with the periods preceding them should be deleted.
- Please insert a hyphen in 17.3 for "FDA-Approved."
- A line must appear at the end of Contents separating it from the FPI (as is done between Highlights and Contents.

FULL PRESCRIBING INFORMATION

- Throughout the FPI, most of the cross-references in brackets are not formatted in the preferred way. We recommend italicizing the entire cross-reference, including the brackets. We also suggest that the cross-references appear within the sentence, i.e., putting the period after the cross-reference instead of before it.

1 Indications and Usage

- *"GELNIQUE is* (b) (4) *indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency."*

  The phrase (b) (4) should be deleted from this sentence. The pharmacologic class should appear in the indication in Highlights, but not in the FPI Indications and Usage section.

2 Dosage and Administration

- We note that the information from the Highlights "Dosage and Administration" section about using the product only topically does not appear here. Any information that appears in a section in Highlights must appear in the corresponding FPI section as well. Please add to this section where appropriate.

3 Dosage Forms and Strengths

- As in Highlights, we suggest using "10%" instead of 100 mg/g here.

4 Contraindications

- We suggest using bullets in this section instead of presenting the contraindications in a sentence. Using bullets will make the individual contraindications easier to read.

(b) (4)

5.1 Urinary Retention

(b) (4)

Please revise this sentence to avoid the use of passive voice (e.g., Administer GELNIQUE with caution to patients with…).

5.2 Gastrointestinal Disorders

- Please consider if the title of this section should be revised. As written, it is unclear if the subject of the section is gastrointestinal (GI) disorders that GELNIQUE can cause or if it discusses the use of GELNIQUE in patients with pre-existing GI disorders. It seems that the latter is a more accurate description of the subject matter. As such, we suggest retitling the section to, "Use in Patients with Gastrointestinal Disorders."

- *"GELNIQUE should be administered with caution to patients with gastrointestinal obstructive disorders because of the risk of gastric retention."*

  As in 5.1, please revise this sentence to avoid the use of passive voice.

- *"GELNIQUE should be used with caution in patients who have gastroesophageal reflux and/or who are concurrently taking drugs (such as bisphosphonates) that can cause or exacerbate esophagitis."*

  Are the warnings against use in patients with GERD or taking drugs that can cause esophagitis because of the decreased GI motility? Or is there another reason for these warnings? If it is not part of the decreased motility discussion, we suggest that this sentence be a new third paragraph in this section.

5.4 Skin Transference

- As mentioned in Highlights, we note some inconsistent recommendations within the label about covering the application site with clothing. Some places (e.g., here and in the corresponding Highlights section) (b) (4) The "Patient Counseling Information" section (17.1), however, says to do so only if close skin contact is anticipated. Please revise the label (and the PPI) to ensure a consistent and accurate recommendation throughout.

5.5 Flammable Gel

(b) (4)

This sentence is somewhat awkward and redundant. We suggest revising to something similar to:

GELNIQUE is an alcohol-based gel and is therefore flammable.

6 Adverse Reactions

- This section should begin with an overview of the safety profile of the drug. This consists of a listing of the most serious adverse reactions (with cross-references), the most common adverse reactions (similar to the list in Highlights), and the most common reasons for discontinuation (if available). We suggest something similar to:

The following serious adverse reactions are discussed elsewhere in the labeling:

- Urinary retention *[see Warnings and Precautions (5.1)]*
- However many others you deem important…

The most common adverse reactions (reported in greater than X%) are…

The most commonly reported reasons for discontinuation are…

6.1 Clinical Trials Experience

- Please delete the term "Phase 3" throughout this entire section. Using phase numbers to describe trials is discouraged in labeling because they are somewhat vague and not helpful.

- Please ensure that adverse reactions (i.e., those that are plausibly causally related to the drug) are called "adverse reactions" throughout this section (in both text and tables) and not "adverse events." As much as possible, this section should focus on "adverse reactions." If there is a compelling reason to discuss "adverse events," then they too should be titled properly.

- *"During the double-blind period, equal proportion of patients in the active (1.8%) and placebo (1.8%) groups discontinued treatment due to an adverse reaction, defined as undesired effects judged by the investigator to be reasonably associated with the use of study medication."*

  Please insert "an" before "equal proportion" in this sentence.

- We recommend deleting the subheading (b) (4) from this section because it is unnecessary.

- Table 1 lists adverse events regardless of causality and the paragraph that follows it discusses those believed to be treatment-related. Is there a compelling reason to present these two sets of data? Presenting two different lists will likely be confusing to the reader. We recommend including only the data that represents what we believe are the drug-related adverse reactions and that most accurately represent the true safety profile of the drug.

- Table 1

  If the table remains in the label, we suggest replacing (b) (4) with "GELNIQUE 1 gram" for clarity. We also recommend rounding off the incidence rates in parentheses to whole numbers for ease of reading.

