FDA Perspective

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Overview

- Regulatory history
- Efficacy
- Safety
- Utilization data
- Risk Evaluation and Mitigation Strategy

Regulatory History

First review cycle:

- New Drug Application submitted March 31, 2016
  - *HYDEXOR is indicated for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting.*
- First Complete Response issued January 31, 2017

Regulatory History (2)

Second review cycle:

- Applicant sent in a response to the CRL on October 12, 2017
- During this second cycle, application was brought to AC
  - At that time, the proposed indication was for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing OINV

Regulatory History (3)

Advisory Committee:

- OINV may decrease over time and promethazine has severe and concerning side effects that are not commonly described with other antiemetics.

- Although the Applicant demonstrated efficacy in analgesia and OINV, the clinical trials demonstrate that the Applicant did not adequately identify a patient population that predictably requires concomitant analgesic and antiemetic therapy.

Regulatory History (4)

- Complete Response Letter issued April 12, 2018
- Post-action meeting held May 17, 2018
  - The Applicant acknowledged the need to adequately identify the intended patient population that requires Hydexor and proposed a modification to the indication such that Hydexor is prescribed for generally 3 days and no more than 5 days to patients expected to be prone to OINV.

Regulatory History (5)

Post-action meeting:

- The Division did not agree with this proposal, citing concerns raised at the AC meeting that this fixed-dose combination would expose many patients to promethazine who did not appear to need an anti-emetic.
- The Division noted that despite studying an enriched population for developing OINV, only approximately 30% of patients in the Norco-treated arm developed OINV on Day 1 and only 18% required rescue with an anti-emetic. The Division noted that the frequency of OINV decreased over the 5-day duration of the study.

Regulatory History (6)

Post-action meeting:

- Based on the discussion, the Applicant proposed to further limit the indication to use in post-surgical patients only and labeling that would include a Contraindication, Boxed Warning, or Warnings and Precaution statement against use in other patient populations.
- The Applicant also emphasized that Hydexor is intended for use on an as-needed basis and would further limit dosing to a maximum of five tablets per day. Approval would be accompanied by a post-marketing observational study to further assess safety. The Applicant noted that the FDA criteria used to capture OINV events (requiring an anti-emetic or experiencing vomiting; a 2-component analysis) excluded other clinically relevant presentations of OINV that could be further analyzed from the secondary endpoints.
- FDA and Applicant agreed that a reanalysis of the secondary endpoints to further identify the benefits of Hydexor in treating OINV would be included in a response to the second Complete Response letter.

Regulatory History (7)

Third review cycle:

- The second resubmission in response to the second CRL was received on August 9, 2018.
- No new efficacy data were submitted in this review cycle.
- Applicant submitted post hoc analyses for three subpopulations from CLCT-003, one of the two Phase 3 trials, to try to address the Agency's concerns regarding the low incidence rate of OINV in patients treated with Norco.

Regulatory History (8)

Third review cycle:

- The review team concluded that "these additional analyses of CLCT-003 still have not demonstrated a patient population that can be prospectively identified as patients who will predictably require concomitant therapy with an opioid analgesic and an antiemetic for every dose."
- On February 8, 2019, a third CR letter was issued that reiterated the previous deficiency:
  - *"…your post hoc analyses of subgroups of the study population have not contributed to a method for prospectively identifying a patient population that requires treatment with an antiemetic with every dose of analgesic as would occur with HYDEXOR, and as required by the Combination Rule 21 CFR 300.50."*

Regulatory History (9)

- Following the third Complete Response letter, the Applicant submitted a request for formal dispute resolution on April 12, 2019.
- In their request, the Applicant requested that the Office Director rescind the third Complete Response letter and approve Hydexor.

Regulatory History (10)

Request denied:

- Although the Applicant's request was denied, Dr. Thanh Hai instructed the Division to reconsider the Applicant's proposed labeling revision and "make revisions so that labeling and instructions for use will sufficiently address the Agency's concerns of respiratory depression when an opioid is used in combination with a CNS depressant. Such revisions might further include restrictions to dosing, patient population, labeling claims, product packaging, and distribution that may require a Risk Evaluation and Mitigation Strategy (REMS) specific to Hydexor."

Regulatory History (11)

Fourth review cycle:

- The application is currently in its fourth review cycle
  - Submission received June 28, 2019
- Response includes revised labeling and a REMS.

Current Proposed Indication

HYDEXOR is indicated for the management of acute post-operative pain severe enough to require an opioid analgesic, for a maximum of 3 days, in adults at high risk for nausea and vomiting with hydrocodone-containing products.

