FDA Briefing Document

Joint Meeting of Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee

November 2, 2020
DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. The new drug application (NDA) 209257 for HYDEXOR (Hydrocodone, Acetaminophen, Promethazine 1.7.5 mg, 2.325 mg, 3.12.5 mg), a fixed-dose combination oral tablet, submitted by Ólas Pharma, Inc. for the short-term (not to exceed 3 days) management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid induced nausea and vomiting, has been brought to this Advisory Committee in order to gain the Committee’s insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.
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1. Division Director Memo

FDA CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE

MEMORANDUM

DATE: October 2, 2020
FROM: Rigoberto Roca, MD
Acting Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine
Office of Neuroscience
Office of New Drugs
CDER, FDA
TO: Chair, Members and Invited Guests Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) Drug Safety and Risk Management Advisory Committee (DSaRM)
RE: November 2, 2020 AADPAC/DSaRM meeting to discuss NDA 209257, Hydexor

At this half-day, joint meeting of AADPAC and DSaRM, we will discuss a new drug application (NDA) from Ólas Pharmaceuticals (“the Applicant”) for an immediate-release, fixed-dose combination formulation of hydrocodone (HC), acetaminophen, and promethazine, with the proposed tradename, Hydexor.

The addition of promethazine to a hydrocodone/acetaminophen combination is intended to reduce or prevent the occurrence of opioid-induced nausea and vomiting (OINV). OINV can be a major problem for some patients receiving opioids for analgesia, and the Applicant’s goal was to address this need. Fixed-dose combination products that contain HC and acetaminophen have been marketed widely in the United States for decades. HC is also available in oral extended-release (ER), single-entity formulations.

This application is on its fourth review cycle and has been discussed at a 2018 Advisory Committee meeting, during its second review cycle. The detailed regulatory history is discussed Section 2.

During the first and second review cycles, the Division concluded that there was substantial evidence of effectiveness for Hydexor with data from two adequate and well-controlled trials.
We do not intend to re-discuss these data at this meeting as the Division has concluded that overall benefit is demonstrated.

However, because of promethazine’s safety profile, the Division and the 2018 Advisory Committee have been concerned that the Applicant did not identify a patient population that predictably requires concomitant therapy with an opioid analgesic and a preemptive antiemetic with every dose to warrant exposure to promethazine. Specifically, although the Phase 3 clinical trials were enriched to enroll a population at risk for OINV, a substantial number of patients treated with the hydrocodone/acetaminophen comparator did not develop OINV. This concern was conveyed in the second Complete Response letter.

Although the Applicant attempted to address this deficiency in a resubmission, a third Complete Response letter was issued that reiterated the need to identify a patient population that requires an opioid and a preemptive antiemetic in order to warrant exposure of patients to promethazine and its associated risks, especially severe CNS sedation.

The Applicant subsequently appealed the Division’s decision to the Office Director. Although the appeal was denied, the Office Director advised the Applicant to submit revised labeling—to narrow the patient population and limit dosing duration—as a resubmission in order to address the residual concerns. In a resubmission, currently under review in a fourth cycle, the Applicant submitted the revised labeling as advised.

Following Divisional input that considered residual safety concerns and input from the 2018 meeting, the Applicant’s current proposed indication reflects a very restricted use and reads as follows:

*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.*

With their revised labeling, the Applicant also now proposes several 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*

1 The Applicant’s proposed indication in their first submission was: HYDEXOR is indicated for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting.
In addition to the revised labeling, the Applicant has proposed a Risk Evaluation and Mitigation Strategy (REMS) with Elements to Assure Safe Use (ETASU)—the drug be dispensed to patients only in certified medically supervised settings such as hospitals and surgical centers. The REMS is needed to ensure that the benefits outweigh the risks of serious adverse outcomes resulting from respiratory depression and the risk of falls or other accidents resulting from excessive sedation.

The current proposed indication and labeling and proposed REMS are central to the purpose of this AC meeting. Efficacy for this product was established in the first two cycles. Safety of this product has been characterized. The remaining issue of concern has been whether an appropriate population can be identified for the safe use of this product. The Applicant is addressing this concern through revised labeling and the proposed REMS.

This FDA background document includes a detailed regulatory history, a summary of the benefits and risks of the product, a summary of the 2018 Advisory Committee meeting, summaries from the Office of Surveillance and Epidemiology—including consideration of the risk of misuse and abuse of this product, drug utilization analyses to characterize the use of hydrocodone-acetaminophen and promethazine in the hospital setting, and details of the REMS program.

When these committees met in 2018 to discuss this product, the Applicant’s proposed indication was much broader: HYDEXOR is indicated for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing opioid-induced nausea and vomiting (OINV). HYDEXOR is indicated when alternative treatments for pain are inadequate.

At that meeting, the committee was concerned that OINV may decrease over time and that promethazine has severe and concerning side effects that are not commonly described with other antiemetics. There was discussion of the need for adequate risk mitigation, since the proposed indication did not restrict use to the inpatient setting.

At the conclusion of the meeting today, we will ask you the following:

*Based on the revised indication and proposed REMS, which restricts the intended population and duration of use for Hydexor significantly from the originally submitted application, have the safety concerns been adequately addressed through labeling/REMS? Vote yes/no. If no, please comment on what additional issues the Applicant needs to address.*

The Division acknowledges that prescribers may prefer to use the components of Hydexor separately and not as a fixed-dose combination. The Division also acknowledges that a different anti-emetic may be preferred by some prescribers. We remind the committee that these issues are in the realm of clinical practice and are not regulatory considerations per se. In fact, preferred use of a product in clinical practice is not the basis for approval of a product. Therefore, we are not asking for additional input about efficacy and predictions for the extent of use of this product should it reach the market. The Agency’s responsibility is to ensure that a product’s benefits outweigh the risks when used as directed in labeling. In this context, we ask that you opine on whether the steps the Applicant has taken shift the risk-benefit balance so that the benefits of Hydexor outweigh the risks.
We ask that the discussion at the meeting today focus on the specific question at hand. Your advice and recommendations are important. We are grateful that you have agreed to join us for this important discussion and look forward to seeing you at the meeting.
2. Regulatory History

This application was submitted as a 505(b)(2) NDA, and the Applicant is relying on the Agency’s previous findings of safety and efficacy for Vicoprofen (hydrocodone bitartrate 7.5 mg/ibuprofen 200 mg, NDA 20716), Ultracet (tramadol hydrochloride 37.5 mg/acetaminophen 325 mg, NDA 21123), and Phenergan (promethazine hydrochloride 12.5 mg, NDA 40596).

Specifically, the Applicant relied in part on prior findings of efficacy and safety for the components of the product by showing bioequivalence to these previously approved products. In addition, the Applicant was required to comply with the “combination rule, “(21 CFR 300.5) and demonstrate that each component of the combination contributed to the claimed effects of the product. Lastly, the Applicant had to show that the addition of promethazine to hydrocodone/acetaminophen resulted in superiority to placebo for the management of pain, and, was safe and effective in preventing and reducing nausea and vomiting in the study population.

Hydexor is provided in one strength and consists of an immediate-release bi-layered tablet with a rapid-release layer containing 12.5 mg of promethazine and a second layer, containing 7.5 mg of HC and 325 mg of acetaminophen, intended to release after the promethazine. Similar to other currently available HC/acetaminophen products, Hydexor has not been formulated with properties intended to deter abuse.

The tablets were developed to be bioequivalent (BE) for both HC and acetaminophen to the approved FDC HC/acetaminophen product, Norco. Therefore, the primary goals of the development program for Hydexor were to: 1) demonstrate BE of Hydexor to Norco for both HC and acetaminophen, 2) demonstrate the efficacy of Hydexor over placebo for management of pain, 3) demonstrate the efficacy of Hydexor over Norco for prevention of nausea and vomiting, and 4) characterize the safety profile of Hydexor in the intended patient population.

Clinical studies were conducted in patients who were prone to opioid-related nausea and vomiting. In two trials, Hydexor was compared to Norco, a hydrocodone/acetaminophen combination tablet (5 mg/325 mg), and placebo.

First and Second Review Cycles (including Advisory Committee meeting)

The Applicant submitted the NDA for Hydexor on March 31, 2016. The following language was proposed under the Indications and Usage section:

**HYDEXOR** contain hydrocodone bitartrate (an opioid analgesic), acetaminophen (a non-opiate, non-salicylate analgesic and antipyretic) and promethazine hydrochloride (an H1 receptor antagonist).

**HYDEXOR** is indicated for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting.
On January 31, 2017, the Division issued a Complete Response letter (CRL) citing four deficiencies. Two of these deficiencies were related to establishing bioequivalence of Hydexor to an approved hydrocodone and acetaminophen product:

1. Data was [sic] not provided to demonstrate that the hydrocodone and acetaminophen components of HYDEXOR and an approved hydrocodone and acetaminophen [sic] product are bioequivalent, and therefore that the lower incidence of nausea and vomiting observed in with HYDEXOR is due to the presence of promethazine in the combination and not due to a lower systemic exposure to hydrocodone.
2. Data was [sic] not submitted to demonstrate that the hydrocodone/acetaminophen component of HYDEXOR is not a new combination, that is, that both hydrocodone and acetaminophen contribute to the analgesic efficacy of HYDEXOR.

On October 12, 2017, a response to the CRL was received. The resubmitted application was discussed at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSARM) on February 14, 2018. The publicly-available summary of the meeting is included below.

At the time of the meeting, the proposed indication for Hydexor was broader: “for the short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing IONV.”

The committee voted 19:2 against approval. The committee was concerned that OINV may decrease over time and that 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.

The second Complete Response letter was issued on April 12, 2018 with a single deficiency:

You have not provided adequate evidence of a patient population that requires treatment with HYDEXOR, as required by the Combination Rule 21 CFR 300.50. A substantial number of patients treated with the hydrocodone/acetaminophen comparator in Studies CLCT-002 and CLCT-003, which were enriched to enroll a population at risk for opioid induced nausea and vomiting (OINV), did not develop OINV (defined as an episode of emesis or requiring antiemetic use) with only 2.4% and 6.4% of patients experiencing OINV on day five of treatment, respectively. As such, you have not adequately identified a patient population that predictably requires concomitant therapy with an opioid analgesic and a preemptive antiemetic with every dose to warrant exposing all patients treated with HYDEXOR to promethazine and its associated risks.

In a post-action meeting held on 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. Below is an example of the proposed revised indication:
For example, “HYDEXOR is indicated for the short-term (generally 3 days and no more than 5 days) management of acute pain severe enough to require an opioid analgesic and the prevention of opioid induced nausea and vomiting (OINV) in patients expected to be prone to nausea and vomiting. HYDEXOR is indicated when alternative treatments for pain are inadequate.”

The Division did not agree with this proposal, citing concerns raised at the AC meeting that this FDC would expose many patients to promethazine who did not appear to need an anti-emetic. Specifically, 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. An excerpt from the Division’s response on the Applicant’s proposal is summarized below:

Therefore, the majority of patients treated with HYDEXOR will not experience a benefit of decreasing OINV but will be exposed to the additional adverse effects related to promethazine. Additionally, the presence of promethazine in HYDEXOR offers less flexibility to tailor the analgesic doses to an individual patient’s pain. In this context, OINV appears to be more appropriately managed with antiemetics on an “as needed” basis.

Because the majority of patients enrolled in your Phase 3 studies were assessed as being at risk for OINV due to known or suspected prior history of OINV and/or nausea and vomiting in response to a hydrocodone challenge, it is unclear how you could further define and/or study a population that would consistently require an antiemetic therapy with every dose of hydrocodone/acetaminophen. The results of the Phase 3 studies do not support the original nor the proposed amended indication. If a patient population can be identified that would require around the clock dosing with promethazine when being dosed with a combination of hydrocodone and acetaminophen, additional clinical studies will be necessary to demonstrate a favorable balance of benefit and risk in this population.

Discussions around this point included a proposal by the Applicant 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.

The Applicant also submitted its summary of the post-action meeting and although there are differences in interpretation of the benefits and risks of Hydexor, both the FDA and Applicant agreed, as summarized in their separate minutes, 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 CRL.
**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.

The Applicant provided new 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. CLCT-003 was selected because patients were dosed in a fixed schedule, thereby assuring a balanced exposure to hydrocodone for both the Hydexor and Norco treatment arms. In addition, the patients in this study were more representative of patients with acute post-operative pain requiring opioid therapy, as the study was conducted in post bunionectomy patients.

Details of these analyses are included in the Appendix 9.1. 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 same deficiency identified in the second CR letter:

“...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.”

**Formal Dispute Resolution**

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, Mary Thanh Hai, rescind the third Complete Response letter and approve Hydexor.

The request was considered by Dr. Mary Thanh Hai, and the appeal was denied. However, 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.”

The complete decisional memo is highly relevant to this meeting and can be found in Appendix 9.2.

**Fourth Review Cycle**

The application is currently in its fourth review cycle after receiving a third Complete Response on August 9, 2018.
FDA Actions to Address Opioid Misuse and Abuse

During the span of the development program for Hydexor, the opioid crisis has continued, and FDA has taken many steps aimed at addressing opioid misuse and abuse. The one most relevant to the benefit-risk of Hydexor took place on August 31, 2016, when FDA announced class-wide safety labeling changes in the form of a boxed warning for certain opioid medications and benzodiazepines to highlight that the combined use of these two classes of drugs has resulted in serious side effects, including respiratory depression and death, as reported in two studies conducted by FDA and additional studies reviewed from published literature.


Although promethazine is not a benzodiazepine, it is labeled as a CNS depressant and is indicated as a sedative. In a public statement, then FDA Commissioner, Dr. Robert Califf stated, “We implore health care professionals to heed these new warnings and more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of using opioids and benzodiazepines- or CNS depressants more generally – together outweigh these risks (emphasis added).”