- *"A majority of treatment-related adverse events were described as mild or moderate in intensity, except for two patients reporting severe headache."*

  This sentence is somewhat promotional in tone and seems to be minimizing the risks associated with the drug. Is the claim that most reactions were mild or moderate adequately supported? If so, can we replace the vague term "a majority" with an actual number?

(b) (4)

7 Drug Interactions

- Please consider if the potential interaction with drugs that can cause or exacerbate esophagitis (e.g., bisphosphonates) should be mentioned under "Drug Interactions." Does its current placement under "Warnings and Precautions" give it enough prominence? It could be mentioned briefly in a sentence here, with a cross-reference to 5.2.

7.1 Other Anticholinergics

- (b) (4)

(b) (4)

8.1 Pregnancy and 8.3 Nursing Mothers

- These sections should be reviewed by the Maternal Health Team.

10 Overdosage

- *"Overdosage with oxybutynin has been associated with anticholinergic effects including CNS excitation, flushing, fever, dehydration, cardiac arrhythmia, vomiting, and urinary retention."*

  Please spell out "central nervous system" in this sentence instead of using the acronym "CNS." The acronym is not used elsewhere in the label and is therefore unnecessary.

- *"Patients should be monitored until symptoms resolve."*

  We suggest revising this sentence to improve clarity and flow, e.g.,

  If overexposure occurs, monitor patients until symptoms resolve.

11 Description

- *"Oxybutynin is an antispasmodic, anticholinergic agent."*

As noted in Highlights, should we be describing this product as (b) (4) a "muscarinic antagonist"?

12.1 Mechanism of Action

- *"The active metabolite, N-desethyloxybutynin, has pharmacological activity on the human detrusor muscle that is similar to that of oxybutynin in in-vitro studies."*

  Please delete the hyphen in "*in-vitro*."

12.3 Pharmacokinetics

- We suggest that the first sentence under "Absorption" clarify the dosing regimen used in the study (presumably 1 gram once daily).

- We note that a table comparing the pharmacokinetics of GELNIQUE versus those of Oxytrol has been deleted from the label. While we agree that these data are not truly necessary for the label, the information may be something that the prescriber would want to know. It might be useful to know that the delivery of oxybutynin from the gel is approximately equal to 4 mg/day of oral oxybutynin. While a detailed table may be more than is necessary, perhaps a summary statement stating such would be useful. If it is included, please use "oral oxybutynin" instead of "Oxytrol."

- *"The resulting plasma concentration AUC ratio of N-desethyloxybutynin metabolite to parent compound following multiple transdermal applications is approximately 1:1 for GELNIQUE."*

  In this sentence under "Metabolism," shouldn't we say "plasma concentration: AUC ratio" or "plasma concentration to AUC ratio" for clarity?

- *"The apparent elimination half-lives including the terminal elimination phase were 64 hours and 82 hours for oxybutynin and DEO, respectively."*

  Please spell out the full term instead of using "DEO" in this sentence. The abbreviation is not used anywhere else in the label.

(b) (4) *less than 0.1% of the administered dose is excreted as the metabolite N-desethyloxybutynin."*

  We suggest deleting (b) (4) from the beginning of this sentence because it is unnecessary.

- We suggest deleting the subheading (b) (4)" because it is unnecessary.

- We suggest adding "Patients" to the end of the subsection headings for "Geriatric" and "Pediatric."

- (b) (4)

  Because this sentence appears in the "Pharmacokinetics" section, it should not be discussing (b) (4) We recommend deleting that part of the sentence or moving it to section 8.3. The same recommendation applies in the "Gender" section.

- Please correct the cross-reference at the end of the "Geriatric" section. It should read, (b) (4) " A similar correction must be made for the cross-reference in the pediatric section that follows.

- In the renal and hepatic impairment sections, please change "insufficiency" to the preferred term "impairment."

14 Clinical Studies

- *"The efficacy and safety of GELNIQUE were evaluated in a single (b) (4) randomized, double-blind, placebo-controlled, parallel group 12-week study for the treatment of overactive bladder with symptoms of urge incontinence, urgency and frequency."*

  As noted under "Adverse Reactions," please delete (b) (4) from the study description.

- *"Patients were randomized to daily applications of GELNIQUE or matching placebo gel."*

  Please add the dose (1 gram) to this sentence for completeness.

(b) (4)

16 How Supplied/Storage and Handling

- The company contact information that currently appears at the end of section 16 should be moved to the end of the label. Section 17 should appear immediately after the text of section 16.

- When this information is moved to the end, the line (b) (4) should be deleted. This statement now appears only on cartons/containers, not in labels. The line "Revised 10/2008" should also be deleted because the revision date now appears in Highlights instead of at the end of labels. Lastly, the company address in Corona, CA currently appears twice. One occurrence should be deleted.

17 Patient Counseling Information

- *"See FDA-approved Patient Labeling (17.3)"*

  This entire line should be italicized (and remain unbracketed).

17.1 Instructions of Use

- Please change the section title to "Instructions for Use."

