

Application number 78-907

Oral Transmucosal Fentanyl Citrate

RISK MINIMIZATION PLAN (RISKMAP)

I. GOALS:

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

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

Mallinckrodt 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

Medication Guide contains black box warning, strongly worded child safety warnings, proper patient selection instructions and clear disposal instructions. Every carton will be supplied with one combined package insert and patient medication guide and 5 additional patient medication guides, consistent with current RLD practice.

- a. Black box warning and conspicuous child safety warning icon—

“WARNING: You MUST keep oral transmucosal fentanyl citrate in a safe place out of the reach of children. Accidental ingestion by a child is a medical emergency and can result in death. If a child accidentally takes oral transmucosal fentanyl citrate, get emergency help right away.”

- b. Contains clear instructions to the patient to **“Read the Medication Guide that comes with oral transmucosal fentanyl citrate** before you start taking it and each time you get a new prescription.”

- c. Describes in plain language the proper use, storage, and disposal instructions for consumed units, partially consumed units and unopened units when no longer needed.

- d. Contains prominent bold warning for proper use: “**Do not bite or chew oral transmucosal fentanyl citrate. You will get less relief for your breakthrough pain.**”
- e. Provides contact phone number, for additional information on the drug product by instructing patients to call the Mallinckrodt Medical Information Department at 888-744-1414 option 2 then 1, for information on this product.
- f. Provides instructions on how to obtain a welcome kit and details welcome kit contents.

B. PLAN TO MONITOR:

The goals of the Oral Transmucosal Fentanyl Citrate Plan to Monitor Program are to:

- determine the effectiveness of the Oral Transmucosal Fentanyl Citrate Risk Management Program by monitoring the potential incidence and outcome of child accidental ingestion, potential product use among opioid non-tolerant populations, offlabel use, and possible diversion and abuse
- trigger intervention when problems are discovered
- make modifications to the Oral Transmucosal Fentanyl Citrate Risk Management Program 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 these pharmacy organizations are unable to participate in this program, Mallinckrodt will commit to substituting another potential supplier to broaden our sample in a timely manner.)

1. Direct Patient Feedback

Mallinckrodt will employ a call back system with chain pharmacies that dispense our product.

a. Chain Pharmacy Call Back System

A call back system will be used to directly query Oral Transmucosal Fentanyl Citrate under this program, patients who receive an Oral Transmucosal Fentanyl Citrate prescription at a participating pharmacy will receive a followup phone call by a company pharmacist. During this call, the following information will be collected:

- Did the patient receive an Oral Transmucosal Fentanyl Citrate Welcome 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.

The partners included in this system include RiteAid, Wal-Mart, and CVS/Caremark. This program will capture real time trends of inappropriate patient selection and child safety issues during the first year of sales, interviewing up to 1,000 patients per chain who fill Oral Transmucosal Fentanyl Citrate prescriptions in each of these pharmacies.

This program will provide timely and specific data on actual patients in a significant, geographically distributed population sample as RiteAid, Wal-Mart and CVS/Caremark stores are well-distributed throughout the country.

CVS/Caremark represents roughly 12% of the pharmacy benefit manager's national market. After the first year of the call back programs, the firm and the FDA may agree to discontinue the call back programs if it can be established that there is no longer a need.

2. Prescription Monitoring

a. IMS Xponent

Prescription data will be routinely monitored. The source of these 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 prescriptions 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).

Mallinckrodt will receive IMS Xponent data 28 days after the end of each month. Therefore, data will be between 28-58 days current.

3. 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 FDA Reporting.

4. Wholesaler Data

Mallinckrodt will obtain and report data on Oral Transmucosal Fentanyl Citrate sales to wholesalers and pharmacy outlets (through wholesaler data) and share with Mallinckrodt account managers. Mallinckrodt's account managers will call on high volume wholesale customers and follow-up with pharmacy outlets to ensure they are employing the "Point of Dispensing" interventions described previously.

Additionally, every two months, Mallinckrodt account managers will follow-up with high volume wholesalers to request information on additional pharmacies that require follow-up. The information will be shared among account managers (with wholesaler and pharmacy customers) for follow-up.

5. Adverse Events

a. Mallinckrodt Standard Operating Procedure

Mallinckrodt has established specific procedures to respond to serious adverse events, which may be associated with Oral Transmucosal Fentanyl Citrate (as per SOP PM-060 provided as Appendix 17). A toll-free number will be staffed to receive adverse event reports. This system can be accessed 24 hours a day.