Limitations of Use:

- *Because of the risk for life-threatening respiratory depression and excessive sedation that may lead to falls or other accidents, HYDEXOR is limited to use in certified, medically supervised healthcare settings, such as hospitals and surgical centers, and should be used only when non-sedating alternatives are either not tolerated or ineffective.*
- *Because of the risk for fatal respiratory depression, do not use in pediatric patients.*
- *Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses [see Warnings and Precautions (5.3)], reserve HYDEXOR for use in patients for whom non-opioid analgesics:*
  - *Have not been tolerated, or are not expected to be tolerated*
  - *Have not provided adequate analgesia, or are not expected to provide adequate analgesia*

Efficacy

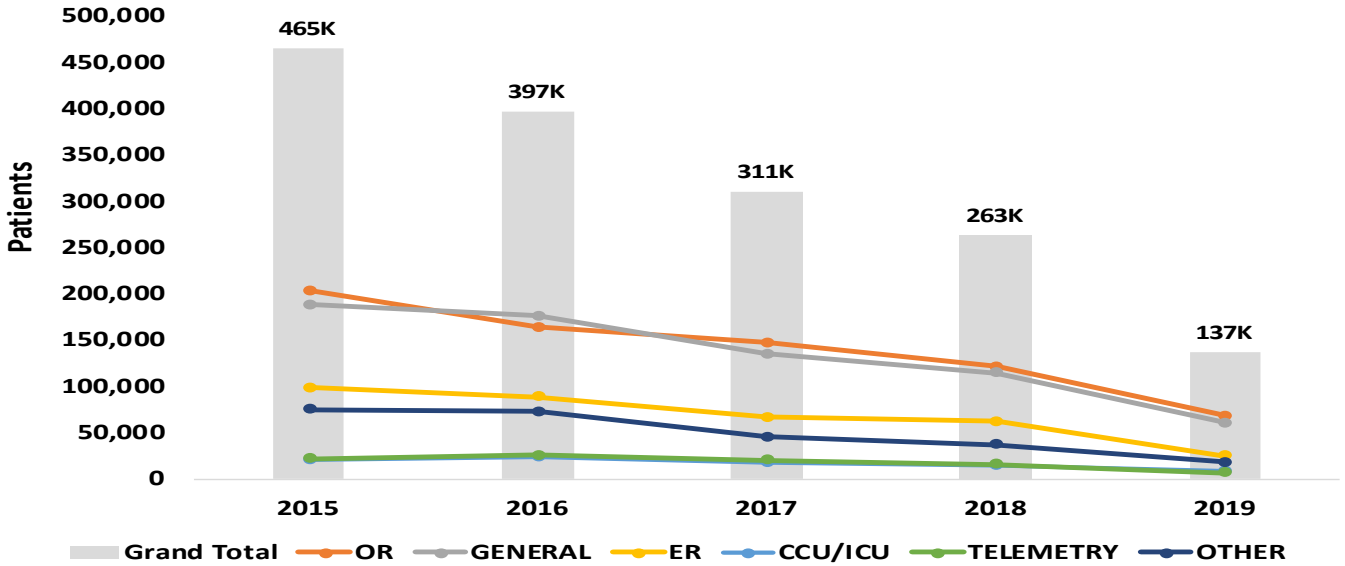
The Applicant submitted the results of two studies:

- Study CLCT-002
  - Conducted in a post-dental surgery patient population
- Study CLCT-003
  - Conducted in a post-bunionectomy patient population

Safety

- Safety profiles of the hydrocodone/acetaminophen combination product, as well as of promethazine have been well characterized
- The safety profile of the proposed combination product has also been well characterized in the drug development program
- Primary concerns revolved around the potential central nervous system depressant effects as a shared risk of hydrocodone and promethazine.

Decline in Patients with Concurrent Inpatient Use of Hydrocodone-Acetaminophen and Promethazine



Nationally Estimated Number of Patients with a Concurrent Hospital Discharge Billing for Hydrocodone-Acetaminophen and Promethazine* on the Same Day, in U.S. Non-Federal Hospitals

Source: IQVIA, Hospital Visit Analyzer™. 2015-2019. Ad-hoc data provided June 2020.
*Single-ingredient promethazine in oral or injectable dosage formulation
OR = operating room, ER = emergency room, CCU = coronary care unit, ICU = intensive care unit
Note: Location of care indicates a patient's hospital location(s) on the day of treatment. The two drugs may have been ordered or administered in different locations, so subtotals may sum to more than the grand totals.

FDA U.S. FOOD & DRUG ADMINISTRATION

Risk Management for Hydexor

Overview

- REMS Overview
- Risks Raised during the Previous Advisory Committee
- Current Risk Management Proposal

Risk Evaluation and Mitigation Strategy (REMS) Overview

REMS Overview

- A REMS is a drug safety program that FDA can require for certain drugs.
- The FDA Amendments Act (FDAAA) of 2007 authorized FDA to require Applicants or Application holders to develop and comply with REMS programs if determined necessary to ensure the benefits of a drug outweigh the risks.
- REMS include strategies beyond labeling to ensure that the benefits of a drug outweigh the risks.
- REMS are designed to achieve specific goals to mitigate risks associated with the use of a drug.
- FDA has authority to require a REMS pre-approval or post-approval.