This last statement reflects a new scientific development based on data reviewed by the Agency, which led to the class-wide safety labeling change. Not only is Hydexor an opioid but it is an opioid combined with a CNS depressant and the benefits of its combined use must be considered against the risk of further CNS depression.

3. Topic for Discussion

Based on the revised indication and proposed REMS, which restricts the intended population and duration of use for Hydexor significantly from the originally submitted application, have the safety concerns raised in the 2018 AC meeting been adequately addressed through labeling/REMS? If no, please comment on what additional issues the Applicant needs to address?
4. Benefits and Risks of Hydexor

4.1. Summary of Clinical Efficacy

Hydexor is also referred to as CL-108 below.

The Applicant submitted results from two pivotal efficacy studies conducted in postoperative pain populations:

- Study CLCT-002 (also referred to in this document as “Study 2”) was conducted in a post-dental surgery pain population.
- Study CLCT-003 (also referred to in this document as “Study 3”) was conducted in a post-bunionectomy pain population.

These studies demonstrated the analgesic efficacy of Hydexor compared to placebo and a lower proportion of patients with opioid-induced nausea and vomiting (OINV) with Hydexor compared to Norco, an approved hydrocodone and acetaminophen fixed-dose combination (FDC) product. In addition, the Applicant demonstrated comparable exposures to hydrocodone and acetaminophen for Hydexor and Norco to support that the lower proportion of OINV observed for Hydexor was due to the presence of promethazine and not because of lower exposures to hydrocodone.

The study populations were enriched for patients more likely to experience OINV. Most patients enrolled (79% in Study 2 and 69% in Study 3) were assessed as being at risk for OINV because of a prior history of OINV and/or nausea and vomiting in response to a hydrocodone challenge. The remainder of the patients were assessed as being at risk for OINV for a variety of other reasons.

Efficacy in OINV was demonstrated over the first 24 hours in Study 2 and over the first 48 hours in Study 3 using the Agency’s preferred outcome measure for this indication, which is a responder definition based on not having any episodes of vomiting and not requiring the use of antiemetic medication. In addition, the Applicant evaluated OINV on a three-component responder definition, which included the above two components as well as a measurement of nausea intensity (i.e., the Nausea Intensity Scale). These results are summarized here:

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CL-108 (N=211)</th>
<th>Norco (N=205)</th>
<th>Placebo (N=50)</th>
<th>Relative Risk Reduction</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two component OINV failures (post-hoc)</td>
<td>24 (11)</td>
<td>65 (32)</td>
<td>2 (4)</td>
<td>64%</td>
<td>0.26 (0.15, 0.44)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Three component OINV failures (primary)</td>
<td>76 (36)</td>
<td>119 (58)</td>
<td>9 (18)</td>
<td>38%</td>
<td>0.37 (0.24, 0.56)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Review
Data is expressed as n (%) unless otherwise specified
Abbreviations: CI, confidence interval; OINV, opioid-induced nausea and vomiting
Table 2. Assessment of the OINV Study Endpoints, Study CLCT-003

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>CL-108 (N=252)</th>
<th>Norco (N=250)</th>
<th>Placebo (N=50)</th>
<th>Relative Risk Reduction</th>
<th>Odds Ratio (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two component OINV failures (primary)</td>
<td>30 (12)</td>
<td>113 (45)</td>
<td>3 (6)</td>
<td>74%</td>
<td>0.16 (0.10, 0.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Three component OINV failures (key sec.)</td>
<td>68 (27)</td>
<td>135 (54)</td>
<td>8 (16)</td>
<td>50%</td>
<td>0.31 (0.21, 0.45)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Review
Abbreviations: CI, confidence interval; OINV, opioid-induced nausea and vomiting

Following the Advisory Committee, the statistical review team performed additional analyses to summarize study drug use and OINV (using the two-component responder definition) by study day.

An OINV treatment effect for Hydexor appears to persist compared to Norco over the five-day study period. In particular, over the first 2-3 days of treatment, the proportion of patients with OINV was markedly lower in Hydexor-treated patients in both studies. This supports the benefit of Hydexor.

Nevertheless, the same data, summarized in the four tables, below, show that most patients treated with Norco did not develop OINV despite the trials having enrolled an enriched population. This finding is consistent in the primary efficacy analysis using both the Agency’s preferred two-component responder definition and the Applicant’s three-component responder definition as well as over the five-day study period. Furthermore, the proportion of Norco-treated patients experiencing OINV decreases over the study period at a faster rate than does the proportion of patients using study drug, with only 2.4% and 6.4% of Norco-treated patients, in each of the efficacy studies respectively, developing OINV on Day 5. These data suggest that an antiemetic requirement does not persist in patients on continued opioid therapy who experienced OINV with initiation of the treatment. It is worth noting that the Agency has not established a specific percentage of patients in the Norco group that would have needed to experience OINV in order to conclude that the results seen were clinically relevant.

Table 3. Study 2 – Summary of Study Drug Usage and OINV by Study Day in Norco-Treated Patients

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Usage, Expressed as Mean Number of Tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
<th>Proportion of Patients With Vomiting (%)</th>
<th>Proportion of Patients With Anti-Emetic Use (%)</th>
<th>Proportion of Patients With OINV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.59</td>
<td>100</td>
<td>19.5</td>
<td>17.6</td>
<td>30.2</td>
</tr>
<tr>
<td>2</td>
<td>2.65</td>
<td>91.7</td>
<td>14.1</td>
<td>7.8</td>
<td>17.6</td>
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<tr>
<td>3</td>
<td>2.18</td>
<td>79.0</td>
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<tr>
<td>4</td>
<td>1.73</td>
<td>69.3</td>
<td>2.4</td>
<td>4.4</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>1.51</td>
<td>58.5</td>
<td>1.5</td>
<td>1.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer
Abbreviations: OINV, opioid-induced nausea and vomiting
### Table 4. Study 2 – Summary of Study Drug Usage and OINV by Study Day in Hydexor-Treated Patients

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Usage, Expressed as Mean Number of Tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
<th>Proportion of Patients With Vomiting (%)</th>
<th>Proportion of Patients With Anti-Emetic Use (%)</th>
<th>Proportion of Patients With OINV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.69</td>
<td>100</td>
<td>9.0</td>
<td>3.8</td>
<td>10.9</td>
</tr>
<tr>
<td>2</td>
<td>2.91</td>
<td>92.4</td>
<td>5.2</td>
<td>1.9</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>2.6</td>
<td>89.1</td>
<td>1.9</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>76.3</td>
<td>0.5</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>1.89</td>
<td>66.4</td>
<td>0.5</td>
<td>0.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer  
Abbreviations: OINV, opioid-induced nausea and vomiting

### Table 5. Study 3 – Summary of Study Drug Usage and OINV by Study Day in Norco-Treated Patients

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Usage, Expressed as Mean Number of Tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
<th>Proportion of Patients With OINV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.12</td>
<td>100</td>
<td>32.0</td>
</tr>
<tr>
<td>2</td>
<td>4.33</td>
<td>98.4</td>
<td>36.0</td>
</tr>
<tr>
<td>3</td>
<td>3.70</td>
<td>96.4</td>
<td>22.4</td>
</tr>
<tr>
<td>4</td>
<td>2.39</td>
<td>79.6</td>
<td>8.0</td>
</tr>
<tr>
<td>5</td>
<td>2.04</td>
<td>67.6</td>
<td>6.4</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer  
Abbreviations: OINV, opioid-induced nausea and vomiting

### Table 6. Study 3 – Summary of Study Drug Usage and OINV by Study Day in Hydexor-Treated Patients

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Usage, Expressed as Mean Number of Tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
<th>Proportion of Patients With OINV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.03</td>
<td>100</td>
<td>8.3</td>
</tr>
<tr>
<td>2</td>
<td>4.40</td>
<td>99.2</td>
<td>7.9</td>
</tr>
<tr>
<td>3</td>
<td>3.92</td>
<td>98.8</td>
<td>6.4</td>
</tr>
<tr>
<td>4</td>
<td>2.72</td>
<td>86.9</td>
<td>0.8</td>
</tr>
<tr>
<td>5</td>
<td>2.30</td>
<td>77.8</td>
<td>1.2</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer  
Abbreviations: OINV, opioid-induced nausea and vomiting

### 4.2. Summary of Clinical Safety

The safety profile of HC/acetaminophen in combination and promethazine are well-characterized, as reflected in approved labeling for hydrocodone/acetaminophen and promethazine. Therefore, the safety review for this application focused on the safety of these three drugs used in combination with emphasis on central nervous system depressant effects as a shared risk of hydrocodone and promethazine.
The Phase 3 safety data submitted in the NDA are derived from the two efficacy studies (Study 2 and Study 3) and Study CLCT-006 (Study 6), which was a Phase 3 open-label safety study in patients with osteoarthritis of the knee or hip.

The three Phase 3 efficacy and safety studies each had a different dosing regimen. In Study 2, patients were administered one dose at randomization, followed by one dose as needed (prn) every 4-6 hours for up to five days. In Study 3, patients were administered one dose at randomization, followed by one dose every 4-6 hours on a fixed schedule for the first 48 hours, then prn on an outpatient basis for Days 3-5. In Study 6, patients were administered one dose prn every 4-6 hours for up to fourteen days.

A total of 709 individuals were exposed to at least one dose of the to-be-marketed formulation of Hydexor. A total of 463 patients were treated with Hydexor across Study 2 and Study 3. A total of 641 patients were treated with Hydexor across all Phase 3 studies, including Study 2, Study 3, and Study 6 (patients with osteoarthritis of the knee or hip). Also, 48 subjects received a higher single dose of Hydexor, either three or five tablets as a single dose, as part of the human abuse-potential study, Study CLCT-007.

The following tables summarize the exposures across the two different pools.

### Table 7. Duration of Exposure Across Study 2 and Study 3

<table>
<thead>
<tr>
<th>Duration of Exposure</th>
<th>CL-108 (N=463) n (%)</th>
<th>Norco (N=455) n (%)</th>
<th>Placebo (N=100) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 day</td>
<td>463 (100)</td>
<td>455 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>At least 3 days</td>
<td>441 (95.2)</td>
<td>407 (89.5)</td>
<td>84 (84)</td>
</tr>
<tr>
<td>At least 5 days</td>
<td>338 (73)</td>
<td>290 (63.7)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>At least 7 days</td>
<td>17 (3.7)</td>
<td>18 (4)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*Source: Clinical Review*

### Table 8. Duration of Exposure Across Study 2, Study 3, and Study 6

<table>
<thead>
<tr>
<th>Duration of Exposure</th>
<th>CL-108 (N=641) n (%)</th>
<th>Norco (N=455) n (%)</th>
<th>Placebo (N=100) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least 1 day</td>
<td>641 (100)</td>
<td>455 (100)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>At least 3 days</td>
<td>617 (96.3)</td>
<td>407 (89.5)</td>
<td>84 (84)</td>
</tr>
<tr>
<td>At least 5 days</td>
<td>511 (79.7)</td>
<td>290 (63.7)</td>
<td>58 (58)</td>
</tr>
<tr>
<td>At least 7 days</td>
<td>187 (29.2)</td>
<td>18 (4)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>At least 14 days</td>
<td>153 (23.9)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Source: Clinical Review*

In the tables above, a patient would contribute to exposure on a given day if even a single tablet of study drug was consumed. Only Study 3 required that patients take Hydexor at the maximally-proposed dosing regimen of every 4-6 hours for the first 48 hours of the study. In the tables above, exposures on days beyond 48 hours consist mostly of patients taking three or fewer tablets on a given day.
Patients administered the maximally-allowed number of tablets per day received approximately 5-6 tablets per day. In Study 3, about 40% of patients received 5-6 tablets per day for the first and second days. In the same study, the average number of tablets per day dropped off to 3 for the third day, 2.6 for the third day, and 2 for the fifth day.

The demographics for the population of patients enrolled across all three Phase 3 studies is shown in the table below. Note that Study 6 significantly increased the number of patients ≥ 65 years that were exposed to Hydexor.

### Table 9. Demographics of Pooled Patient Population, Studies 2, 3, and 6

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CL-108 (N=641)</th>
<th>Norco (N=455)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at baseline (Years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>40.6 (18.4)</td>
<td>33 (14.3)</td>
<td>32 (14)</td>
</tr>
<tr>
<td>Median</td>
<td>38</td>
<td>27</td>
<td>26</td>
</tr>
<tr>
<td>Q1, Q3</td>
<td>23, 57</td>
<td>21, 45</td>
<td>20, 44.0</td>
</tr>
<tr>
<td>Min, max</td>
<td>18, 86</td>
<td>18, 68</td>
<td>18, 62</td>
</tr>
<tr>
<td>Age subgroup at baseline, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>568 (88.6)</td>
<td>449 (98.7)</td>
<td>100 (100)</td>
</tr>
<tr>
<td>≥65 years</td>
<td>73 (11.4)</td>
<td>6 (1.3)</td>
<td>0</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>151 (23.6)</td>
<td>84 (18.5)</td>
<td>25 (25)</td>
</tr>
<tr>
<td>Female</td>
<td>490 (76.4)</td>
<td>371 (81.5)</td>
<td>75 (75)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>536 (83.6)</td>
<td>389 (85.5)</td>
<td>84 (84)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>67 (10.5)</td>
<td>30 (6.6)</td>
<td>10 (10)</td>
</tr>
<tr>
<td>Asian</td>
<td>18 (2.8)</td>
<td>19 (4.2)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>20 (3.1)</td>
<td>17 (3.7)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Source: Clinical Review

Abbreviations: SD, standard deviation

### 4.2.1. Serious Adverse Events and Discontinuations Due to AEs

There were no serious adverse events attributed to Hydexor. There were no discontinuations due to AEs in the Hydexor groups in the Phase 3 efficacy studies. In Study 6, there were three such discontinuations. One was a fall two days after the last dose of Hydexor in an 84-year-old woman. One was a case of moderate nausea with mild hyperhidrosis. One patient experienced severe abdominal discomfort, diarrhea, somnolence, and tachycardia. All the events resolved after Hydexor discontinuation.