17.2 Important Anticholinergic (b) (4)

- Please change (b) (4) to "adverse reactions" in the section title and in any text that follows.

17.3 FDA Approved Patient Labeling

- Please insert a hyphen in "FDA-Approved."
- Please note that the patient labeling is not the subject of this review.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Iris Masucci
1/15/2009 12:44:56 PM
DDMAC PROFESSIONAL REVIEWER

Laurie Burke
1/15/2009 01:43:57 PM
INTERDISCIPLINARY

Department of Health and Human Services

Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research

Office of Surveillance and Epidemiology

Date:	December 31, 2008
To:	Scott Monroe, MD, Director Division of Reproductive and Urologic Products
Thru:	Kristina C. Arnwine, PharmD, Acting Team Leader Denise P. Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Loretta Holmes, BSN, PharmD, Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Label and Labeling Review
Drug Name:	Gelnique (Oxybutynin Chloride) Gel 10 %
Application Type/Number:	NDA 22-204
Applicant:	Watson Laboratories, Inc.
OSE RCM #:	2008-768

Contents

EXECUTIVE SUMMARY

The results of the Label and Labeling Risk Assessment found the presentation of information on the proposed container label, carton and insert labeling is vulnerable to confusion that could lead to medication errors. Specifically, DMEPA is concerned with the Applicant's inappropriate use of (b) (4) lettering in the presentation of the proprietary name. This inappropriate use of (b) (4) lettering may also provide an opportunity for the Applicant to promote this product as a (b) (4) This was a concern of DDMAC's during the review process and they recommended against the use of this name because *"…the proposed trade name implies that this drug product is* (b) (4) *or* (b) (4) *in comparison with other drug products approved for the treatment of overactive bladder."* Although, the Division disagreed with DDMAC, DMEPA recommends the Division consult DDMAC concerning the presentation of the proposed proprietary name, "Gelnique", on the container labels and carton labeling to limit the potential for misleading advertisements, etc., once this application is approved especially since DDMAC was concerned that this proprietary name was misleading.

Additionally, there are other areas where information such as the presentation of the established name, total drug content of the sachet, and usual dosage statement need to be modified, clarified, or relocated in order to make the labels and labeling less vulnerable to medication errors.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

1 BACKGROUND

1.1 INTRODUCTION

This review was written in response to a request from the Division of Reproductive and Urologic Products for assessment of the proposed container label, carton and insert labeling of Gelnique. The container label, carton and insert labeling were provided for our review and comment.

1.2 REGULATORY HISTORY

The proposed proprietary name, Gelnique, was reviewed under separate cover (OSE Review 2008-768).

1.3 PRODUCT INFORMATION

Gelnique (Oxybutynin Chloride Gel) is an (b) (4) anticholinergic agent indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency. The recommended dosage is the contents of one sachet applied once daily to dry, intact skin on the abdomen, upper arms/shoulders, or thighs. Application sites should be rotated. Application of Gelnique should not be made to the same site on consecutive days. Each sachet contains a one gram unit dose (100 mg/g) of Oxybutynin Chloride Gel. Gelnique sachets will be packaged in cartons containing 30 sachets. At the mid-cycle meeting with the Division on August 25, 2008, we learned that this product is advantageous because it is less irritating to the skin than the Applicant's currently marketed Oxytrol transdermal patch.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff conducting a label, labeling, and/or packaging risk assessment (see 2.1 Label and Labeling Risk Assessment). The primary focus for the assessment is to identify and remedy potential

sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the healthcare professional, patient, or consumer. [1]

2.1 LABEL AND LABELING RISK ASSESSMENT

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis staff to conduct a label, labeling, and/or packaging risk assessment (see Section 3, Results). The primary focus of the assessments is to identify and remedy potential sources of medication errors prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [2]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container label and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the United States Pharmacopeia-Institute for Safe Medication Practices Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[3]

Because the Division of Medication Error Prevention and Analysis staff analyzes reported misuse of drugs, the Division of Medication Error Prevention and Analysis staff is able to use this experience to identify potential errors with all medications similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provide recommendations that aim at reducing the risk of medication errors.

The Division of Medication Error Prevention and Analysis reviewed the follwing revised labels and labeling submitted by the Applicant. See Appendix A for pictures of the labels and labeling.

- Container Label (submitted on September 11, 2008)
- Carton Labeling (submitted on September 11, 2008)
- Insert Labeling (no image, submitted on December 5, 2008)

3 RESULTS

3.1 LABEL AND LABELING RISK ASSESSMENT

Review of the labels and labeling identified several potential sources of medication error.

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[2] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors html. Last accessed 10/11/2007.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

3.1.1 General Comments for All Labels and Labeling

The established name is not consistently presented throughout all the labels and labeling.

3.1.2 Container Label and Carton Labeling

The [redacted] (b) (4) "Gel" are used for the first three letters and the [redacted] (b) (4) are used for the last five letters in "Gelnique"

The white print on purple colored background is difficult to read due to poor color contrast.

