Application number 77-312

Oral Transmucosal Fentanyl Citrate

RISK MINIMIZATION PLAN(RISKMAP)

I. GOALS:

The Oral Transmucosal Fentanyl Citrate (OTFC) Risk Management Program (RMP) is designed to address three key potential risk situations:

1) accidental ingestion of OTFC by children
2) improper patient selection (prescriptions to and usage by opioid non-tolerant patients)
3) diversion or abuse

BARR has designed and developed a comprehensive program with the primary goal of making every reasonable effort to reduce the risk of potential untoward events in the unintended populations to the extent possible.

II. RMP ELEMENTS:

A. MEDICATION GUIDE

A Medication Guide, located at the end of the Package Insert (see Attachment 1), has been written for OTFC, and five copies will be packaged in every shelf carton. Extra copies will be broadly available for use by physicians, nurses, pharmacists, caregivers, and patients upon request. The Guide will be included in the OTFC Welcome Kit. It will be available in Spanish as well.

- The first page of the OTFC Medication Guide contains a boxed warning and redundant child warning with graphics for emphasis.
- The OTFC Medication Guide explicitly addresses, in plain language, preventing access by children. These messages include:
  -Child Safety messages
  -Safe storage instructions for whole and partially consumed units
  -Disposal directions for used and unused units and a 1-800 number for additional disposal assistance. Patients calling the 1-800 number will receive a more personalized “walk through” of disposal instructions. If additional assistance is required, callers will be referred to their local DEA office for information.
- It contains emergency information on what should be done in case of accidental ingestion by a child or any opioid non-tolerant person.

-A prompt to call 911 if the patient or child is not awake and alert
-A prompt to call 1-800-222-1222 Poison Control hotline if the patient or child is awake
-instructions for care of the patient or child who is having trouble breathing or not breathing at all

- It contains proper patient selection messages
- Strong language has been used throughout the OTFC Medication Guide. In all warning statements, the word "must" is used instead of the word "should". The warning language "can be harmful or fatal to a child" and "can cause injury or death in people who are not already taking prescription opioid pain medicines. ..is used.

B. PLAN TO MONITOR:

1. SURVEILLANCE ACTIVITIES

The goals of the *Oral Transmucosal Fentanyl Citrate* surveillance program are to:

- Determine the effectiveness of the *Oral Transmucosal Fentanyl Citrate* RMP by monitoring the incidence and outcome of child accidental ingestion, product use among opioid non-tolerant populations, and diversion and abuse;
- Evaluate intervention when appropriate;
- Make modifications to the *Oral Transmucosal Fentanyl Citrate* RMP to improve its effectiveness.

The following pages summarize the various means by which *Oral Transmucosal Fentanyl Citrate* use and safety data will be collated and analyzed. (In the event that any of the pharmacy organizations are unable to participate in this program, Barr Laboratories will commit to substituting another potential supplier to broaden our sample in a timely manner.)

1.1 Direct Patient Feedback

A call back system will be used to directly query Oral Transmucosal Fentanyl Citrate patients. Under this program, Barr Laboratories, Inc. will arrange to have a 3rd party (e.g. Walgreens) contact a representative sample of patients who receive a new Oral Transmucosal Fentanyl Citrate prescription. During this call, information related to the safe use of the product, such as the following, will be collected:

• Did the patient receive a Child Safety Kit?

• Was the patient already on a strong opioid when they received the Oral Transmucosal Fentanyl Citrate prescription?

• Was the patient or caregiver provided with the appropriate safety messages?

• What titration process has been used to this point?

• Are there any children in the home or with access to the home?

• How is the patient or caregiver storing and disposing of the product?

• Provide a child safety reminder

This program will capture real time trends of inappropriate patient selection and child safety issues among patients who fill Oral Transmucosal Fentanyl Citrate prescriptions in a geographically distributed population sample. This information will be reported in quarterly RMP reports. After the first year of the call back program, Barr Laboratories and the FDA may agree to discontinue the call back program if it can be established that there is no longer a need.