### 4.2.2. Opioid-Induced Side Effects

The incidence and severity of nine expected opioid-induced AEs was based on proactive monitoring with the Opioid Symptoms Scales (OSS). The nine terms included in the OSS were: confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizziness. OINV was not measured on the OSS but was captured as an efficacy measure as described earlier. For each opioid symptom, patients completed separate 0-to-10 Likert scales in response to the instruction: “For each symptom
you’ve had over the past 6 hours (or 24 hours), circle the number that describes how severe it was for you.”

Patients completed the OSS questionnaire before and regularly after repeated uses of assigned study medication over 5 days in Study 2 and Study 3. Subjects rated each symptom, on a 0-10-point scale (rating severe events between 7-10, moderate events between 4-6, mild events 1-3, and no symptoms as 0), before taking study medication. In Study 2, patients completed the OSS pre-treatment, at the end of the 6-hour initial evaluation period, and nightly for the five-day treatment period. In Study 3, the OSS was completed by patients at the end of the initial 6-hour evaluation period, at 24 and 48 hours in-clinic, and nightly on Days 3, 4, and 5.

In the context of this active surveillance, observed background rates in the placebo group were relatively high. For example, background rates (any severity) were 77%, 69%, 36%, 36%, and 35% respectively for headache, drowsiness, difficulty concentrating, itchiness, and lightheadedness/dizziness. In contrast, the spontaneously-reported incidence of drowsiness in the Hydexcelor-treated patients in Study 6 was 18%.

In Study 3, patients were required to take one dose of study medication every 4-6 hours for 48 hours and the average number of doses per day was 4.7. In contrast, in Study 2, patients self-dosed as needed and the average number of doses per day was 2.5. As a result, the incidence of AEs in the pooled efficacy studies represents a range of exposure to drug.

The following table shows the OSS results for the pooled efficacy studies.

<table>
<thead>
<tr>
<th>Opioid-Induced Symptom</th>
<th>CL-108 (N=463) n (%)</th>
<th>Norco (N=455) n (%)</th>
<th>Placebo (N=100) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>149 (32.2)</td>
<td>106 (23.3)</td>
<td>10 (10.0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>205 (44.3)</td>
<td>216 (47.5)</td>
<td>20 (20.0)</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>241 (52.1)</td>
<td>206 (45.3)</td>
<td>36 (36.0)</td>
</tr>
<tr>
<td>Difficulty voiding</td>
<td>47 (10.2)</td>
<td>38 (8.4)</td>
<td>6 (6.0)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>431 (93.1)</td>
<td>403 (88.6)</td>
<td>69 (69.0)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>331 (71.5)</td>
<td>288 (63.3)</td>
<td>53 (53.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>328 (70.8)</td>
<td>328 (72.1)</td>
<td>77 (77.0)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>251 (54.2)</td>
<td>239 (52.5)</td>
<td>36 (36.0)</td>
</tr>
<tr>
<td>Lightheaded/dizzy</td>
<td>303 (65.4)</td>
<td>303 (66.6)</td>
<td>35 (35.0)</td>
</tr>
</tbody>
</table>

Source: Clinical Review
Abbreviations: OSS, Opioid Symptom Scales

For the pooled efficacy studies, over the 5-day treatment period, the mean severity of most opioid side effects was rated as mild (1-3 on the 0-10 OSS) in the CL-108 and Norco groups. The exception was drowsiness, which was rated as mild by 77 subjects (16.6%), moderate (4-6 on the OSS) by 143 subjects (30.9%), and severe (7-10 on the OSS) by 211 subjects (45.6%). Severe drowsiness was reported by 46% of Hydexcelor-treated patients and by 29% of Norco-treated patients.
OSS Results in Study CLCT-002

The proportion of subjects with at least one severe symptom (rated 7-10 on the OSS questionnaire) over the 5 days of the study was 54.0% (114 subjects) in the CL-108 group and 52.2% (107 subjects) in the Norco treatment group as shown in the table below. However, drowsiness was the most commonly reported severe side effect following CL-108 treatment and Norco treatments, affecting 46% (97 subjects) of subjects and 37.1% (76 subjects), respectively.

Table 11. Summary of the Severe (Rated 7-10 on the OSS Questionnaire) Opioid-Induced Symptoms Over 5 Days (Study 2)

<table>
<thead>
<tr>
<th>Opioid-Induced Symptom</th>
<th>CL-108 (N=211)</th>
<th>Norco (N=205)</th>
<th>Placebo (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of severe OSS opioid-induced symptoms</td>
<td>664</td>
<td>423</td>
<td>61</td>
</tr>
<tr>
<td>Number of subjects with at least one severe OSS</td>
<td>114 (54)</td>
<td>107 (52.2)</td>
<td>20 (40)</td>
</tr>
<tr>
<td>Confusion</td>
<td>14 (6.6)</td>
<td>5 (2.4)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>17 (8.1)</td>
<td>23 (11.2)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>25 (11.8)</td>
<td>18 (8.8)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Difficulty voiding</td>
<td>4 (1.9)</td>
<td>1 (0.5)</td>
<td>0</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>97 (46)</td>
<td>76 (37.1)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>26 (12.3)</td>
<td>15 (7.3)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Headache</td>
<td>41 (19.4)</td>
<td>36 (17.6)</td>
<td>14 (28)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>11 (5.2)</td>
<td>11 (5.4)</td>
<td>0</td>
</tr>
<tr>
<td>Lightheaded/dizzy</td>
<td>41 (19.4)</td>
<td>37 (18)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

Source: Clinical Review
Abbreviations: OSS, Opioid Symptom Scales

OSS Results in Study 3

In Study 3, dosing was fixed for 48 hours followed by as-needed dosing. Over the entire 5-day treatment period, there was no difference in the number of subjects reporting constipation, headache, lightheadedness, difficulty voiding, and itchiness for CL-108 when compared to those treated with Norco as shown in the table below. However, there were more occurrences of drowsiness, confusion, difficulty concentrating, and dry mouth with CL-108 treatment than in the Norco treatment group.
### Table 12. Summary of the Severe (Rated 7-10 on the OSS Questionnaire) Opioid-Induced Symptoms

<table>
<thead>
<tr>
<th>Opioid-Induced Symptom</th>
<th>CL-108 (N=252) n (%)</th>
<th>Norco (N=250) n (%)</th>
<th>Placebo (N=50) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of severe OSS opioid-induced symptoms</td>
<td>Days 1-2</td>
<td>Days 3-5</td>
<td>Days 1-2</td>
</tr>
<tr>
<td>389 (77.5)</td>
<td>276 (77.5)</td>
<td>222 (88.8)</td>
<td>157 (62.4)</td>
</tr>
<tr>
<td>Number of subjects with at least one severe OSS</td>
<td>Days 1-2</td>
<td>Days 3-5</td>
<td>Days 1-2</td>
</tr>
<tr>
<td>125 (49.6)</td>
<td>83 (32.9)</td>
<td>88 (35.2)</td>
<td>54 (21.6)</td>
</tr>
<tr>
<td>Confusion</td>
<td>6 (2.4)</td>
<td>2 (0.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>16 (6.3)</td>
<td>30 (11.9)</td>
<td>18 (7.2)</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>20 (7.9)</td>
<td>7 (2.8)</td>
<td>8 (3.2)</td>
</tr>
<tr>
<td>Difficulty voiding</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>105 (41.7)</td>
<td>46 (18.3)</td>
<td>53 (21.2)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>38 (15.1)</td>
<td>31 (12.3)</td>
<td>17 (6.8)</td>
</tr>
<tr>
<td>Headache</td>
<td>27 (10.7)</td>
<td>19 (7.5)</td>
<td>27 (10.8)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>15 (6)</td>
<td>13 (5.2)</td>
<td>11 (4.4)</td>
</tr>
<tr>
<td>Lightheaded/dizzy</td>
<td>18 (7.1)</td>
<td>12 (4.8)</td>
<td>19 (7.6)</td>
</tr>
</tbody>
</table>

Source: Clinical Review
Abbreviations: OSS, Opioid Symptom Scales

For Study 3, the severity of the nine targeted opioid-related symptoms is shown in the following graph.

**Figure 1. Severity of Opioid-Related Symptoms (11-Point Intensity Rating Scale; Mean and Standard Deviation) Over First 48 Hours (Excluding OINV), Study 3**

Treatment Group: C = CL-108, N = Norco, P = Placebo.
OSS01 = Itchiness, OSS02 = Constipated, OSS03 = Dry Mouth, OSS04 = Drowsy, OSS05 = Headache, OSS06 = Lightheaded/Dizzy, OSS07 = Difficult to Pass Urine, OSS08 = Confused, OSS09 = Difficult to Concentrate.

Source: Clinical Study Report, Study CLCT-003
Over the first five days of the study, the incidence of moderate-severe drowsiness was greater with Hydextor (75%) than with Norco (56%). The following figures demonstrate that both the incidence and severity of drowsiness were related to the number of doses taken per day.

**Figure 2. Frequency of Drowsiness Versus Number of Doses per Day, Study 3**

![Graph showing frequency of drowsiness versus number of doses per day](image)

Treatment Group: C = CL-108, N = Norco, P = Placebo.
Source: Clinical Study Report, Study CLCT-003

**Figure 3. Severity of Drowsiness (11-Point Intensity Rating Scale; Mean and Standard Deviation) Versus Number of Doses per Day, Study CLCT-003**

![Graph showing severity of drowsiness versus number of doses per day](image)

Treatment Group: C = CL-108, N = Norco, P = Placebo.
Source: Clinical Study Report, Study CLCT-003
At comparable dosing regimens, there was an excess in the frequency and severity of drowsiness with Hydexor compared to Norco.

4.2.3. Other Notable Events of Special Interest

The Applicant identified adverse events (AEs) of special interest: respiratory depression/dyspnea, hypotension and syncope, and pyrexia. The findings from the clinical trials are briefly summarized here.

**Respiratory Depression/Dyspnea**

There was no evidence of an increased risk of respiratory depression with Hydexor compared to Norco. There was one report of dyspnea in a Hydexor-treated patient in Study 3. The event was reported on study day two, was mild, and considered unlikely related to drug. No change in study drug occurred as a result of this event and the patient completed the treatment period without recurrence.

**Hypotension and Syncope**

AEs of hypotension were very infrequent. Five events of ‘hypotension’ were reported in Study 3 and were not more frequent in the Hydexor group. In Study 2, one AE of ‘blood pressure decreased’ was reported in one subject in the Hydexor group and in one subject in the Norco group.

In the pooled data for Study 2 and Study 3, AEs of syncope were reported in five (1.1%) subjects in the Hydexor group, in no subjects in the Norco group, and in one (1%) subject in the placebo group. These five events occurred in one subject in Study 2 and four subjects in Study 3. There were no reported cases of syncope in Study 6. None of the cases of syncope were serious adverse events and all recovered without recurrence and the patients continued in the study. Review of the narratives provided for the eight cases of syncope/presyncope in Hydexor-treated patients did not raise any additional concern.

**Temperature Elevations**

Neuroleptic Malignant Syndrome has been reported in association with promethazine alone or in combination with antipsychotic drugs. Clinical manifestations include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic dysfunction. In the three studies, there were no AEs reported in any of the subjects who experienced pyrexia that are consistent with Neuroleptic Malignant Syndrome, including mental status change, muscle rigidity, or autonomic dysfunction.

There were reports of pyrexia in Studies 2 and 3, but this is not unexpected in a population of postsurgical patients. Across the pooled studies, the incidence of ‘pyrexia’ and/or ‘body temperature increased’ were similar in the placebo group as in the Hydexor group: pyrexia was
reported in five (1.1%) subjects in the Hydexor group, one (0.2%) subject in the Norco group, and three (3.0%) subjects in the placebo group. AEs of body temperature increased were reported in six (1.3%) subjects in the Hydexor group and in no subjects in the Norco or placebo groups. All but two of the events were mild. The remaining two events were moderate.

Only one event of pyrexia was reported in Study CLCT-006. The event was mild and lasted three days, resolving without sequelae.

4.2.4. Common Adverse Events

The table below shows the common AEs for the pooled Phase 3 efficacy studies, excluding OINV and the nine OSS AEs, as discussed above. These data do not identify any events of concern.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CL-108 (N=463)</th>
<th>Norco (N=455)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of TEAEs</td>
<td>50</td>
<td>60</td>
<td>42</td>
</tr>
<tr>
<td>Number of subjects with at least one TEAE, n (%)</td>
<td>49 (10.6)</td>
<td>54 (11.9)</td>
<td>28 (28.0)</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 (0.4)</td>
<td>5 (1.1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>5 (1.1)</td>
<td>1 (0.2)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Alveolar osteitis</td>
<td>8 (1.7)</td>
<td>17 (3.7)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Body temperature increased</td>
<td>6 (1.3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>0</td>
<td>8 (1.8)</td>
<td>0</td>
</tr>
<tr>
<td>Syncope</td>
<td>5 (1.1)</td>
<td>0</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

Source: Clinical Review

Abbreviations: OINV, opioid induced nausea and vomiting; OSS, Opioid Symptom Scales; TEAE, treatment-emergent adverse event

4.2.5. Vital Signs, Laboratory Findings, and Electrocardiography

Blood pressure, pulse, respiratory rate, oxygen saturation, and temperature were assessed in the three studies.