The graphic is more prominent than the proprietary name, established name, and strength.

3.1.3 Carton Labeling

The statement of total drug content of the sachet contains three different units of measure (i.e., 1 gram unit dose, 1.14 mL, and 100 mg/g) and is too prominent.

The "Usual Dosage" statement contains incomplete instructions for administration of the product.

The proprietary name is located next to the net quantity statement.

3.1.4 Insert Labeling

Specific sections of wording in Section 17.1 and Section 17.2 need clarification.

The diagrams in Section 17.2 under "How should I use Trade name" are not labeled or referenced appropriately in the written instructions.

4 DISCUSSION

4.1 LABEL AND LABELING RISK ASSESSMENT

The Label and Labeling Risk Assessment identified areas where information such as the presentation of the established name, total drug content of the sachet, and usual dosage statement need to be modified, clarified, or relocated in order to make the labels and labeling less vulnerable to medication errors. DMEPA is also concerned with the Applicant's inappropriate use of [redacted] (b) (4) lettering in the presentation of the proprietary name.

4.1.1 Presentation of the Proprietary Name

The first three letters of the name "Gel" are printed [redacted] (b) (4) and the last four letters of the name [redacted] (b) (4) on the container label and carton labeling. The use of different fonts and capitalization in the name lends undue emphasis to certain portions of the name. [redacted] (b) (4)

Moreover, the Applicant's presentation of the name with special emphasis on the two syllables in the name (i.e., "Gel" and "nique") may be read as [redacted] (b) (4) DMEPA notes that DDMAC expressed concerns with the name and objected to the name "Gelnique" because: [redacted] (b) (4) Although, the Division disagreed with DDMAC's

recommendation, DMEPA believes that the current presentation of the name and the inappropriate use of (b) (4) letters will provide an opportunity for the Applicant to promote this product as a (b) (4) However, DDMAC would be able to provide the Division more direction on the Applicant's ability to use the proprietary name, labels and labeling in such manner".

4.1.2 Inconsistent Presentation of the Established Name and Strength

The established name and strength are inconsistently presented throughout the labels and labeling. On the container label and carton labeling it is presented as "oxybutynin chloride topical gel, 10%", however, in the insert labeling it is presented as "10% oxybutynin chloride gel". The established name and strength should be presented in a consistent manner throughout all labels and labeling. We concur with the October 2, 2008 CMC recommendation that the established name and strength be presented as follows:

PROPRIETARY NAME (oxybutynin chloride) Gel 10%

4.1.3 Total Drug Content of Sachet

The statement of total drug content of the sachet contains three different units of measure (gram, milliliter, and milligram). The statement of total drug content states: "Each sachet contains 1 gram unit dose (1.14 mL) of 100 mg/g oxybutynin chloride, USP". The multiple expressions of the total drug content may lead to confusion with determining how the dose should be prescribed, especially since the Dosage and Administration section states the dose as "the contents of one sachet". The statement of total drug content of the sachet is located on the principal display panel, top panel, and a side panel of the carton labeling. Deleting the statement from the principal display panel and top panel while retaining it on the side panel will give it less prominence and help to decrease the likelihood that such confusion will occur. Additionally, the statement "Each sachet contains 1 gram unit dose" located on the principal display panel and top panel should also be deleted in order to minimize any potential confusion.

4.1.4 Prominence of the Graphic

DMEPA notes that the container labels and carton labeling contain a graphic presented immediately above the proprietary name, established name, and strength. This graphic is more prominent than important information such as the proprietary and established names. Since the graphic is so prominent, it is the first thing that is noticed on the labels and labeling. When identifying this product for selection from the shelf, the dispenser's eye should be drawn to the proprietary name, established name and strength instead of the graphic. Deleting or decreasing the prominence of this graphic will ensure that the proprietary name, established name, and strength have more prominence than the graphic.

4.1.5 Duplicate Proprietary Name Presentation

The proprietary name is positioned next to the net quantity statement on the carton labeling. Although this is not a safety concern, this presentation of the proprietary name is duplicative and adds clutter to the carton labeling. The proprietary name can be deleted from this location without compromising the safe use of the product.

4.1.6 Usual Dosage Statement Contains Incomplete Administration Instructions

The "Usual Dosage" statement on the carton labeling goes beyond specifying the dosage by providing instructions for administration of the product. However, the instructions are incomplete (e.g., there are no

instructions to wash hands after applying Gelnique). Our concern is that patients may see this information and assume the instructions are complete. Therefore, our preference is that the "Usual Dosage" statement be changed to: "See accompanying prescribing information..." Additionally, if this is done, the "Physician" statement, "See accompanying prescribing information", can be deleted.