Reports can be logged by clinicians, pharmacists, home caregivers, patients, sales representatives or others. All reports are logged into a computer database and investigated. Any adverse event, as defined by current federal regulations, receives immediate investigation and follow-up by Mallinckrodt, according to our established procedures (as per SOP PM-065 provided as Appendix 18).

b. Special Safety Commitments

Reports of all serious adverse events to the FDA will be made in accordance with current Federal Regulations. Based on an agreement between FDA and the sponsor, the following type 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 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 processed and 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, literature, poison control centers, etc).

c. Literature Monitoring

In addition to specific event reporting, Mallinckrodt monitors scientific and lay literature for adverse events (per SOP PM-080, included as Appendix 19). Our “clipping service” sources Meltwater News and Factiva electronic media monitoring sources. Any significant findings will be included in the quarterly report (as per 21 CFR §314.80).

d. Poisoning and Overdose

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

i. Central 1-800 Poison Control Number

As an industry product surveillance member of the American Association of Poison Control Centers (AAPCC), Mallinckrodt may publish the toll free poison

control number in its material. 1-800-222-1222 is a nationwide number that provides access to nearest of 61 USpoison control centers serving the caller based on the area code and exchange of the caller. The number is functional 24 hours a day in the 50 United States, the District of Columbia, the US Virgin Islands and Puerto Rico. Any significant findings will be included in the quarterlyreport (as per 21CFR §314.80).

ii. National Poison Data Base (NPDS)

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data Base (NPDS), which is the only comprehensive poisoning surveillance database in the United States.

AAPCC uses this system to publish an annual report of all poisonings. This database will be monitored for Oral Transmucosal Fentanyl Citrate exposures and will be included in the analysis for FDA quarterly reports.

e. Abuse

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

i. Routine Mallinckrodt Interaction with DEA

As a DEA registrant, Mallinckrodt is required to develop andimplement a system to monitor suspicious orders per the Controlled Substances Act. Through Mallinckrodt’s standard procedures, we can identify and intervene if diversion is suspected. This procedure includes investigation and immediate action upon confirmation of a suspicious order that includes reporting to local DEA office.

ii. Drug Abuse Warning Network (DAWN)

The Drug Abuse Warning Network (DAWN) is an ongoing national survey of nonfederal, 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 ED drug episodes or drug mentions are generated for all such hospitals. The DAWN system also collects data on drug-related deaths from a nonrandom sample of medical examiners located in 41 metropolitan areas. The Substance Abuse and Mental Health Services Administration (SAMHSA) division of the Department of Health and Human Services (DHHS) supports DAWN. Mallinckrodt currently subscribes to the DAWN Live! Database. Access to product data is only generated by SAMSHA upon product approval. Upon approval of Oral Transmucosal Fentanyl Citrate, Mallinckrodt will begin reporting on emergency room visits associated with the Fentanyl molecule.

iii. Pharmacy Level Diversion

Mallinckrodt currently reviews the following data sources for reports of diversion or abuse: RxPatrol (online database of pharmacy thefts, robberies, and burglaries) and RxNews (email distribution) from the National Association of Drug Diversion Investigators (NADDI). Mallinckrodt has developed a product identification chart (provided as Appendix 20) to facilitate investigation of diversion. Upon approval of

Oral Transmucosal Fentanyl Citrate, Mallinckrodt will revise the product identification chart to include the new product. When a report of diversion is received involving molecules that Mallinckrodt markets, a member of Mallinckrodt's staff contacts the source and provides the product identification chart to confirm whether our product is involved. Mallinckrodt will provide a quarterly report of number of cases reported, investigated, confirmed, and any additional action taken. Mallinckrodt is also a subscriber to the RADARS® System. This subscription provides information from several signal detection systems on trends of abuse and diversion. Upon approval for Oral Transmucosal Fentanyl Citrate, Mallinckrodt will begin expand its subscription to include data on this product.

6. Promotional Message Audit

See section **Surveillance** Section 8 for additional information.

Intervention

1. Off-Label Usage

Individual Prescribers and Groups of Prescribers

Whenever a problem of off-label usage becomes known and individual prescribers are identified, the following activities will take place:

1. A letter from Covidien's Product Monitoring will be sent to all identified prescribers to emphasize the approved indication and appropriate patient selection. The letter must have FDA review and approval before it is issued.
2. Prescribing patterns will be monitored for the physicians in question. If a problem persists, a Medical Science Liaison will visit the physician/s to gather information and remind them of appropriate prescribing of *Oral Transmucosal Fentanyl Citrate*.

2. Accidental Ingestion

In the event of an unintended pediatric exposure, Mallinckrodt will initiate our standard operating procedure for adverse events detailed in section Plan to Monitor Section 5 of this RMP.

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 Plan to Monitor Section 5b, Special Safety Commitments). In addition to the reporting requirements of 21 CFR §314.80(c), these 15-day Alert reports will be sent to the Division of Prescription Drug Compliance and Surveillance (HFD-330) and to the Office of Generic Drugs (OGD). Mallinckrodt will provide a quarterly report to the FDA compiled from all data collected by the methods

described under the Oral Transmucosal Fentanyl Citrate Surveillance, Plan to Monitor and Interventions Sections of this document. This report will describe and provide data on any concerns for child safety, diversion, and abuse. Mallinckrodt 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. This report will be provided as part of the Oral Transmucosal Fentanyl Citrate quarterly report to the ANDA during the first year of commercial availability. The sponsor and FDA will then determine requirements for further reports and their frequency thereafter.

C. WELCOME KIT

- Fanny Pack
- Lock & Keys
- Child Safety Lock
- Child Resistant Temporary Storage Container
- Home Warning Stickers
- Brightly Colored Warning Flyers
- Daily Diary

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
- Children's Booklet
- Diary Marker
- Patient Safety Video

APPENDIX A: SUPPORTING DOCUMENT

- Medication Guide
- Welcome Kit Components