The blood pressure changes observed are consistent with the AE profile for promethazine and known alpha-adrenergic blocking effects.

The mean change in sitting diastolic blood pressure (DBP) from baseline to six hours post-dose was -7.4 mm Hg for Hydexor, -5.1 mm Hg for Norco, and -2.7 mm Hg for placebo. The percentage of subjects with potentially clinically significant (PCS) abnormalities of low DBP (defined as ≤ 50 mm Hg and ≥ 15 mm Hg decrease from baseline) was greater in the Hydexor group compared to the Norco group from three hours to six hours post-dose. In Study 3 (with fixed dosing), the percentages of Hydexor-treated patients with PCS values for low DBP at 6, 12, and 24 hours were 22%, 18%, and 17%, respectively, versus 14%, 8%, and 17% for Norco-treated patients.
Similar trends in the percentage of subjects with PCS abnormalities of low systolic blood pressure (SBP) (defined as \( \leq 90 \) mm Hg and \( \geq 20 \) mm Hg decrease from baseline) were observed. In Study 3, the percentages of Hydexor-treated patients with PCS values for low SBP at 6, 12, and 24 hours were 6\%, 6\%, and 6\%, respectively, versus 3\%, 2\%, and 2\% for Norco-treated patients. The mean change in SBP from baseline to six hours post-dose was -8.9 mm Hg for Hydexor, -6.1 mm Hg for Norco, and -2.2 mm Hg for placebo.

Analysis of changes in respiratory rate, oxygen saturation, and temperature did not raise any additional concerns.

Review of laboratory assessments and electrocardiographic data did not raise any concerns for drug-related changes.

5. Formal Dispute Resolution Request

Please read the Office Director’s complete decisional memo, included in Appendix 9.2.

6. Office of Surveillance and Epidemiology (OSE)

As part of the NDA Review, in order to fully understand the potential risks of Hydexor, our colleagues in OSE discuss relevant epidemiological aspects as well as data on drug utilization for the components of Hydexor.

**Epidemiology of Misuse and Abuse of Hydrocodone and Promethazine**

Misuse, abuse, and associated adverse outcomes are safety concerns for all opioid analgesics and are part of FDA’s benefit-risk evaluation for these drugs. Furthermore, for all regulatory decisions related to opioid analgesics, FDA considers the benefit-risk assessment to include broader public health risks, including those related to misuse and abuse in patients as well as others in the household and community.

For the February 2018 joint advisory committee meeting discussing this fixed dose hydrocodone/promethazine/acetaminophen product, OSE’s Division of Epidemiology II (DEPI) provided a review of the epidemiology of misuse and abuse of hydrocodone and promethazine. The review included data that show that both hydrocodone and promethazine are commonly used nonmedically and contribute to morbidity and mortality in the U.S. It also found that misuse and abuse of promethazine and opioids also occur together, and anecdotal evidence suggests that some, but not all, individuals who abuse opioids believe promethazine enhances opioids’ desirable euphoric as well as sedative effects.
Under the current NDA submission, however, the hydrocodone/promethazine/acetaminophen product would be approved with a REMS limiting the product’s use to inpatient settings, where its administration would be supervised, and the risks of misuse and abuse would be substantially mitigated. Therefore, DEPI has not conducted a new review of misuse and abuse patterns to inform the benefit-risk assessment for this product.

**Drug Utilization**

OSE conducted drug utilization analyses to characterize the use of hydrocodone-acetaminophen and promethazine in the hospital setting. Overall, the inpatient use of hydrocodone-acetaminophen and single-ingredient promethazine each declined from 2015 to 2019. During this time, the total number of patients with a hospital billing for single-ingredient promethazine decreased 67%, from approximately 3.5 million patients in 2015 to 1.1 million patients in 2019. Of those patients, the majority (~98%) had a discharge billing for injectable promethazine (Figure 4 below). Similarly, the total number of patients with a hospital billing for hydrocodone-acetaminophen also declined, from approximately 12 million patients in 2015 to 7 million patients in 2019 (data not shown).

**Figure 4. Nationally Estimated Number of Patients With a Hospital Discharge Billing for Promethazine* Stratified by Route of Administration, From U.S. Non-Federal Hospitals**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total Promethazine</th>
<th>Injectable</th>
<th>Oral</th>
<th>Rectal</th>
</tr>
</thead>
<tbody>
<tr>
<td>2015</td>
<td>3,503,442</td>
<td>3,491,465</td>
<td>13,730</td>
<td>1,224</td>
</tr>
<tr>
<td>2016</td>
<td>2,778,926</td>
<td>2,730,978</td>
<td>41,236</td>
<td>1,239</td>
</tr>
<tr>
<td>2017</td>
<td>1,948,926</td>
<td>1,918,803</td>
<td>30,852</td>
<td>780</td>
</tr>
<tr>
<td>2018</td>
<td>1,665,845</td>
<td>1,637,131</td>
<td>29,590</td>
<td>516</td>
</tr>
<tr>
<td>2019</td>
<td>1,141,813</td>
<td>1,116,722</td>
<td>27,010</td>
<td>215</td>
</tr>
</tbody>
</table>


*Single-ingredient promethazine

To understand patterns of concurrent use of hydrocodone-acetaminophen and promethazine products in the hospital, we obtained patient estimates projected to the national level with a concurrent hospital discharge billing for hydrocodone-acetaminophen and promethazine on the same day. The analyses revealed that the concurrent use of hydrocodone-acetaminophen and single-ingredient promethazine in the hospitals declined during the study-period. In 2019, approximately 137,000 hospitalized patients had a concurrent discharge billing for hydrocodone-
acetaminophen and promethazine on the same day with approximately half of those patients spending some time that day in the operating room (Figure 5 below).

**Figure 5. Nationally Estimated Number of Patients With a Concurrent Hospital Discharge Billing for Hydrocodone-Acetaminophen and Promethazine* on the Same Day, Stratified by Location of Care, From U.S. Non-Federal Hospitals**

<table>
<thead>
<tr>
<th>Location of Care</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grand Total</td>
<td>464,566</td>
<td>396,804</td>
<td>310,666</td>
<td>262,574</td>
<td>136,888</td>
</tr>
<tr>
<td>OR</td>
<td>203,418</td>
<td>164,467</td>
<td>147,545</td>
<td>121,429</td>
<td>68,475</td>
</tr>
<tr>
<td>GENERAL</td>
<td>188,681</td>
<td>176,655</td>
<td>135,246</td>
<td>115,066</td>
<td>60,586</td>
</tr>
<tr>
<td>ER</td>
<td>98,699</td>
<td>89,355</td>
<td>67,118</td>
<td>62,201</td>
<td>24,937</td>
</tr>
<tr>
<td>CCU/ICU</td>
<td>20,806</td>
<td>24,863</td>
<td>17,680</td>
<td>14,333</td>
<td>8,845</td>
</tr>
<tr>
<td>TELEMISTRY</td>
<td>22,408</td>
<td>25,757</td>
<td>20,519</td>
<td>16,361</td>
<td>7,390</td>
</tr>
<tr>
<td>OTHER</td>
<td>75,081</td>
<td>72,740</td>
<td>45,513</td>
<td>37,450</td>
<td>18,653</td>
</tr>
</tbody>
</table>

* Single-ingredient promethazine in oral or injectable dosage formulation

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.

Abbreviations: CCU, coronary care unit; ER, emergency room; ICU, intensive care unit; OR, operating room

Findings from this analysis should be interpreted in the context of known limitations:

- Concurrent use was defined as both drugs of interest – hydrocodone/acetaminophen and promethazine – administered on the same day. The two drugs were not necessarily taken at the same time, ordered by the same health care practitioner, or ordered together intentionally.
- Location of care data are not mutually exclusive because patients may change location in the hospital within the same day. The two drugs may not have been administered in the same location of care.
- Drug utilization data do not provide information on indication for use; therefore, patients with concurrent use may or may not have been administered promethazine for opioid induced nausea and vomiting (OINV).
OSE’s Division of Risk Management summarizes the aspects of REMS as it related to the Applicant’s proposal.

**Background on REMS**

Section 505-1 of the Food, Drug, and Cosmetic Act (FDCA), added to the law by the Food Drug Administration Amendments Act of 2007 (FDAAA), authorizes the FDA to require applicants or application holders to develop and comply with a risk evaluation and mitigation strategies (REMS) for a drug if the Agency determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: Medication Guide or patient package insert, a 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), and implementation system. All REMS approved for drugs or biologics under New Drug Applications (NDA) and Biologics License Applications (BLA) must have a timetable for submission of assessments of the REMS. These assessments are prepared and submitted by the application holder and reviewed by FDA.

A Medication Guide provides FDA approved patient-focused labeling and can be required as part of the approved labeling if FDA determines one or more of the following apply:

- Patient labeling could help prevent serious adverse events.
- The product has serious risks that could affect a patient’s decision to use or continue to use the drug.
- Patient adherence to directions is crucial to product effectiveness.

A communication plan consists of FDA-approved materials used to aid a sponsor’s implementation of the REMS and/or inform healthcare providers about the serious risk of a drug. This can include, for example, “Dear Healthcare Professional” letters, collaboration with professional societies, and education pieces (such as letters, drug fact sheets) to inform prescribers of the risks and the safe use practices for the drug.

Elements to assure safe use (ETASU) can include one or more of the following requirements:

- Healthcare providers who prescribe the drug have particular training or experience or special certifications
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug may be dispensed only in certain healthcare settings
- The drug may be dispensed to patients with evidence of safe-use conditions
- Each patient must be subject to monitoring
- Patients must be enrolled in a registry
Because ETASU can impose significant burdens on the healthcare system and potentially impact patient access to treatment, ETASU are required only if FDA determines that the product could be approved only if, or would be withdrawn unless, ETASU are required to mitigate a specific serious risk listed in the labeling. Accordingly, the statute [FDCA 505-1(f)(2)] specifies that ETASU:

- Must be commensurate with specific serious risk(s) listed in the labeling.
- Cannot be unduly burdensome on patient access to the drug.
- To minimize the burden on the healthcare delivery system, must, to the extent practicable, conform with REMS elements for other drugs with similar serious risks and be designed for compatibility with established distribution, procurement, and dispensing systems for drugs.

Risk Management Issues in Last Review Cycle

At the February 14, 2018 Advisory Committee meeting the Applicant communicated that their proposed indication for Hydexor was for short-term management of acute pain severe enough to require an opioid analgesic while preventing and reducing OINV and labeling would include that treatment was for less than 14 days with a dosing schedule of 1 tablet every 4-6 hours as the maximum daily dosage. The proposed use for this product would have included outpatient treatment of pain and prevention of OINV, and it was proposed that Hydexor would join the Opioid Analgesic REMS, a class-wide REMS that includes opioids intended for outpatient use that are not subject to another REMS. The Applicant had also proposed packaging for 3, 5 or 7 days of therapy, that would be child-resistant blister packs and contain a total of 18, 30, or 42 tablets, respectively, and an 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.

As discussed, the majority of the Committee members did not agree that the Applicant’s clinical program for Hydexor supported safe and effective use of the fixed-dose combination product. Committee members had significant concerns about the use of Hydexor in a broader patient population and the duration of use, as the patients studied in the clinical trials were post-operative and despite this being an enriched population, not every patient experienced OINV. Additional concerns raised by the Committee members included: lack of dosing flexibility with a fixed-dose combination product that would expose patients to unnecessary side effects of promethazine when it is not needed, lack of data on the risk of sedation and drop in blood pressure in the elderly population (patients aged 65 and older), and the proposed drug packaging that may encourage patients to finish the package when Hydexor should be used only as needed. When asked for more details on how they would implement the proposed buyback program, the Applicant stated that they were in conversations with various groups (e.g. DEA) and had not worked out details. Most committee members expressed their concern that the Applicant’s proposed risk management strategies for Hydexor were not adequate, particularly due to concerns about the lack of effectiveness of the proposed packaging and uncertainty about the feasibility of the drug buyback program at the federal or state level.

Following the AC meeting, the second Complete Response letter communicated to the Applicant the need to better identify the patient population that would require concomitant therapy with an opioid and a preemptive antiemetic for OINV as this fixed dose-combination would expose many patients to additional risks with no added benefit. The Agency remains concerned about the risk
of CNS depression with the combined use of an opioid analgesic and promethazine and that the risk of excessive sedation may result in falls or other accidents. Since Hydexor includes an opioid, it also carries the risk of life-threatening respiratory depression, addiction, abuse and misuse.

**Current Risk Management Proposal**

To address concerns raised during the previous review cycle including the risk of life-threatening respiratory depression and the risk of falls or other accidents resulting from excessive sedation, the Applicant has revised their proposal. The current proposed indication is:

*For 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. Use should be 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.*

The Applicant is no longer proposing packaging for 3, 5 or 7 days of therapy as Hydexor will only be used in medically supervised settings and not for use in the home. By limiting Hydexor to post-operative use (i.e. hospitals, surgical centers), the risks of abuse, misuse and addiction are much less likely than in outpatient settings. In addition, the Applicant is proposing to not use Hydexor in skilled nursing facilities where patients are likely to be older and more at risk for respiratory depression and falls due to excessive sedation.