4.1.7 Insert Labeling

We identified several areas where clarity or slight modifications in the text are needed in order to help ensure the safe use of the product. For instance, there is a sentence in Section 17.1 that states*: "It is recommended that application sites be kept covered if close skin-to-skin contact is anticipated."* However, it is not clear how or with what the area should be covered. This is important information for healthcare practitioners and patients to know. Our concerns stem from postmarketing surveillance of medication errors which identified cases where users have applied occlusive dressings such as plastic wrap over topically applied products and altered the product absorption which led to serious adverse events and even death. Our intention is not to imply that such adverse events will occur with the use of this product but to emphasize that the instructions for use can be enhanced such that they are as complete and clear as possible; the goal being to minimize or prevent improper use of the product. There are also areas in Section 17.2 of the package insert labeling that we have identified as needing clarification or modification and these are addressed in Section 6, Recommendations, of this review.

5 CONCLUSIONS

The Label and Labeling Risk Assessment found the presentation of information on the proposed container label, carton and insert labeling vulnerable to confusion that could lead to medication errors. Specifically, there are areas where information such as the presentation of the proprietary name, established name, statement of total drug content of the sachet, and usual dosage statement need to be modified, clarified, or relocated in order to make the labels less vulnerable to medication errors.

The Division of Medication Error Prevention and Analysis believes the risks we have identified can be addressed and mitigated prior to drug approval and provides recommendations in Section 6 that aim at reducing the risk of medication errors.

6 RECOMMENDATIONS

6.1 COMMENTS TO THE DIVISION

DMEPA recommends against the use of (b) (4) lettering in the presentation of the proprietary name. Additionally, DMEPA also recommends the Division consult DDMAC concerning the presentation of the proposed proprietary name, "Gelnique", on the container labels and carton labeling to limit the potential for misleading advertisements, etc., once this application is approved especially since DDMAC was concerned that this proprietary name was misleading.

DMEPA's recommendations concerning the duplicate proprietary name presentation and the presentation of the statement of total drug content of the sachet were discussed with the CMC reviewer. They are in agreement with our recommendations per email communications of December 12, 2008.

We would appreciate feedback on the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any correspondence to the Applicant pertaining to this issue. If you have further questions or need clarifications, please contact Cherye Milburn, OSE Project Manager, at 301-796-2084.

6.2 COMMENTS TO THE APPLICANT

1. All Labels and Labeling

a. The established name is not consistently presented throughout the labels and labeling. Ensure that the established name is consistently presented throughout all labels and labeling. The recommended presentation is as follows:

PROPRIETARY NAME (oxybutynin chloride) Gel 10%

2. Container Label and Carton Labeling

(b) (4)

3. Carton Labeling

(b) (4)

(b) (4)

4. Insert Labeling

a. Section 17.1. states: "It is recommended that application sites be covered if close skin-to-skin contact is anticipated." Please specify what are considered to be appropriate and inappropriate coverings.

b. Section 17.2 under "How should I use Trade name". Please label the diagrams (e.g., Diagram 1, Diagram 2) and refer to these diagrams, as appropriate, in the text portion of the instructions.

1 pp withheld immed. after this page as (b)(4) Draft labeling.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Loretta Holmes
12/31/2008 01:20:29 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
12/31/2008 01:29:51 PM
DRUG SAFETY OFFICE REVIEWER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-0700
FAX 301-796-9744

Maternal Health Team Review

Date: Nov. 10, 2008 **Date Consulted:** Sept. 30, 2008

From: Tammie Brent, RN MSN
Regulatory Reviewer, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Team Leader, Maternal Health Team (MHT)
Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Reproductive and Urologic Products (DRUP)

Drug: Oxybutynin Chloride Topical Gel; NDA 22-204

Subject: Pregnancy and Nursing Mothers labeling

Materials Reviewed: Pregnancy and Nursing Mothers subsections of Oxybutynin Chloride Topical Gel labeling.

Consult Question: Please review the package insert.

INTRODUCTION

On March 26, 2008, Watson Laboratories, Inc. submitted a new drug application (NDA) 22-204 to the Division of Reproductive and Urologic Products (DRUP) for Oxybutynin Chloride Topical Gel. The sponsors proposed indication for Oxybutynin Chloride Topical Gel is for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency and frequency.

On September 30, 2008, DRUP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the Oxybutynin Chloride Topical Gel package insert, and provide comment. This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Oxybutynin Chloride Topical Gel labeling.

BACKGROUND

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 29, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of Oxybutynin Chloride Topical Gel labeling.

SUMBMITTED MATERIAL

Sponsors Proposed Pregnancy and Nursing Mothers Labeling

8.1 Pregnancy

Pregnancy Category B

(b) (4)

Subcutaneous administration to rats at doses up to 25 mg/kg (approximately 50 times the human exposure based on surface area) and to rabbits at doses up to 0.4 mg/kg (approximately 1 times the human exposure) revealed no evidence of harm to the fetus due to oxybutynin chloride. The safety of TRADENAME administration to women who are or who may become pregnant has not been established. Therefore, TRADENAME should not be given to pregnant women unless, in the judgment of the physician, the probable clinical benefits outweigh the possible hazards.