1.2 Prescription Monitoring

1.2.1 IMS Xponent

Prescription data will be routinely monitored. The source of this data will be IMS Xponent, the largest sample available of Oral Transmucosal Fentanyl Citrate prescriptions, segmented by physician specialty to determine prescribing trends. The IMS Xponent data sample represents preseciptions from over one million prescribers and over 35,000 retail pharmacies. Additionally, IMS Xponent captures 60 million mail order prescriptions per year. These data provide the prescriber's name, the physician specialty and zip code. These data will be analyzed by comparing the proportion of prescriptions being written by specialties such as hematologists/oncologists (appropriate patient selection) to usage by specialties such as surgeons (inappropriate patient selection). Barr Laboratories will receive data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

1.2.2 IMS National Disease and Therapeutic Index

National prescription data segmented by physician specialty and by indication from IMS National Disease and Therapeutic Index (NDTI) will be analyzed. These data will be reported to the FDA on a quarterly basis as described in Section 7.0.

1.2.3 Wholesaler Data

Barr will only sell to accounts with valid DEA licenses. The accounts include, wholesalers, distributers, retail drug distribution centers and hospitals. Barr's product will not be shipped directly to pharmacies. Barr Laboratories will receive information on retail pharmacy sales. This information will be used to determine high-volume Oral Transmucosal Fentanyl Citrate pharmacies. A letter will be sent to those pharmacies emphasizing key safety messages and proper use of the product. Barr Laboratories will include the number of letters sent to pharmacies in the quarterly RMP reports.

1.3 Adverse Events

1.3.1 Standard Operating Procedure

The processing of adverse event reports is guided by a Standard Operating Procedure summarized below.
A toll-free number will be available to receive adverse event reports. This system can be accessed 24 hours a day. Adverse events will be logged into a computer database and followed up as necessary by the company's pharmacovigilance department.

(a) Each incident report is reviewed to confirm the initial report classification, the reported ADE term, and to assess the report for seriousness, relatedness, and expectedness, based on criteria outlined in 21 CFR 314.80.

(b) Reports associated with Oral Transmucosal Fentanyl Citrate are also reviewed to determine reportability based upon the three key risk situations described in Sections 1.0. These key risk situations are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. They apply to reports from any source (e.g. call-in, poison control centers, etc).

1.3.2 Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. The following types of adverse experiences will also be reported to the FDA within 15 days.

• Any unintended pediatric exposure, whether or not serious and whether or not unexpected, will be processed and reported to the FDA as a 15-Day Alert.

• Any serious adverse drug experience which is determined to occur in the context of diversion or abuse (i.e. use by an individual other than for whom it was prescribed), whether or not the experience is unexpected, will be processed and reported to the FDA as a 15-Day Alert.

• Any serious adverse drug experience which is determined to occur in the context of "off-label use" (i.e. that is used outside of the approved indication for Oral Transmucosal Fentanyl Citrate) whether or not the experience is unexpected, will be reported to the FDA as a 15-Day Alert.

Definitions of "serious adverse drug experiences", "adverse drug experience", "unexpected adverse drug experiences," and "15-day Alert report," are stated in 21 CFR §314.80. These Special Safety Commitments are in addition to the requirement for reporting of adverse experiences set down in 21 CFR §314.80. The above apply to reports from any source (e.g. call in, poison control centers, etc.).

1.3.3 Literature Monitoring

In addition to specific event reporting, Barr maintains a system to monitor the literature for adverse events. This review is conducted weekly or at the time a specific literature citation is reported. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80)

1.4 Poisoning and Overdose

Quarterly reports to FDA will include poison information, trends, and interventions derived from the following sources:

1.4.1 Toll-Free Poison Control Number

A toll-free number will be established to receive emergency calls when Oral Transmucosal Fentanyl Citrate has potentially been accidentally ingested and the patient or child is awake and alert. This system allows a near real time surveillance of all poisoncontrol calls. This number will be highly publicized in all patient education materials. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

1.4.2 Toxic Exposure Surveillance System (TESS)
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Toxic Exposure Surveillance System (TESS) reports all contacts with U.S. Poison Control Centers. This database will be monitored for Oral Transmucosal Fentanyl Citrate exposures. These data are available once yearly and will be included in the analysis for FDA quarterly reports.

1.5 Abuse

Quarterly reports to FDA will include information from the following sources:

1.5.1 DEA Interaction
Barr Laboratories, Inc. will maintain communications with DEA and state drug control authorities. Barr Laboratories, Inc. will institute a proactive program to identify possible diversion. If Barr Laboratories, Inc. receives any order that deviates from past order patterns for a particular strength, at a particular distribution center, without a reasonable explanation, Barr Laboratories, Inc. will not satisfy the order and will alert DEA for follow-up and investigation.