The Applicant’s proposed REMS consists of certification of healthcare settings and restriction of distribution and dispensing of Hydexor to the certified medically supervised healthcare settings. These settings would be required to have policies and procedures in place to manage acute opioid overdose including life-threatening respiratory depression, have fall precaution protocol(s) on-site, establish policies and procedures to discontinue Hydexor after 3 days and verify that Hydexor is not dispensed for use outside of the certified healthcare setting. The proposed REMS also includes an implementation system and a timetable for submission of assessments. The proposed elements would mitigate the risk of life-threatening respiratory depression and the risk of falls or other accidents resulting from excessive sedation as the patients would be monitored and not have access to tablets in their homes. If Hydexor is approved, the proposed REMS will address the safety concerns raised by the February 2018 Advisory Committees by ensuring that patients are only administered Hydexor in a certified medically supervised setting where patients can be monitored for respiratory depression and the risk of falls or other accidents resulting from excessive sedation. Additionally, 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 assessment plan for this proposed REMS remains under review but would likely include the following assessment 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; and surveillance data of adverse events of special interest. The Applicant would be required as defined in the timetable for assessment to submit to FDA an assessment of the REMS to determine whether the REMS is meeting its goals. One metric to assess the effectiveness of the REMS could be whether Hydexor use is actually
limited to certified medically supervised settings that have established policies and procedures to manage respiratory depression, have fall precautions, and discontinue Hydexor after three days.

8. Advisory Committee Meeting

A joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM) was held for this NDA on February 14, 2018. The committees were asked to discuss the overall risk-benefit profile of the product and whether it should be approved. The following is a list of the questions posed to the committees and a summary of the discussion that took place. These comments and the final vote should be considered in the context of that targeted population and potential duration of use proposed at that meeting.

1. **DISCUSSION:** Does the Applicant’s clinical program support the safe and effective use of Hydexor as an analgesic and for prevention of opioid-induced nausea and vomiting (OINV) that is limited to use in individuals likely to experience OINV?

   **Committee Discussion:** The majority of the committee did not agree that the Applicant’s clinical program supports the safe and effective use of Hydexor as an analgesic and for prevention of opioid-induced nausea and vomiting (OINV) that is limited to use in individuals likely to experience OINV. Most committee members agreed that a fixed dose combination limits the ability to tailor the dose of the drug based on an individual’s needs, thus reducing clinical flexibility. Some committee members noted that the risk of adverse events and unintentional overdose associated with promethazine in the combination product outweighs the little benefit shown in the data.

2. **DISCUSSION:** There are currently no immediate-release, hydrocodone-acetaminophen combination products with abuse-deterrent properties that are approved and on the market. Do you have concerns that Hydexor does not have abuse-deterrent properties?

   **Committee Discussion:** Some committee members stated that they did not have concerns that Hydexor does not have abuse-deterrent properties since the current abuse-deterrent formulations do not seem to be making much of an impact and that there is not much evidence of abuse of hydrocodone combination products and promethazine. One committee member noted concerns that Hydexor could be a gateway for drug abuse for those individuals that experienced OINV and questioned the Applicant’s commitment to risk mitigation, stating that Hydexor packaging encourages round-the-clock use and that a well-formulated risk mitigation plan need to be implemented.

3. **DISCUSSION:** Epidemiological data suggest that misuse and abuse of promethazine, either alone or in combination with opioids or other drugs, have resulted in emergency department visits, contact with poison control centers, and
Please discuss whether you think Hydexor poses greater risks than currently-marketed hydrocodone-acetaminophen products.

**Committee Discussion:** Overall, the majority of the committee agreed that Hydexor poses greater risks than currently marketed hydrocodone-acetaminophen products. Some committee members added that the proposed fixed-dose combination includes 7.5 mg of hydrocodone, which is higher than the usual starting dose of this drug. Also, the presence of promethazine could result in additional adverse events and drug-drug interactions that would not be experienced with the currently marketed hydrocodone-acetaminophen products. Some committee members noted that although there would be some misuse and abuse of Hydexor, the risk of serious promethazine toxicity, hospitalization or death with the currently suggested packaging would be low. The committee generally felt that the benefits of Hydexor did not outweigh the risks.

4. **VOTE:** Should Hydexor be approved?

   **Vote Result:** Yes: 2   No: 19   Abstain: 0

**Committee Discussion:** The majority of the committee agreed that Hydexor should not be approved. Some of the committee members who voted “No” stated that their vote was based on the lack of dosing flexibility and that the ramifications of the risks associated with Hydexor did not outweigh its benefit. Some committee members added that an antiemetic may not be needed with every dose of analgesic, and that a fixed-dose combination of Hydexor would expose patients to unnecessary side effects of promethazine when it is not needed. Other committee members agreed that the Applicant’s proposed risk mitigation strategies are not convincing. One committee member who voted “Yes” viewed Hydexor as another opioid option and noted that its risks are no greater than what is currently on the market. Additionally, this member noted that that the population receiving Hydexor would be those who were prone to OINV and that the medication would be taken as needed. The other committee member who voted “Yes” stated that the overall benefits outweighed the risks but also suggested that additional toxicity data are needed in the setting of patients who took more than six pills a day of Hydexor.

9. **Appendix**

   **9.1. Additional Analyses in Third Cycle**

The following is excerpted from the Combined Clinical Memo from the third review cycle. It summarizes the Applicant’s new analyses to try and address the Agency’s concerns regarding the low incidence of OINV in patients treated with Norco:
Complete Response Submission (3rd Cycle) - Additional Analysis

The following is excerpted from the third cycle review:

In the current submission the Applicant provided new analyses for three subpopulations from the Phase 3 trial CLCT-003 to try to address the agency’s concerns regarding the low incidence rate of OINV in patients treated with Norco. CLCT-003 was selected as patients were dosed on a fixed schedule, thereby assuring a balanced exposure to hydrocodone for both the Hydexor and Norco treatment arms. Furthermore, the patients in this study were more representative of patients with acute post-operative pain requiring opioid therapy, as the study was conducted in post bunionectomy patients.

It is noted that the Applicant did not conduct or submit additional analyses on CLCT-002.

The Applicant’s additional analyses focused on the following patient populations, endpoints, and time periods in CLCT-003:

- Patient populations:
  - All patients treated with CL-108 who did not use a rescue antiemetic and patients treated with Norco who did use a rescue antiemetic.
  - All patients treated with CL-108 or Norco who experienced nausea (NIS greater than 0).
  - All ITT patients treated with CL-108 or Norco
- Endpoint evaluations:
  - Nausea and vomiting related endpoints (Incidence of nausea, Severity of nausea, Incidence of vomiting, Incidence of retching)
  - Analgesic endpoint (Reduction in pain intensity as measured using SPID)
- Intervals of evaluations:
  - 0-6, -12, -18, -24, -30, -36, -42, and -48 hours

The nausea intensity scale (NIS) was the main instrument used to measure nausea in the study. As discussed in the clinical review by Dr. Jiang during the first cycle, the Division consulted the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Clinical Outcomes Assessment (COA) staff for their evaluation regarding the use of the NIS in a clinical trial.

DGIEP’s concerns are summarized below:

- There was a lack of data to support the cutoffs used to define mild, medium, and severe nausea
- There is no precedent for the use of the NIS to define nausea to support approval of marketing applications
COA staff concerns are summarized below:

- There was sufficient evidence of content validity and psychometric properties to support the NIS to measure the severity and occurrence of nausea
- There was inadequate information to assign specific NIS score to specific severity categories

This complete response submission includes additional analysis which consists of the following three comparisons: all patients treated with Hydexor who did not use a rescue antiemetic and patients treated with Norco who did use a rescue antiemetic, all patients treated with Hydexor or Norco who experienced nausea (NIS greater than 0), and all patients treated with Hydexor or Norco.

**Comparison #1: Patients who received CL-108 without using a rescue antiemetic compared to Norco patients who used rescue antiemetic in Study CLCT-003**

The Applicant noted that there was a clear separation in reported pain between patients in the Norco treatment arm who used anti-emetic rescue medication to patients in the CL-108 treatment arm who didn’t use anti-emetic rescue medication. The Applicant argued that treating OINV only after it occurs is less effective than prevention based on these analyses.
Table 14. Efficacy Outcomes of Treatment With CL-108 Without a Rescue Antiemetic and Norco With a Rescue Antiemetic (Study CLCT-003 ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>0-6 hours</th>
<th>0-12 hours</th>
<th>0-18 hours</th>
<th>0-24 hours</th>
<th>0-30 hours</th>
<th>0-36 hours</th>
<th>0-42 hours</th>
<th>0-48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPID™</strong> (mean; NIS &gt; 0)</td>
<td>9.6a</td>
<td>8.7a</td>
<td>20.5a</td>
<td>17.7a</td>
<td>30.4a</td>
<td>25.7a</td>
<td>42.9a</td>
<td>35.1b</td>
</tr>
<tr>
<td><strong>Severity of Nausea</strong> (mean)</td>
<td>7.5c</td>
<td>6.5d</td>
<td>17.3c</td>
<td>15.5c</td>
<td>26.6c</td>
<td>21.9c</td>
<td>38.4c</td>
<td>29.3c</td>
</tr>
<tr>
<td><strong>Incidence of Vomiting</strong> (%)</td>
<td>7.7b</td>
<td>10.8c</td>
<td>13.1d</td>
<td>24.9c</td>
<td>20.5c</td>
<td>17.4c</td>
<td>38.3c</td>
<td>47.1b</td>
</tr>
<tr>
<td><strong>Incidence of Retching</strong> (%)</td>
<td>3a</td>
<td>8.8a</td>
<td>7.7a</td>
<td>14.8b</td>
<td>7.8b</td>
<td>19a</td>
<td>8.3b</td>
<td>20.7a</td>
</tr>
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<td></td>
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<td>12.2a</td>
<td>14.5a</td>
<td>24.7a</td>
<td>14.8a</td>
<td>24.7a</td>
<td>14.4a</td>
<td>26.8a</td>
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Source: Applicant's submission
When evaluating the number of patients with opioid-induced nausea defined using the Applicant-preferred nausea endpoint (NIS) and any score greater than 0, there were fewer patients treated with CL-108 who experienced nausea than patients using Norco over the 48-hour observation period.

The selected cutoff of NIS score greater than 0 includes the mildest levels of nausea (NIS score 1-3) which are less associated with vomiting and do not require clinical intervention such as use of antiemetic rescue, medications as shown the table below:

**Figure 6. Antiemetic Use vs. NIS Score (CLCT-003)**

![Graph showing antiemetic use vs. NIS score](image)

Source: James Travis

The Applicant also evaluated the pain intensity for patients with an NIS score greater than 3 and showed fewer patients treated with CL-108 had nausea than patients treated with Norco.

The Applicant’s post hoc analysis used for Comparison #2, still has not identified a patient population that requires concomitant antiemetic therapy to address the CR deficiency.

**Comparison #3: All CL-108-Treated patients compared to Norco-treated patients in Study CLCT-003**

The Applicant’s final post hoc analyses expand the analysis population to the entire study population in both treatment arms.
Table 15. Efficacy Outcomes of CL-108-Treated Patients and Norco-Treated Patients (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>0-6 hours</th>
<th>0-12 hours</th>
<th>0-18 hours</th>
<th>0-24 hours</th>
<th>0-30 hours</th>
<th>0-36 hours</th>
<th>0-42 hours</th>
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<tr>
<td>SPID (mean)</td>
<td>9.8%</td>
<td>9.1%</td>
<td>21.9%</td>
<td>18.7%</td>
<td>32.4%</td>
<td>26.9%</td>
<td>45.7%</td>
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<tr>
<td>Incidence of Nausea (%)</td>
<td>39.7%</td>
<td>58.8%</td>
<td>46.4%</td>
<td>64.8%</td>
<td>50.8%</td>
<td>69.6%</td>
<td>52.4%</td>
<td>71.6%</td>
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<tr>
<td>Severity of Nausea (mean)</td>
<td>3.0%</td>
<td>6.4%</td>
<td>6.1%</td>
<td>16.1%</td>
<td>8.9%</td>
<td>26.7%</td>
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<tr>
<td>Vomiting (%)</td>
<td>1.2%</td>
<td>5.2%</td>
<td>3.6%</td>
<td>9.6%</td>
<td>4.0%</td>
<td>13.2%</td>
<td>4.4%</td>
<td>14.8%</td>
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<tr>
<td>Reaching (%)</td>
<td>4.8%</td>
<td>7.2%</td>
<td>7.9%</td>
<td>16.0%</td>
<td>9.1%</td>
<td>17.2%</td>
<td>9.1%</td>
<td>19.2%</td>
</tr>
</tbody>
</table>

Source: Applicant’s submission
The Applicant argued that the vast majority of Norco-treated patients experienced nausea (NIS greater than 0), with an incidence of 71.6% at 24 hours and 80.8% at 48 hours, compared to only 52.4% at 24 hours and 57.1% at 48 hours in the patients treated with CL-108, and that this represents adequate support for the use of CL-108. The use of the NIS is not the Agency preferred measure for nausea as discussed above, and the Applicant’s definition of nausea as any score greater than 0 over-emphasizes minor levels of nausea which may not be significant to the patients. Accordingly, we have traditionally relied upon a more objective measure of clinically relevant nausea, supplemental anti-emetic use. The majority of patients (55%) in the Norco treatment arm at 48 hours, in this enriched population, did not require supplemental anti-emetic use or report vomiting. Therefore, using the full spectrum of NIS scores is not a clinically relevant endpoint to justify exposing everyone to promethazine.

**Summary and Conclusion**

**Summary of findings:**

The findings from the Applicant’s three comparisons on CLCT-003 are summarized below. Statistical significance was not evaluated for these post-hoc secondary analyses.

1. The 45% of Norco-treated patients who used rescue antiemetics had lower pain control than Hydexor-treated patients who did not use rescue antiemetics. However, Norco-treated patients who did not use an antiemetic and Hydexor-treated patients who did not use antiemetics reported similar levels of pain control.

2. Among the patients who reported any nausea (NIS greater than 0), Hydexor-treated patients had lower cumulative NIS scores and developed vomiting and retching less frequently than Norco-treated subjects. Hydexor-treated subjects in this population also had better pain control than Norco-treated patients.