8.2 Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADENAME is administered to a nursing woman.

RECOMMENDATIONS

Provided below are the MHT's recommended revisions to the sponsors' proposed labeling. Appendix A of this review provides a track changes version of labeling that highlights all changes made.

8.1 Pregnancy

Pregnancy Category B

There are no adequate and well-controlled studies of topical or oral oxybutynin use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at oxybutynin exposures up to 50 times and 1 time the therapeutic human exposure, respectively, did not impair fertility or produce fetal harm. Studies in mice and hamsters were also negative. Because animal reproduction studies are not always predictive of human response, oxybutynin should be used during pregnancy only if clearly needed, [*see Nonclincial Toxicology, (13.3)*].

8.2 Nursing Mothers

It is not known whether oxybutynin is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TRADENAME is administered to a nursing woman.

CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for Oxybutynin Chloride Topical Gel is provided on page 3 of this review. Appendix A of this review also provides a track changes version of labeling.

Appendix A –

Track Changes Version of Labeling

21 pp withheld following this page as (b)(4) draft labeling.

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/s/

Tammie Brent-Steele
1/15/2009 11:51:50 AM
CSO

Karen Feibus
1/16/2009 08:06:27 AM
MEDICAL OFFICER
I have reviewed and concur with these recommendations. These labeling recommendations were provided to the Division in mid November 2008, and this review is being placed in DFS now at the Division's request to provide accurate archiving.

Lisa Mathis
1/16/2009 02:17:44 PM
MEDICAL OFFICER

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: September 29, 2008

TO: Celia Hayes, Regulatory Project Manager
C. Nguyen, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch 1
Division of Scientific Investigations

THROUGH: Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA: 22-204

APPLICANT: Watson Laboratories, Inc.

DRUG: Oxybutynin chloride topical gel

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency

CONSULTATION REQUEST DATE: June 11, 2008

DIVISION ACTION GOAL DATE: November 14, 2008

PDUFA DATE: January 27, 2009

I. BACKGROUND:

The conduct of protocol #OG05009 entitled "A Multi-Center, Double-Blind, Placebo-Controlled Study of the Efficacy and Safety of Daily Dosing with Oxybutynin Topical Gel to Treat the Symptoms of Overactive Bladder" was inspected at the clinical sites of Drs. Deeths and Schmidt. These two sites were chosen because of their relatively large enrollment numbers.

Subjects diagnosed with overactive bladder with symptoms of urge urinary incontinence, urgency and urinary frequency were treated with one gram of the study drug topically on a daily basis for up to 12 weeks. Subjects returned to the clinic following 1, 4, 8 and 12 weeks of treatment after completing 3-day urinary diaries, quality of life (QoL) questionnaires, and blood sampling for plasma drug concentrations and for monitoring of adverse events.

The primary objective of this study was to compare the efficacy of daily treatment of a 1 gram dose of 10% oxybutynin gel with placebo gel treatment during the 12-week study period. The protocol's efficacy assessments were based on diary data and questionnaire responses. The primary efficacy endpoint in this study was the change from baseline (CFB) in the number of urinary incontinence episodes per day to endpoint (Week 12 [LOCF]).

II. RESULTS (by Site):

Name of CI, CRO or Sponsor Location	**Protocol #: / # of Subjects/**	**Inspection Dates**	**Final Classification**
Leah Schmidt, D. O. 6261 North La Cholla, Suite 281 Tucson, AZ 85741	Protocol # OG05009/ 24/	15-16 Jul 2008	NAI
Harry Deeths, M.D. 10040 Regency Circle, Suite 375 Quality Clinical Research Omaha, NE 68114	Protocol # OG05009/ 35/	13-18 Aug 2008	NAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field and complete review of EIR is pending.

1. Leah Schmidt, D. O.
   6261 North La Cholla, Suite 281
   Tucson, AZ 85741

   a. **What was inspected**: 24 subjects were randomized to the study. The records for 12 subjects were reviewed including, but not limited to, consent forms, laboratory results, inclusion/exclusion criteria, ECGs, physical examinations, adverse events, concomitant medications, subject diaries, and test article accountability.

   b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

   c. **Assessment of data integrity**: Data appear acceptable in support of the respective application.