REMS Components

- A REMS can include:
  - Medication Guide or Patient Package Insert
  - Communication Plan for healthcare providers
  - Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
  - Elements to Assure Safe Use (ETASU)
    - May include restricted distribution
  - Implementation System
- Must include a timetable for submission of assessments of the REMS*

**This requirement applies to NDAs and BLAs only. ANDAs (generics) are not required to include a timetable for submission of assessments for REMS.*

Elements to Assure Safe Use

- Certification and/or specialized training of healthcare providers who prescribe the drugs
- Certification of pharmacies, practitioners or healthcare settings that dispense the drug
- Dispensing/administration of drug in limited settings, e.g., hospitals
- Each patient using the drug is subject to certain monitoring
- Drug is dispensed/administered only with evidence of safe-use conditions, e.g., pregnancy test
- Enrollment of treated patients in a registry

Risks Raised during the Advisory Committee on February 14, 2018

Applicant's Proposed Indication and Use

Presented at the February 2018 AC

- Short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid induced nausea and vomiting (OINV).
- Treatment for less than 14 days with a dosing schedule of 1 tablet every 4-6 hours as the maximum daily dosage
- Use of product would have included both inpatient and outpatient treatment of pain and prevention of OINV

Applicant's Proposed Mitigation Plan

Presented at the February 2018 AC

- Hydexor was proposed to join the Opioid Analgesic REMS.
- Packaging for 3, 5 or 7 days of therapy that would be child-resistant packs.
- Opioid buyback program which would allow patients to return unused tablets for disposal.
- Collectively, the Applicant believed this would reduce the number of unused tablets available for abuse, misuse and diversion.

Concerns Raised by the Advisory Committee

Presented at the February 2018 AC

- The intended use was in a broad patient population and the duration of use was up to 14 days.
- Lack of dosing flexibility with a fixed-dose combination formulation thereby exposing patients to promethazine and its side effects, when it is not needed
- Lack of data on the risk of sedation and drop in blood pressure in the elderly population
- Proposed drug packaging that may encourage patients to finish the package when Hydexor should be used only as needed.
- Limited details on proposed buyback program implementation
- Most committee members expressed their concern that the Applicant's proposed risk management strategies for Hydexor were not adequate.

Agency Communications to the Applicant after the February 2018 Advisory Committee

- Applicant was advised of the need to narrow the patient population, as Hydexor is a fixed-dose combination that would expose many patients to additional risks with no added benefit.
- Agency raised concerns about the risk of CNS depression with an opioid analgesic and promethazine and that the risk of excessive sedation may result in falls or other accidents.
- Agency raised concerns about the risk of life-threatening respiratory depression, addiction, abuse and misuse as Hydexor includes an opioid.

Applicant's Current Risk Management Proposal

Applicant's Revisions to Address the AC's Concerns

AC Concerns – Feb 2018	Proposed labeling in the current submission
Use of Hydexor in a broad patient population and the duration of use was up to 14 days	Indicated only for the management of acute post-operative pain severe enough to require an opioid analgesic, for a maximum of 3 days, in adults at high risk for nausea and vomiting with hydrocodone-containing products
Lack of data on the risk of sedation and drop in blood pressure in the elderly population	Should only be used when non-sedating alternatives are either not tolerated or ineffective Should not be used in skilled nursing facilities where patients are likely to be older and more risk of respiratory depression and falls due to excessive sedation

Applicant's Revisions to Address the AC's Concerns

AC Concerns – Feb 2018	Proposed labeling in the current submission
The proposed drug packaging for 3, 5 or 7 days may encourage patients to finish the package when Hydexor should be used only as needed.	Hydexor will only be used in certified medically supervised settings, thus the drug packaging is no longer being developed.
Limited details on proposed drug buyback program implementation	No longer applicable as use is in certified medically supervised settings.

Applicant's Current REMS Proposal

REMS Goal

– Mitigate the risk of life-threatening respiratory depression and the risk of falls or other accidents resulting from excessive sedation by ensuring that Hydexor is dispensed only to patients in certified medically supervised healthcare settings.

Elements to Assure Safe Use

– Hydexor is to be dispensed only in certified healthcare settings such as hospitals and surgical centers.

Healthcare Settings that Dispense Must:

Establish policies and procedures to:

- Manage acute opioid overdose including life-threatening respiratory depression
- Have fall precaution protocol(s) on-site
- Discontinue Hydexor after 3 days
- Verify that Hydexor is not dispensed for use outside of the certified healthcare setting

REMS Assessments

The assessment plan for this REMS will include the following categories to capture processes and outcomes metrics:

- REMS implementation and operations data
- REMS enrollment and utilization data
- REMS infrastructure and performance data
- Compliance and audit data
- Surveillance data of adverse events of special interest

The REMS Would Accomplish the Following:

- The FDA believes the proposed REMS would ensure that patients are only administered Hydexor in a certified, medically supervised setting for a limited time, where patients can be monitored for respiratory depression and the risk of falls or other accidents resulting from excessive sedation.
- Limiting Hydexor to post-operative use (i.e. hospitals, surgical centers) mitigates the risks of abuse, misuse and addiction, as patients and others would not have access to tablets in their home.
- Additionally, in a certified setting, prescribers can determine if Hydexor should be discontinued due to intolerance of side effects or changes in a patient's analgesic and antiemetic needs
- The Applicant will be required to submit REMS assessment reports to determine the effectiveness of the REMS to ensure that Hydexor is only used in healthcare settings that are certified in the REMS.