3. For the entire ITT study population, fewer Hydexor-treated patients were shown to have experienced nausea (NIS greater than 0) than Norco-treated patients, with lower cumulative NIS scores, less frequent vomiting and retching and better pain control than subjects treated with Norco.

4. However, Hydexor-treated patients reported increased severe drowsiness compared to Norco-treated patients as detailed in Section 8.

**Discussion:**

The additional analyses from CLCT-003 are based on analgesic, and nausea/vomiting related endpoints or clinical outcomes, which are discussed separately as follows:

The main driver for differences in the analgesic outcome between Hydexor and Norco appears to be the lower pain control reported by Norco-treated patients who required rescue antiemetics. The additional analgesic benefit may be a result of 1) subjects with improved emetic control are able to hold down pills (in this case, hydrocodone and APAP) better and 2) the movement associated with vomiting may potentially exacerbate acute pain.

One of the key limitations of these new analyses is that any benefit demonstrated was found only as a result of analyzing subpopulations. Most patients in the Norco treatment arm did not vomit or require use of antiemetic rescue. When patients treated with CL-108 without rescue
antiemetic use are compared to Norco without rescue antiemetic use, there is no difference in pain outcomes. Therefore, the benefit in pain intensity reported for patients who received Hydexor without using a rescue antiemetic compared to Norco patients who used rescue antiemetic does not apply to a majority of the study population.

The Applicant still has not adequately identified a patient population that predictably requires concomitant therapy with an opioid analgesic and a preemptive antiemetic with every dose to warrant exposing all patients treated with hydrocodone/acetaminophen to promethazine and its associated risks to address the CR deficiency.

Any benefit in pain control must be considered in the overall risk-benefit context, as preemptively treating patients with Hydexor was associated with higher rates of AEs, such as severe CNS sedation.

The antiemetic benefit of Hydexor was reviewed and agreed upon in the first review cycle. The Applicant argued that there was a high prevalence of nausea in this study (CLCT-003), with 71.6% of Norco-treated patients reporting a positive NIS score in the first 24 hours, and 80.8% in the first 48 hours. However, the clinical significance of the low NIS scores reported is unclear. Antiemetic use is a direct measure of the significance of nausea to patients.

Therefore, if a patient did not use available antiemetics then that level of nausea was tolerable to them. The majority (55%) of Norco-treated patients did not use an antiemetic medication in the first 48 hours of the study as shown in Table 2: Primary efficacy of CLCT-003, and we must balance these findings with the increase in severe CNS sedation reported by Hydexor-treated patients. Therefore, using NIS scores as endpoint for nausea does not reflect only clinically relevant nausea.

**Conclusion:**

The Applicant’s 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.
### 9.2 Formal Dispute Resolution Appeal

#### DOCUMENT INFORMATION PAGE
This page is for FDA internal use only. Do NOT send this page with the letter.

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<td>LaShawn Dionat 4.18.2019</td>
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**Version:** 04/24/2015

#### END OF DOCUMENT INFORMATION PAGE
The letter begins on the next page.
NDA 209257

Ölas Pharma, Inc.
Attention: George A. Scott, Jr., JD, MBA
Chief Legal Officer & General Counsel
1150 South U.S. Highway 1
Jupiter, FL 33477

Dear Mr. Scott:

Please refer to your New Drug Application (NDA) submitted pursuant to Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Hydexor (hydrocodone bitartrate, acetaminophen, and promethazine hydrochloride) tablets.

I also refer to your April 12, 2019, request for formal dispute resolution received on April 12, 2019. The appeal concerned the Division of Anesthesia, Analgesia, and Addiction Products’ February 8, 2019, Complete Response Letter (CRL).

I also refer to the meeting held between FDA and Ölas Pharma, Inc. on April 29, 2019, where the issues raised in your request for formal dispute resolution were discussed.

I also acknowledge receipt of the requested additional clarifying information on May 24, 2019.

I have carefully reviewed the materials you submitted in support of your appeal, as well as FDA reviews, Advisory Committee meeting transcript and slides, meeting minutes, and the complete response letters dated January 31, 2017, April 12, 2018, and February 8, 2019. I have also met with reviewers from the Division of Anesthesia, Analgesia, and Addiction Products (hereafter referred to as the Division), FDA staff assigned to review the Hydexor NDA, and conferred with Dr. Robert Temple, Senior Advisor to the Office of New Drugs (OND).

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

**I. Background**

NDA 209257 for Hydexor, a fixed-dose combination (FDC) product containing 7.5 mg hydrocodone, 325 mg acetaminophen, and 12.5 mg promethazine, was submitted to FDA on March 31, 2016. The following language was proposed under the Indications and Usage section:

*HYDEXOR contains hydrocodone bitartrate (an opioid analgesic) acetaminophen (a non-opiate, non-salicylate analgesic and antipyretic) and promethazine hydrochloride (an H1 receptor antagonist).*
HYDEXOR is indicated for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting.

On January 31, 2017, the Division issued a CRL citing four deficiencies. Two of these deficiencies were related to establishing bioequivalence of Hydexor to an approved hydrocodone and acetaminophen product. Specifically, those two CRL deficiencies stated the following:

1. Data was not provided to demonstrate that the hydrocodone and acetaminophen components of HYDEXOR and an approved hydrocodone and acetaminophen product are bioequivalent, and therefore that the lower incidence of nausea and vomiting observed with HYDEXOR is due to the presence of promethazine in the combination and not due to a lower systemic exposure to hydrocodone.

2. Data was not submitted to demonstrate that the hydrocodone/acetaminophen component of HYDEXOR is not a new combination, that is, that both hydrocodone and acetaminophen contribute to the analgesic efficacy of HYDEXOR.

On October 12, 2017, a response to the CRL was received. The resubmitted application was discussed at a joint meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSARM) on February 14, 2018 which voted 19 versus 2 against approval of Hydexor.

On April 12, 2018, the Division issued a second CRL citing one deficiency:

1. You have not provided adequate evidence of a patient population that requires treatment with HYDEXOR, as required by the Combination Rule 21 CFR 300.50. A substantial number of patients treated with the hydrocodone/acetaminophen comparator in Studies CLCT-002 and CLCT-003, which were enriched to enroll a population at risk for opioid-induced nausea and vomiting (OINV), did not develop OINV (defined as an episode of emesis or requiring antiemetic use) with only 2.4% and 6.4% of patients experiencing OINV on day five of treatment, respectively. As such, you have not adequately identified a patient population that predictably requires concomitant therapy with an opioid analgesic and a preemptive antiemetic with every dose to warrant exposing all patients treated with HYDEXOR to promethazine and its associated risks.

An End-of-Review (EOR) meeting between representatives of Ōlas Pharma, Inc. (hereafter referred to as the Applicant) and the FDA Hydexor review team was held on May 17, 2018. The minutes from this meeting summarized the discussion surrounding eleven questions posed by the Applicant. Relevant to the deficiency identified in the April 12, 2018, CRL, Ōlas stated it 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. Below is an example of the proposed revised indication:
The Division did not agree with this proposal, citing concerns raised at the AC meeting that this FDC would expose many patients to promethazine who did not appear to need an anti-emetic. Specifically, 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. An excerpt from the Division’s response on the Applicant’s proposal is summarized below:

Therefore, the majority of patients treated with HYDEXOR will not experience a benefit of decreasing OINV but will be exposed to the additional adverse effects related to promethazine. Additionally, the presence of promethazine in HYDEXOR offers less flexibility to tailor the analgesic doses to an individual patient’s pain. In this context, OINV appears to be more appropriately managed with antiemetics on an “as needed” basis.

Because the majority of patients enrolled in your Phase 3 studies were assessed as being at risk for OINV due to known or suspected prior history of OINV and/or nausea and vomiting in response to a hydrocodone challenge, it is unclear how you could further define and/or study a population that would consistently require an antiemetic with every dose of hydrocodone/acetaminophen. The results of the Phase 3 studies do not support the original nor the proposed amended indication. If a patient population can be identified that would require around the clock dosing with promethazine when being dosed with a combination of hydrocodone and acetaminophen, additional clinical studies will be necessary to demonstrate a favorable balance of benefit and risk in this population.

Discussions around this point included a proposal by the Applicant 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.

The Applicant also submitted its summary of the EOR meeting and although there are differences in interpretation of the benefits and risks of Hydexor, both the FDA and Applicant agreed, as summarized in their separate minutes, 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 2nd CRL.
The 2nd resubmission in response to the 2nd CRL was received on August 9, 2018, and included additional analyses of CLCT-003 with focus on selected patient subgroups and endpoints and secondary endpoints to address the 2nd CRL deficiency. On February 8, 2019, the Division issued a 3rd CRL reiterating the same deficiency identified in the 2nd CRL letter and stating that “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.”

II. Formal Dispute Resolution Request

Your Formal Dispute Resolution Request (FDRR) requests that FDA withdraw the February 2019 CRL and approve Hydexor. Your FDRR challenges the CRL based on two principle arguments presented in Sections VI.A and VI.B of your FDRR.

A. The Combination Rule Does Not Require Effectiveness with Every Dose in Every Patient

B. FDA’s Regulations Commit the Division to Honoring its Agreements from the HYDEXOR End-of-Phase 2 meeting

Sections VI.C through VI.F of your FDRR contain materials that are supplementary to your key arguments. In the subsequent section of this response to your appeal, I will consider information from Sections VI.C through VI.F in my analysis and consideration of your FDRR.

III. Analysis and Consideration of FDRR

A. The Combination Rule Does Not Require Effectiveness with Every Dose in Every Patient

Under VI.A. you specifically cite the following language from the February 2019 CRL:

“…..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.”

You argue that the Division has incorrectly interpreted the Combination Rule, as you have interpreted the above excerpt as the Division requiring proof of effectiveness with “every dose” and “every patient” rather than requiring that each drug in the FDC contributes to a claimed effect. In the case of Hydexor, the claimed effect is that the hydrocodone/acetaminophen components demonstrate analgesic efficacy and that the promethazine component prevents OINV.

During the April 29, 2019, meeting I asked the Division to explain whether it expected proof of effectiveness with every dose in every patient. Dr. Sharon Hertz, Division Director for DAAAP, explained that since Hydexor is a FDC containing promethazine, with inherent risks of CNS depression, it is important that patients receiving Hydexor actually require an anti-emetic. While the Division agrees with the Applicant that Hydexor reduces the incidence of OINV compared to
Norco, and has a superior analgesic effect compared to placebo, the Division concluded that the two pivotal trials did not demonstrate that Hydexor is safe and effective for a significant patient population requiring such concurrent therapy as defined in the labeling for the drug, as stated under 21 CFR 300.50. The Division based this conclusion on the observation that many patients in the Norco control arm did not develop OINV despite having been selected based on characteristics predicting a high likelihood of developing such an event.

The Division clarified at the April 29, 2019, meeting that, despite the statement in the CRL, there was not a requirement for proof of effectiveness with “every dose” and in “every patient”. At issue is the conclusion by the Division that the anti-emetic component of Hydexor was not needed by a majority of patients in the two pivotal studies. As such, these patients will only assume the risks of promethazine. I note that early on in product development the Division raised this concern to the Applicant. In the November 8, 2007, Pre-IND meeting minutes the Division stated the following:

“According to 21 CFR 300.50(a) the fixed dose combination must be shown to be safe and effective for a significant [emphasis added] patient population requiring such concurrent therapy….Unless prospective identification of patients likely to experience vomiting or nausea is possible,…use of this product as intended will result in the majority of patients receiving unnecessary medication with promethazine.”

It appears that the Applicant understood that the study population had to be selected based on criteria that would likely identify those who would need an anti-emetic (i.e., enrichment strategy). Whether the Applicant understood or if the Division specified what criteria had to be met to identify a significant patient population requiring Hydexor will be discussed below as I address your second argument.

**B. FDA’s Regulations commit the Division to Honoring Its Agreements from the HYDEXOR End-of-Phase 2 Meeting**

Your 2nd argument alleges that the February 2019 and April 2018 CRLs shifted the standard for approval and disregarded prior agreements between the Division and the Applicant at the EOP2 meeting. You summarize those agreements as follows from the FDA’s EOP2 meeting minutes:

“In these studies, you must demonstrate that the effect of CL-108 [HYDEXOR] is superior to placebo on pain and superior to hydrocodone/acetaminophen on nausea and vomiting.”

You further reiterate this in an excerpt from the FDA briefing document for the February 14, 2018, Advisory Committee meeting:

1) Demonstrate BE [bioequivalence] of HYDEXOR to Norco for both HC and acetaminophen,
2) Demonstrate the efficacy of HYDEXOR over Norco for prevention of OINV, and
3) Characterize the safety profile of HYDEXOR for the stated indication
You state that since the clinical development program met the above requirements with no unexpected outcomes, FDA is required to abide by its agreements. You further reference 21CFR 312.47(b)(1)(v) to support your argument that the Division must uphold its EOP2 agreement unless there has been a significant scientific development subsequent to this meeting.

I have reviewed the EOP2 meeting minutes, FDA reviews of the two pivotal trials, communications between the Division and the Applicant throughout development, and the FDA AC briefing materials and slides and agree with the Division and Applicant that the trial results met the criteria for establishing Hydexor’s claimed effect on analgesia and prevention of OINV. For completeness, the following excerpt from the FDA’s AC background material supports a conclusion that FDA determined Hydexor to be effective as an analgesic and for the prevention of OINV.

From Page 61 of FDA AC Background Materials for Hydexor AC meeting February 14, 2018:

The results from the analysis of the data from each study demonstrated statistically significant improvement in pain when compared to placebo and a statistically significant reduction in OINV when compared to Norco regardless of how the OINV endpoint was defined. Both studies actively enriched and only enrolled patients who were more likely to experience nausea and vomiting. Consequently, it is not possible to extrapolate the effectiveness of this product to patients who are not expected to be prone to nausea and vomiting.