2. Harry Deeths, M.D.
   10040 Regency Circle, Suite 375
   Quality Clinical Research
   Omaha, NE 68114

   a. **What was inspected**: 61 subjects were screened and randomized to the study, with 23 completing the study. All subjects signed consent forms. The records for 45 subjects were reviewed including, but not limited to, patient eligibility criteria, physician notes, laboratory results, urinary diaries, concomitant medications, adverse event logs, and test article accountability.

   b. **General observations/commentary**: Review of the records noted above revealed no significant discrepancies/regulatory violations.

   c. **Assessment of data integrity:** Data appear acceptable in support of the respective application.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The data generated by the clinical sites of Drs. Schmidt and Deeths appear acceptable in support of the respective application.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

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/s/

Roy Blay
10/2/2008 09:09:53 AM
CSO

Constance Lewin
10/3/2008 08:05:19 AM
MEDICAL OFFICER

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Memorandum

Date: July 29, 2008

From: Dr. Thomas J. Moskal, Regulatory Review Officer
Division of Drug Marketing, Advertising and Communication

To: Ms. Celia Hayes, Project Manager
Division of Reproductive and Urologic Drug Products

Subject: Comments on Draft Labeling - NDA22-204, Oxybutynin Chloride Topical Gel

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** Pre-decisional Agency Information**

DDMAC has reviewed the proposed package insert (PI) and patient package insert (PPI) for NDA 22-204, Oxybutynin Chloride Topical Gel.

Package Insert (PI)

Highlights

Under **Dosage and Administration**, we recommend adding the statement *"Patients should wash hands immediately after product application"* following either the first or second sentence.

Full Prescribing Information

Under **section 2, Dosage and Administration**, we recommend adding the statement *"TRADENAME should not be applied to recently shaved skin surfaces"* following the first sentence.

Under **section 2, Dosage and Administration**, we recommend adding the statement *"Patients should wash hands immediately after product application"* to the end of that paragraph.

Under **section 5.2, Gastrointestinal Disorders**, we recommend adding the phrase *"and myasthenia gravis"* following the phrase *"…conditions such as ulcerative colitis, intestinal atony…"* All three conditions are given as examples on the PI for Oxytrol.

Section 6.1, paragraph 6 contains the statement (b) (4) We suggest that the primary review division confirm the suggestion that the (b) (4) of treatment-related adverse events are, in fact, (b) (4)

In **section 7.1** the term *"somnolence"* has not been included preceding *"…and other anticholinergic-like effects..."* as it has on the PI for Oxytrol.

Section 8.3, Geriatric Use states *"No* (b) (4) *differences in safety or effectiveness were observed between these patients and younger patients."* 21 CFR 201.57(c)(9)(v)(B) provides that the Geriatric Use section must contain specific statements or reasonable alternatives. The statement provided in the draft PI is not consistent with statements required by the regulation. We refer the primary review division to that section of the regulation for determination of appropriate language for this section of the PI. Specifically we recommend replacing the term (b) (4) with *"overall"*, and including the statement *"…and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out."*

Section 12.2 under *Absorption* includes a short paragraph and Table 3 that discuss a study comparing the steady-state pharmacokinetics of TRADENAME and 3.9 mg/day Oxytrol. We suggest the trade name "Oxytrol" be replaced with "oxybutynin transdermal system" or "transdermal oxybutynin".

(b) (4)

(b) (4)

Regarding **section 17.1**, DDMAC discourages use of the phrase (b) (4) " and suggests deleting this phrase from the first sentence of the second paragraph. Other occurrences of this phrase correspond with those present on the PI for

Oxytrol. The reviewing division may wish to consider the utility of this phrase in this section.

Also in **section 17.1** we note that the term (b) (4) has not been included preceding (b) (4) as in the PI for Oxytrol. Also missing from the draft PI is the statement (b) (4)

Patient Package Insert (PPI)

Under the question ***"How should I use TRADENAME?"*** we noticed an apparent error under Step 7. In the statement *"Avoid …emerging the application site in water…"* The word "*emerging"* appears to be incorrect. We suggest replacing that term with either "immersing" or "submerging".

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Thomas Moskal
8/4/2008 10:17:53 AM
DDMAC REVIEWER

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-204 Supplement # Efficacy Supplement Type SE-

Proprietary Name: (potential trade names currently under review)
Established Name: oxybutynin chloride topical gel
Strengths: 10% (100mg/gram)

Applicant: Watson
Agent for Applicant (if applicable):

Date of Application: March 26, 2008
Date of Receipt: March 27, 2008
Date clock started after UN:
Date of Filing Meeting: May 14, 2008
Filing Date: May 26, 2008
Action Goal Date (optional): January 27, 2009 User Fee Goal Date: January 27, 2009

Indication(s) requested: Treatment of patients with overactive bladder with symptoms of urge urinary incontinence urgency and frequency

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic ☐ Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format ☐
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES ☐ NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES ☒
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, 3 Years NO ☐
NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
YES ☒ NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☒ NO ☐

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES ☒ NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES ☒ NO ☐
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 67,126

- Are the trade, established/proper, and applicant names correct in COMIS? YES ☒ NO ☐
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) August 2, 2005 NO ☐
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) December 12, 2007 NO ☐
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO ☒
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES ☒ NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES ☒ NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES ☒ NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES ☒ NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☒ NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO ☐

- Establishment Evaluation Request (EER) submitted to DMPQ? YES ☒ NO ☐

- If a parenteral product, consulted to Microbiology Team? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: May 14, 2008

NDA #: 22-204

DRUG NAMES: Oxybutinin Chloride Topical Gel

APPLICANT: Watson

BACKGROUND:

Oxybutynin chloride topical gel 10% (OTG 10%) is an anticholinergic product developed by Watson Laboratories, Inc., as a topical gel formulation for once a day dosing for the treatment of overactive bladder. The sponsor is seeking approval of this product for the "treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency." The proposed dose is one sachet containing 1 g of 10% oxybutynin gel (100 mg oxybutynin) once daily with no specific dose adjustments for specific populations. OTG 10% has not been approved for marketing in any country.