1.5.2 Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of non-federal, short-stay general hospitals that have a 24-hour emergency department (ED). A representative sample of these hospital EDs submit data, and national estimates of drug episodes or drug mentions are generated for all such hospitals. The DAWN system collects information on deaths related to drug abuse that were identified and submitted

voluntarily by participating death investigation jurisdictions across the United States. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. This database will also be monitored to identify issues which have not surfaced through standard DEA interactions.

1.5.3 State Drug Control Authorities or State Pharmacy Boards

Reports of diversion or abuse received from state drug control authorities will be investigated and submitted to the FDA as part of the quarterly report.
None included. See comments from the firm above.

1.6 INTERVENTION

1.6. Off-Label Usage

1.6.1 Individual Prescribers

Because off-label use may, in some circumstances, suggest improper patient selection, off-label use will be noted and reported as a 15-Day Alert Report if associated with a serious adverse event, regardless of whether that event is listed in the package insert (i.e., is “expected”) or not (i.e., is “unexpected”). In addition, when the first incident of off-label prescribing becomes known to Barr Laboratories during surveillance activities and individual prescribers are identified, a letter from Barr Laboratories, Inc. will be sent to those prescribers to emphasize the approved indication and proper patient selection. The letter must have FDA review and approval before it is issued. The number of letters sent to prescribers will be provided in the quarterly RMP reports.
Prescribing patterns for the physicians in question will be monitored. If the problem persists they will be reminded of appropriate prescribing of Oral Transmucosal Fentanyl Citrate.

1.6.2 Groups of Prescribers

If groups of physicians (such as a particular specialty) are identified as having prescribed Oral Transmucosal Fentanyl Citrate inappropriately, and these prescriptions represent potential off-label usage greater than 15% of total quarterly Oral Transmucosal Fentanyl Citrate prescriptions, Barr Laboratories will send a letter to the appropriate professional society (i.e., American College of Surgeons, American Society of Anesthesiologists) to provide key safety messages and instructions for the proper use of the product.
Prescribing patterns will be monitored for the physician groups in question and should the level continue to exceed 15% of total Oral Transmucosal Fentanyl Citrate prescriptions for two additional quarters, the groups will be reminded of appropriate prescribing of Oral Transmucosal Fentanyl Citrate.

1.6.3 Accidental Ingestion

In the event of an unintended pediatric exposure, Barr Laboratories, will initiate their standard operating procedure for reporting adverse events detailed in section 5.3 of this RMP.

1.7 FDA REPORTING

Adverse drug experiences will be reported in accordance with 21 CFR §314.80, with the additional commitment that unintended pediatric exposures, and any serious adverse events and deaths associated with diversion or off-label use will be handled and processed as 15-day Alert reports (see Section 5.3.2 Special Safety Commitments). In addition, Barr Laboratories, Inc. will provide a quarterly RMP report to the FDA compiled from all data collected by the methods described under the Oral Transmucosal Fentanyl Citrate Surveillance Activities (see Section 5.0 of this document). This report will describe and provide data on any concerns related to accidental pediatric exposure, diversion or abuse, and improper patient selection. Barr Laboratories, Inc. will also describe any trends and associated interventions made as a result of concerns raised and will also describe any proposed changes to the Oral Transmucosal Fentanyl Citrate Risk Management Plan. These reports will be cumulative and contain current information and identified safety trends. The frequency of RMP reporting will be evaluated one year after Barr's Oral Transmucosal Fentanyl Citrate, OTFC, has entered the market to determine if another reporting timeframe such as bi-annual reporting may be more appropriate. At this time, Barr Laboratories, Inc. will discuss a proposal with FDA for optimal reporting requirements.

C. WELCOME KIT

- Fanny Pack with lock & keys
- The Child Safety Lock
- Child-Resistant temporary storage container
- Home warning stickers
- Daily Diary
- Brightly Colored Warning Flyers.

The following components will not be approved as part of the RiskMap. However, you may distribute them as promotional materials, to the extent that the content of the materials are in compliance with the Act and implementing regulations.

- refrigerator magnets
- the diary marker
- the safety video
- the children's booklet.

APPENDIX A: SUPPORTING DOCUMENT

- Medication Guide
- Welcome Kit Components