DGIEP reviewed the efficacy data and concurred that less OINV was observed with Hydexor than Norco in the two efficacy studies. DGIEP noted that “[w]hile the primary efficacy assessment time point was 24 hours for Study CLCT-002 and 48 hours for Study CLCT-003, CR [complete response, defined as no emetic episode and no use of rescue medication] rates were measured in each treatment group on each day of the 5-day study period. In Study CLCT-002, the difference in CR rate (preferred DGIEP endpoint, post-hoc analysis) between the CL-108 and Norco treatment groups was found to be nominally statistically significant out to 96 hours. In Study CLCT-003, the difference was found to be nominally statistically significant for each of the five study days (p<0.001)…These results provide information to support the durability of the efficacy of CL-108 for the prevention of OINV for up to 5 days.”

Based on the above summary, I believe the Division has honored its agreement at the EOP2 meeting by accepting the results of CLCT-002 and 003 in support of the marketing application. However, even though the two pivotal studies established effectiveness as defined at the EOP2 meeting, approval of an application is a weighing of benefits against risks in the intended population. This weighted assessment is not performed at the EOP2 meeting but after receipt of the marketing application wherein FDA can review the results of pivotal studies, consider these results in light of the proposed labeling, and also take into consideration recommendations from Advisory Committee members. Finally, as we are in the midst of an opioid epidemic in the U.S., I would be remiss to not consider any FDA actions that have been taken in this space since the EOP2 meeting and whether they were appropriately applied in the Division’s regulatory decision. On this last point, I believe it is relevant to your application as FDA action taken to address the opioid epidemic since your EOP2 meeting may signal new scientific development.
FDA Actions to Address Opioid Misuse and Abuse

Since your EOP 2 meeting in January 2014, there have been numerous FDA activities aimed at addressing the opioid crisis in the U.S. The one most relevant to the benefit-risk assessment of Hydexor took place on August 31, 2016. On this date, FDA announced class-wide safety labeling changes in the form of a boxed warning for certain opioid medications and benzodiazepine to highlight that the combined use of these two classes of drugs has resulted in serious side effects including respiratory depression and death, as reported in two studies conducted by FDA and additional studies reviewed from published literature.


Although promethazine is not a benzodiazepine, it is labeled as a CNS depressant and as you have pointed out on page 30 of the FDRR, it is indicated as a sedative. In a released statement, then FDA Commissioner, Dr. Robert Califf stated, “We implore health care professionals to heed these new warnings and more carefully and thoroughly evaluate, on a patient-by-patient basis, whether the benefits of using opioids and benzodiazepines- or CNS depressants more generally – together outweigh these risks (emphasis added).”

This last statement reflects a new scientific development based on data reviewed by the Agency, which led to the class-wide safety labeling change. Not only is Hydexor an opioid but it is an opioid combined with a CNS depressant and the benefits of its combined use must be considered against the risk of further CNS depression.

Advisory Committee Recommendations

Under Section VI.C. of your FDRR you discuss the February 14, 2018, AC deliberations and majority vote against approval. You argue that the negative vote was largely the result of a “philosophical bias against fixed-dose combinations” and did not constitute a “significant scientific development”. You supported your argument with selected quotes of committee members who voted against approval. Depending on one’s position, the quotes you provided in your FDRR could be dissected and interpreted as a philosophical bias against FDC products or a weighing of benefits to risks with the latter exceeding the former. In other words, selective highlighting of texts from the transcript can result in different conclusions on the rationale behind a vote. And finally, a philosophical concern does not exclude the possibility that a vote was based on a weighing of benefit to risk of Hydexor. The two, a philosophical position and a benefit-risk conclusion, are not mutually exclusive.

I have reviewed the 222-page transcript of the Advisory Committee meeting and it should be noted that on February 14, 2018, the AC panel was considering your application based on the indication proposed at that time. The Chief Medical Officer of Charleston Laboratories (Dr. Tim Smith) stated that the proposed indication for Hydexor was “for the short-term management of
acute pain severe enough to require an opioid analgesic while preventing and reducing OINV”, a much broader patient population than proposed in your last resubmission. Dr. Smith further stated that the proposed duration of use was “generally less than 14 days” with a proposed dosing schedule of one tablet every 4 to 6 hrs as needed for a maximum daily dosage of six tablets. The duration proposed at the Advisory Committee meeting was also longer than proposed in your recent resubmission. Consequently, the results of AC member votes should be considered in the context of the targeted population and potential duration of use proposed at this meeting.

From my review of the questions posed to the Applicant after its presentations and the panel member discussions prior to voting, it is apparent that members wanted to consider more details of the data than had been presented. For example, many members wanted to learn more about your risk mitigation plan (e.g., “buy-back” program and proposed packaging) and expressed skepticism on the effectiveness of these proposals because they have either not been evaluated, have been difficult to implement due to federal or state regulations (Dr. Higgins pg 140), or may encourage use of all dispensed drug despite an absence for need for any component of the product (Ms. Robotti pg 158-159). There were questions on the choice of dose selected for your FDC product (Dr. Michna pg 72-75). There were questions about the targeted population (e.g., type of procedure), the prescribers (e.g., type of surgeon), and the setting in which Hydexor would be prescribed (e.g., post-surgical or office-delivered) (Dr. Zacharoff pg 151-153).

The AC panel members did not specifically cite the FDA’s August 31, 2016, safety labeling change for opioids and benzodiazepines in their rationale for the vote but Dr. Bateman’s comment on pg 177-178 references literature that upholds the regulatory action taken by FDA to heighten the safety warning for the combined use of opioids and CNS depressants.

“In our briefing materials, the label for Phenergan was included, and there’s a warning about the risk of fatal respiratory depression associated with its use and recommends avoiding it in patients with compromised respiratory function that might be at heightened risk. There’s more and more literature coming out about the risk of overdose in patients that are co-prescribed opioids and other sedatives or other drugs that cause respiratory depression like benzodiazepines and gabapentanoids.”

Overall, I do not agree with your suggestion that the Advisory Committee votes represented a philosophical position that was not evidence-based or that it was a misapplication of the Combination Rule. I believe that the members applied a benefit-risk assessment after reviewing the evidence provided in the background materials and in response to questions raised during the meeting. The majority of members concluded that this fixed-dose combination product, where lack of flexibility in dosing may potentially lead to unnecessary exposure to a drug and its risks without evidence of an effective risk-mitigation strategy, should not be approved.

Division of Anesthesia, Analgesia, and Addiction Products Reviews of NDA 209257

At our April 29, 2019, meeting, you complained that throughout development and interactions during the original review cycle, you were not made aware of any concerns in your program that forewarned of a complete response action. I believe that certain statements in the initial FDA
reviews and the following closing remarks from the Division at the February 14, 2018, AC meeting support your position.

“In conclusion, Hydexor appears to be safe and effective in the proposed patient population with some increase in CNS effects compared to hydrocodone-acetaminophen alone. Hydexor is not intended to be an abuse-deterrent formulation, and that’s the same as all of the other marketed and approved hydrocodone-acetaminophen combination products that are on the market.”

Given this closing remark, I can understand why you did not anticipate the complete response action. I believe the Division was surprised by the advisory committee vote but, as should be expected of FDA staff, they considered the points raised by the AC members and performed additional analyses of data provided with the original submission as a matter of due diligence in response to the negative AC vote. That additional analysis included identifying the proportion of patients in the Norco-treatment group in CLCT-002 and 003 who developed OINV over the course of the studies. The following tables summarize their findings.

<p>| CLCT-002 – Summary of Study Drug Usage and OINV by Study Day in Norco-treated Patients |</p>
<table>
<thead>
<tr>
<th>Study Day</th>
<th>Study Drug Usage, expressed as mean number of tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
<th>Proportion of Patients with Vomiting (%)</th>
<th>Proportion of Patients with Anti-Emetic Use (%)</th>
<th>Proportion of Patients with OINV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.59</td>
<td>100</td>
<td>19.5</td>
<td>17.6</td>
<td>30.2</td>
</tr>
<tr>
<td>2</td>
<td>2.65</td>
<td>91.7</td>
<td>14.1</td>
<td>7.8</td>
<td>17.6</td>
</tr>
<tr>
<td>3</td>
<td>2.18</td>
<td>79.0</td>
<td>3.9</td>
<td>3.9</td>
<td>7.8</td>
</tr>
<tr>
<td>4</td>
<td>1.73</td>
<td>69.3</td>
<td>2.4</td>
<td>4.4</td>
<td>6.8</td>
</tr>
<tr>
<td>5</td>
<td>1.51</td>
<td>58.5</td>
<td>1.5</td>
<td>1.0</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer

<p>| CLCT-002 – Summary of Study Drug Usage and OINV by Study Day in Hydexor-treated Patients |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1</td>
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<td>2.91</td>
<td>92.4</td>
<td>5.2</td>
<td>1.9</td>
<td>5.7</td>
</tr>
<tr>
<td>3</td>
<td>2.6</td>
<td>89.1</td>
<td>1.9</td>
<td>1.9</td>
<td>3.8</td>
</tr>
<tr>
<td>4</td>
<td>2.2</td>
<td>76.3</td>
<td>0.5</td>
<td>0.9</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>1.89</td>
<td>66.4</td>
<td>0.5</td>
<td>0.9</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Source: FDA Statistical Reviewer
Because this analysis was NOT conducted in the initial review of your application, the first CRL did not communicate the concern that your program failed to identify a population in which a significant proportion of patients would require an anti-emetic with an opioid-analgesic each time pain control was necessary.

The above analyses show that by the end of the study treatment period, very few patients experienced OINV despite the trials’ enrichment strategy. However, the decline in patients reporting OINV by Day 5 may also represent a decline in pain, resulting in less dosing of the opioid, and/or development of tolerance to the side effects of an opioid. Although Day 5 was not the prespecified timepoint for efficacy analysis and had confounders to interpretation, these additional analyses do raise concern over the proposed duration of treatment (originally out to 14 days). If we focus only on Day 1 in CLCT-002 and Days 1-2 for CLCT-003, the timepoints for efficacy analysis in these two trials, respectively, the percentage of patients developing OINV in the Norco group was higher, approximately 30%. To reiterate that efficacy was established, I would also point out that a smaller percentage of Hydexor-treated patients developed OINV during these time points (~11% and 8% at the corresponding timepoints for efficacy analyses in CLCT-002 and 003, respectively).

Admittedly, 30% of patients in the Norco group developing OINV in Days 1 to 2 post-procedure is not a majority of the population. Whether it represented a significant percentage is up for debate as the Division did not specify during development or after the 2nd CRL what threshold would be acceptable.
In your second re-submission you performed additional analyses of CLCT-003 to show that more patients in the Norco treatment group developed OINV than summarized in FDA’s analyses. The difference was the result of including patients who reported a Nausea Intensity Score (NIS) > 0 as additional evidence of OINV. The following table summarizes the results from your re-analysis.

Table 6: Efficacy Outcomes of CL-108-treated Patients and Norco®-treated Patients (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>0-6 hours</th>
<th>0-12 hours</th>
<th>0-18 hours</th>
<th>0-24 hours</th>
<th>0-30 hours</th>
<th>0-36 hours</th>
<th>0-42 hours</th>
<th>0-48 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea Intensity Score &gt;0 (%)</td>
<td>40.9</td>
<td>58.8</td>
<td>46.4</td>
<td>64.8</td>
<td>50.8</td>
<td>69.6</td>
<td>52.4</td>
<td>71.6</td>
</tr>
<tr>
<td>Severity of Nausea (mean)</td>
<td>3.0</td>
<td>6.4</td>
<td>1.1</td>
<td>6.1</td>
<td>8.9</td>
<td>26.7</td>
<td>10.7</td>
<td>33.7</td>
</tr>
<tr>
<td>Vomiting (%)</td>
<td>1.2</td>
<td>5.2</td>
<td>3.6</td>
<td>9.6</td>
<td>4.0</td>
<td>13.2</td>
<td>4.4</td>
<td>14.8</td>
</tr>
<tr>
<td>Retching (%)</td>
<td>4.8</td>
<td>7.2</td>
<td>7.0</td>
<td>16.0</td>
<td>9.3</td>
<td>17.2</td>
<td>9.1</td>
<td>19.2</td>
</tr>
</tbody>
</table>

* Statistically significant difference of p < 0.05 between CL-108 and Norco® treatment groups.
* Statistically significant difference of p < 0.01 between CL-108 and Norco® treatment groups.
* Statistically significant difference of p < 0.001 between CL-108 and Norco® treatment groups.
* Defined as NIS > 0

NIS = nausea intensity scale; SPID = summed pain intensity differences.

This analysis shows that 80.8% of Norco-treated patients experienced NIS >0 at some time during hours 0-48 and had a consistently higher mean severity score.

Efficacy based on the NIS was not accepted by the Division based on consult recommendations from FDA’s Clinical Outcomes and Assessment (COA) team. In their consult they concluded that while the NIS appears fit-for-purpose to document occurrence of nausea, they did not agree with the proposed cut-off values for rating severity of nausea (i.e., mild 1-3, moderate 4-7, severe 8-10) as there is no literature to support such cut-off values. The Division of Gastrointestinal and Inborn Errors Products (DGIEP) also recommended against using the NIS results for efficacy assessment and recommended using the endpoints relied upon for approval of post-operative nausea and vomiting (PONV), which is comprised of vomiting and rescue with an anti-emetic. It should be noted that your proposed indication has changed since the original NDA submission and is currently for the management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid induced nausea and vomiting (OINV) in patients expected to be prone to nausea and vomiting. As you are now proposing to limit Hydrexor’s use to the post-operative setting, this is more aligned with a development program for an anti-emetic for PONV and standards for establishing efficacy should be the same. That said, I acknowledge that efficacy was established with both the 2-component and 3-component endpoints, hence I believe there is validity in accepting the analyses based on the NIS as supportive evidence that a significant proportion of patients experienced symptoms that could merit treatment with an anti-emetic.
I also note that 22.4% of Norco-treated patients experienced vomiting from 0-48 hours as opposed to 6% in the Hydexor group. Vomiting is clearly an unpleasant experience and may have negative consequences in the post-operative setting. Reducing the incidence of vomiting within the first 48 hrs post-operatively does not seem to be a trivial finding and should be considered relevant in the benefit-risk assessment of Hydexor.