ATTENDEES:

George Benson, M.D., Acting Deputy Director, Division of Reproductive and Urologic Products (DRUP)
Christine Nguyen, M.D.,Medical Officer, DRUP
Lynnda Reid, Ph.D., Pharmacology/Toxicology Supervisor, DRUP
Myong-Jin Kim, Pharm.D., Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Laurie McLeod-Flynn, Ph.D., Pharmacologist, DRUP
Sonia Castillo, Ph.D., Statistician, Division of Biometrics (DB III)
Donna Christner, Ph.D., Chemistry Reviewer, Office of Pharmaceutical Science, Office of New Drug Quality Assessment, Division of Premarketing Assessment II (OPS/ONDQA/DPA II)
Rajiv Agarwal, Ph.D., Chemistry Reviewer, OPS/ONDQA/DPA II
LaiMing Lee., Ph.D., Clinical Pharmacologist, OCP
Celia Hayes, MPH, RD Regulatory Health Project Manager, DRUP
Margaret Kober,R.Ph., M.P.A., Chief, Project Management Staff, DRUP

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	**Reviewer**
Medical:	Christine Nguyen
Secondary Medical:	George Benson
Statistical:	Sonia Castillo
Pharmacology/Toxicology:	Laurie McLeod-Flynn
Chemistry:	Rajiv Agarwal
Environmental Assessment (if needed):	
Biopharmaceutical:	LaiMing Lee
Microbiology, sterility:	

Microbiology, clinical (for antimicrobial products only):

Regulatory Project Management:	Celia Hayes
Other Consults:	
OSE	Cherye Milburn
PEDS	Rosemary Addy
Microbiology	Jim McVey
DSI	Roy Blay

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES ☒ NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? ☐ NO ☒
  YES

PHARMACOLOGY/TOX N/A ☐ FILE ☒ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☒

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Sterile product? YES ☐ NO ☒
  If yes, was microbiology consulted for validation of sterilization?
  YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

☐ No filing issues have been identified.

☒ Filing issues to be communicated by Day 74. List (optional):

Clinical

1. Skin safety, especially skin sensitization, will be a review issue.
2. The changes from baseline in the Incontinence Impact Questionnaire total score and subscales and in the King's Health Questionnaire domain scores are currently considered exploratory endpoints. The Division does not anticipate including data from these questionnaires in labeling.
3. Provide case narratives for all subjects/patients who discontinued prematurely due to an adverse event.
4. For Study OG05009, provide summaries for the following laboratory outliers:
   - AST ≥ 3X ULN and ≥ 5X ULN
   - ALT ≥ 3X ULN and ≥ 5X ULN
   - Total bilirubin ≥ 2X ULN
   - Creatinine ≥ 2X ULN
   - These summaries should be provided for placebo and OTG groups in the double-blind phase, and for the treatment group with < 12 weeks OTG exposure and the treatment group with ≥ 12 weeks of OTG exposure in the double-blind and open-label phases.
5. Define what changes in laboratory parameters are considered as "clinically significant" in Table 12-10 (page 88) of the Study Report for OG05009.
6. For Study OG05009, provide summaries of clinically significant changes in vital signs for the absolute change from baseline (e.g., systolic BP change ≥ 20 mmHg) separately from those exceeding a pre-defined value (e.g., systolic BP ≥ 180 mmHg).
7. We acknowledge your plans to fulfill the PREA requirements and will determine the acceptability of your proposed plans prior to the PDUFA date of January 27, 2009.

Chemistry

8. Update the NDC number on the container labels, and include the NDC number on the Package Insert in the How Supplied section and in the DLDE section of the SPL label.
9. Provide color mock-ups for the carton and immediate container labels, including any logos, to allow full review of these labels.

Pharmacology/Toxicology

10. The four leachable substances found in the drug product (b) (4) will be a review issue. Provide reviewable toxicology data for these substances justifying their safe use under chronic dermal exposure conditions for our review.

11. The metabolite PCGA and the (b) (4) impurities will be review issues. We suggest you provide structure activity analyses for these substances for our review.

ACTION ITEMS:

1. ☐ Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. ☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

3. ☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

4. ☒ If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

5. ☒ Convey document filing issues/no filing issues to applicant by Day 74.

Celia R Hayes
Regulatory Project Manager

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Celia R Hayes

6/12/2008 12:44:20 PM

CSO