Opioid Conversion Information in Approved Labeling

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Outline

- Background
- Opioid conversion information in approved product labeling
- Opioid Risk Evaluation and Mitigation Strategy (REMS)
- Safety labeling changes (SLC)
- Conclusions

Background

- Treatment of acute and chronic pain conditions have largely focused on prescription drugs, mainly opioids, and not multidisciplinary care
- A subset of patients are switched from one opioid or route of administration to another ("opioid rotation")
  - Intolerable side effects
  - Inadequate analgesia
  - Other reasons (e.g., drug-drug interactions, logistical, change in clinical status)
- Sections of labeling with relevant information on opioid conversion
  - Dosage and administration
  - Warnings and precautions
  - Clinical studies

Summary of findings in approved labeling

- Immediate release opioids
  - General information on conversion in the dosage and administration
  - No specific conversion tables
- Extended-release opioids
  - General information on conversion in dosage and administration
  - When conversion tables used in clinical trials is submitted with the application for approval they are included in dosage and administration
- Sources of opioid conversion information
  - Published literature
  - Consensus guidelines
  - Clinical trial data

Dosage and Administration

2.2 Initial Dosage

Use of [TRADENAME] as the First Opioid Analgesic

Initiate treatment with [TRADENAME] in a dosing range of X to X mg every X to X hours as needed for pain.

Conversion from Other Opioids to [TRADENAME]

There is inter-patient variability in the potency of opioid drugs and opioid formulations. Therefore, a conservative approach is advised when determining the total daily dosage of [TRADENAME]. It is safer to underestimate a patient's 24-hour [TRADENAME] dosage than to overestimate the 24-hour [TRADENAME] dosage and manage an adverse reaction due to overdose.

Conversion from [TRADENAME] to Extended-Release [active moiety]

The relative bioavailability of [TRADENAME] compared to extended-release [active moiety] is unknown, so conversion to extended-release [dosage form] must be accompanied by close observation for signs of excessive sedation and respiratory depression.

ER/LA Opioids

- Dosage and Administration:
  - All labeling includes general and/or specific information on opioid conversion
    - "…substantial inter-patient variability in the relative potency of different opioid drugs and products…safer to underestimate dose and provide rescue medication than to overestimate…"
- Warnings and Precautions
  - Respiratory Depression and Death
    - "Overestimating the [tradename]dosage when converting patients from another opioid product can result in fatal overdose"
- Clinical studies

Conversion from other opioids to HYSINGLA ER

Table 1. Conversion factors to HYSINGLA ER (Not Equianalgesic Doses)

Opioid	Oral dose (mg)	Approximate oral conversion factor
Codeine	133	0.15
Hydromorphone	5	4
Methadone	13.3	1.5
Morphine	40	0.5
Oxycodone	20	1
Oxymorphone	10	2
Tramadol	200	0.1

- Section 2.2
  - This is **not** a table of equianalgesic doses
  - The conversion factors in this table are only for the conversion **from** the listed oral opioid **to** HYSINGLA ER
  - This table **cannot** be used to convert from HYSINGLA ER to another opioid. Doing so… may result in fatal overdose

Conversion from other opioids to OXYCONTIN for Pediatric patients 11 years and older

Prior Opioid	Conversion Factor	
	Oral	Parenteral*
Oxycodone	1	--
Hydrocodone	0.9	--
Hydromorphone	4	20
Morphine	0.5	3
Tramadol	0.17	0.2

*For patients receiving high-dose parenteral opioids, a more conservative conversion is warranted. For example, for high-dose parenteral morphine, use 1.5 instead of 3 as a multiplication factor.

- Section 2.2
  - Must be on and tolerating opioids for at least 5 days
  - This is **not** a table of equianalgesic doses
  - The conversion factors in this table are only for the conversion **from** the listed oral opioid **to** OXYCONTIN
  - This table **cannot** be used to convert from OXYCONTIN to another opioid. Doing so… may result in fatal overdose

Changes in approved opioid labeling

- In 2016 the FDA revised the package insert for all opioid analgesics
  - Standardized misuse and abuse language in boxed warning across all products and made additional changes based on other safety issues
  - Included clearer instructions regarding initial dosage, dosage modifications when switching from one opioid to another and when titrating the dosage
- In 2018 the FDA expanded the Risk Evaluation and Mitigation Strategy (REMS) to include immediate release opioids used in the outpatient setting and it is outlined in all opioid analgesic labeling

What is a REMS?

- Risk Evaluation and Mitigation Strategies (REMS) are drug safety programs that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh the risks
- REMS include a risk mitigation goal and may be comprised of information communicated to and/or required activities to be undertaken by one or more participants (e.g., health care providers, pharmacists, patients) who prescribe, dispense or take the medication.
- REMS are designed to reinforce medication use behaviors and actions that support the safe use of medications with serious safety concerns
- REMS can be required at the time of drug approval or during the postmarket period if new safety information becomes available

Opioid Analgesics REMS

- All extended-release, long-acting, and immediate release opioid analgesics intended for outpatient use are required to participate in the REMS
- The goal is to educate prescribers and other healthcare providers (including pharmacists and nurses) on the treatment and monitoring of patients with pain
- Intervention/Strategy:
  - The primary component of the Opioid Analgesic REMS is healthcare provider education based on the "Opioid Analgesic REMS Education Blueprint for Health Care Providers Involved in the Treatment and Monitoring of Patients with Pain"
    - Blueprint states that "safe conversion from other opioids" and "concepts and limitations of the conversion charts in labeling and the limitations of relative potency or equianalgesic dosing in literature" be included in these programs
  - Patient Counseling Document
  - Medication Guide

Conclusions

- Not all IR, ER/LA opioids have the exact same information on opioid conversion. The content of the label is specific to the data provided for the product being approved
- When conversion factor tables are provided for an opioid analgesic and are supported by clinical data, those tables may be included in the label
- All opioid labels have information regarding risks of initiating an opioid analgesic, making dosing changes, converting from one opioid to another, and discontinuing products.