You also analyzed analgesic effects in the subgroup of Norco-treated patients who received a rescue anti-emetic compared to the Hydexor-treated group who did not receive a rescue anti-emetic and concluded that treating OINV after it has occurred results in less analgesic control.

The Division countered that the improved pain control in the Hydexor group may reflect that pre-emptive treatment with an anti-emetic allows for patients to better tolerate oral analgesic, but I believe this supports the Applicant’s case for pre-emptive management of OINV. However, this subgroup analysis does not support a conclusion of overall better analgesia with Hydexor versus Norco given the primary efficacy finding of similar analgesia in the overall population and the Division’s analysis of SPID comparing subgroups in both treatment arms who did NOT receive a rescue anti-emetic. The relevant point from the above analyses is still whether patients can be identified before treatment who are likely to need an anti-emetic and thus to avoid risk of giving the anti-emetic patients who do not require it.

I requested additional clarifying information in the subgroup of patients in CLCT-002 who were enrolled based on testing positive for OINV with a hydrocodone challenge. The rationale behind this request was to determine if identifying patients at risk for future OINV could be improved after the first dose of an opioid resulted in OINV. These analyses did not show a markedly greater proportion of patients in the Norco-treatment group who tested positive on the hydrocodone challenge developing OINV relative to the overall study population, which also enrolled patients based on the nausea prone questionnaire supplemented by some patients enrolled based on investigator discretion.

Risks discussed at the AC meeting included CNS depression and potential for abuse, misuse and addiction. Although there were some residual concerns regarding risk for abuse, this was based
on limited data and overall, it did not appear that Hydexor posed any greater of a risk for abuse, misuse and addiction relative to hydrocodone/acetaminophen FDC products available. As both hydrocodone and promethazine can cause CNS depression, the Division carefully reviewed the safety data for adverse events related to CNS depression. There were no serious adverse events related to CNS depression. The proactively collected symptoms on the Opioid Symptoms Scales (OSS) questionnaire identified a higher rate of severe drowsiness with Hydexor use compared to Norco but none of these cases were serious AEs. The difference between Hydexor and Norco for incidence of severe drowsiness was more pronounced in CLCT-003 on Days 1 through 2 when patients were given regularly fixed-intervals of study medication (42% vs 21%). In Study CLCT-002, where patients were administered study drug on an as-needed basis, the difference was less pronounced (46% vs 37%). The clinical review also identified hypotension as a signal of greater risk with Hydexor over Norco, but there were no cases of hypotension that were deemed serious.

Based on my reading of the FDA reviews and the AC background materials, the above safety findings were not unexpected and consideration was given by the Division to labeling the overall benefits vs risks for Hydexor. The negative AC vote clearly shifted the Division’s position. I do not consider that change in position evidence of the Division reneging on agreements laid out at the EOP2 meeting, but rather a further re-weighing of risks and benefits based on the external expert advice provided by the Advisory Committee. As stated earlier, the agreements from the EOP2 meeting outlined what data would be acceptable to support a marketing application submission and not result in a refuse-to-file. Although these agreements would also provide some reassurance of a favorable regulatory decision, that final decision still required a review of the results from the submitted data and consideration of any new developments since the EOP2 meeting which would include FDA’s safety labeling change requirement for opioids and benzodiazepines (CNS depressants) and the AC meeting recommendations.

Following the AC meeting, the Applicant realized that the original proposed indication/labeling was not acceptable and discussions at the EOR meeting included a proposal for more restricted use in terms of patient population and recommended duration. The following table compares the Highlights of Prescribing section from the two proposed labels side-by-side.

<table>
<thead>
<tr>
<th>March 31, 2016 submission</th>
<th>August 9, 2018 resubmission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boxed Warning</strong></td>
<td></td>
</tr>
<tr>
<td>WARNING: HEPATOTOXICITY, PEDIATRIC USE</td>
<td>WARNING: ADDICTION, ABUSE, AND MISUSE, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL INGESTION, NEONATAL OPIOID WITHDRAWAL SYNDROME, HEPATOTOXICITY, CYTOCHROME P450 3A4 INTERACTION, CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS, PEDIATRIC USE</td>
</tr>
<tr>
<td>See full prescribing information for complete boxed warning</td>
<td>See full prescribing information for complete boxed warning</td>
</tr>
<tr>
<td>• HYDEXOR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product (5.1)</td>
<td>• HYDEXOR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. (Error! Reference source not found.)</td>
</tr>
<tr>
<td>• HYDEXOR is contraindicated in pediatric patients less than 2 years due to potentially fatal respiratory depression from its promethazine component. HYDEXOR is not indicated in any pediatric patients since safety and effectiveness have not been established (5.2)</td>
<td>• Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation. (Error! Reference source not found.)</td>
</tr>
<tr>
<td></td>
<td>• Accidental ingestion of HYDEXOR, especially in children, can result in a fatal overdose. (Error! Reference source not found.)</td>
</tr>
<tr>
<td></td>
<td>• Prolonged use of HYDEXOR during pregnancy can result in</td>
</tr>
</tbody>
</table>
- Neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated. (Error! Reference source not found.)
- HYDEXOR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. (Error! Reference source not found.)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone. (Error! Reference source not found., Error! Reference source not found., Error! Reference source not found.)
- Concomitant use with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. (Error! Reference source not found., Error! Reference source not found.)
- HYDEXOR is contraindicated in patients 65 years or older due to potentially increased risk of drowsiness, somnolence and effects on blood pressure. (5.7)
- HYDEXOR is contraindicated in pediatric patients less than 2 years due to potentially fatal respiratory depression from its promethazine component. HYDEXOR is not indicated in any pediatric patients since safety and effectiveness have not been established. (Error! Reference source not found.)

### Indications and Usage

HYDEXOR is indicated for the relief of moderate to severe pain while preventing or reducing the associated opioid-induced nausea and vomiting (1)

HYDEXOR is indicated for the short-term (generally 3 days and no more than 5 days) management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid induced nausea and vomiting (OINV) in patients expected to be prone to nausea and vomiting. HYDEXOR is indicated when alternative treatments for pain are inadequate. (Error! Reference source not found.)

### Limitations of Use:

Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses (Error! Reference source not found.), reserve HYDEXOR for use in patients for whom alternative pain treatment options [e.g., 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

### Dosage and Administration

The usual adult dosage is one tablet every 4 to 6 hours as needed for pain. Dosage should be adjusted according to the severity of the pain and the response of the patient. The total daily dosage should not exceed 6 tablets. Tolerance to hydrocodone can develop with continued use (2)

- Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse. (Error! Reference source not found.)
- Initiate treatment with one tablet every 4 to 6 hours as needed for pain. (Error! Reference source not found.)
- Do not stop HYDEXOR abruptly in a physically dependent patient. (Error! Reference source not found.)

### Contraindications

- Pediatric patients less than 2 years due to the potentially fatal respiratory depression from its promethazine component. HYDEXOR is not indicated in any pediatric patients since safety and effectiveness have not been established (4)
- Known hypersensitivity to any component of HYDEXOR and in patients known to have had an idiosyncratic reaction to promethazine or other phenothiazines. Patients known to be sensitive to other opioids may exhibit cross-sensitivity to hydrocodone (4)
- Pediatric patients less than 2 years due to the potentially fatal respiratory depression from its promethazine component. HYDEXOR is not indicated in any pediatric patients since safety and effectiveness have not been established (Error! Reference source not found.)
- Patients 65 years or older due to potentially increased risk of drowsiness, somnolence and effects on blood pressure (Error! Reference source not found.)
- Significant respiratory depression (Error! Reference source not found.)
<table>
<thead>
<tr>
<th>Warnings and Precautions</th>
<th>Acute or severe bronchial asthma in an unmonitored setting in absence of resuscitative equipment (Error! Reference source not found.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Known or suspected gastrointestinal obstruction, including paralytic ileus (Error! Reference source not found.)</td>
</tr>
<tr>
<td></td>
<td>Known hypersensitivity to any component of HYDEXOR and in patients known to have had an idiosyncratic reaction to promethazine or other phenothiazines. Patients known to be sensitive to other opioids may exhibit cross-sensitivity to hydrocodone (Error! Reference source not found.)</td>
</tr>
</tbody>
</table>

Subsequent to our April 29, 2019, meeting I asked you to comment on whether you would consider modifying the indicated population and duration of therapy to inpatient use only and in postoperative procedures in which OINV may be a barrier to wound healing. In your May 19, 2019, response you stated that you were further willing to modify the indication to the following:

**HYDEXOR** is indicated for the short-term (generally 3 days) management of acute post-operative pain severe enough to require an opioid analgesic and the prevention of opioid-induced nausea and vomiting (OINV) in patients who are at risk for or have a history of nausea and vomiting. HYDEXOR is for use in patients undergoing procedures in which OINV may be a barrier to wound healing. HYDEXOR is for use in medically supervised healthcare settings, such as hospitals, surgical centers, and skilled nursing facilities. HYDEXOR is indicated when alternative treatments for pain are inadequate.

The underlying concern expressed by the Division and the AC members that pre-emptive dosing of promethazine with an opioid analgesic may still expose some patients who would not otherwise develop nausea and/or vomiting with the opioid analgesic to the risks of promethazine remains. However, by limiting dosing duration and the intended population in your above
proposal, I believe this improves the benefit-risk calculus and can serve as a starting point for further labeling negotiations.

Given the concerns of CNS depression with the combined use of an opioid analgesic and promethazine, the duration of use in your label should not be vague (e.g., *generally 3 days*) but rather should be a recommendation to not exceed three days of treatment with Hydexor.

**Path Forward**

The specific action you requested was that I rescind the February 9, 2019, CRL and approve Hydexor. As outlined in my response, I believe the Division’s benefit-risk assessment of Hydexor evolved based on new developments arising from consideration of the AC meeting and recent FDA class safety labeling changes for opioids. Consequently, I deny your request. However, I believe the Division should reconsider your recent proposed labeling revision as a resubmission to the 3rd CRL. I am instructing the Division to consider it 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. I encourage you to work closely with the Division. If alignment cannot be reached, another complete response might ensue.

Questions regarding next steps as described in this letter should be directed to Mavis Darkwah, PharmD, Senior Regulatory Project Manager, Division of Anesthetics, Analgesia and Addiction Products, Office of Drug Evaluation II at (240) 402-3158.

This constitutes the final decision at the Office of Drug Evaluation II level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, MD, Director, OND, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center’s Formal Dispute Resolution Project Manager, Melissa Sage. Any questions concerning your appeal should be addressed to Melissa Sage at (301) 796-6449.

Sincerely,

[See appended electronic signature page]

Mary Thanh Hai, MD
Acting Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY T THANH HAI
06/21/2019 11:27:44 AM
HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use HYDEXOR safely and effectively. See full prescribing information for HYDEXOR.

HYDEXOR™ (hydrocodone bitartrate, acetaminophen, promethazine HCl) tablets, for oral use, CII

Initial U.S. Approval: 20XX

WARNING: RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION AND EXCESSIVE SEDATION; HYDEXOR REMS PROGRAM, ADDICTION, ABUSE, AND MISUSE, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL INGESTION, HEPATOTOXICITY, CYTOCHROME P450 3A4 INTERACTION, CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS, PEDIATRIC USE

See full prescribing information for complete boxed warning.

- Due to the risk of serious harm including life-threatening respiratory depression and falls or other accidents resulting from excessive sedation, HYDEXOR is limited to use in adult patients in certified, medically-supervised settings. (5.1)
- Because of the potential for serious harm due to the additive effects of two central nervous system depressants contained in combination, HYDEXOR is only available through a restricted program called the HYDEXOR REMS. (5.1, 5.2)
  - HYDEXOR is limited to use in certified, medically-supervised healthcare settings such as hospitals and surgical centers.
  - HYDEXOR should be used only when non-sedating alternatives are either not tolerated or ineffective.
- HYDEXOR exposes users to risks of addiction, abuse, and misuse, which can lead to overdose and death. (5.3)
- Serious, life-threatening, or fatal respiratory depression may occur. Monitor closely, especially upon initiation. (5.4)
- HYDEXOR is contraindicated in all pediatric patients due to potentially fatal respiratory depression. (4, 5.4)
- Accidental ingestion of HYDEXOR, especially in children, can result in a fatal overdose. (5.4)
- Concomitant use with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) can result in a fatal overdose of hydrocodone. (5.5, 7.2, 7.3)
- HYDEXOR contains acetaminophen. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen-containing product. (5.6)
- Concomitant use with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death. (5.7, 7.1)

INDICATIONS AND USAGE

HYDEXOR contains hydrocodone bitartrate (an opioid agonist), acetaminophen, and promethazine hydrochloride (a phenothiazine). 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 with vomiting with hydrocodone-containing products.(1)

Limitations of Use (1)

- 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,
WARNING: ADDICTION, ABUSE, AND MISUSE, LIFE-THreatENING RESPIRATORY DEPRESSION, ACCIDENTAL INGESTION, NEONATAL OPIOID WITHDRAWAL SYNDROME, HEPATOTOXICITY, CYTOCHROME P450 3A4 INTERACTION, RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS, PEDIATRIC USE
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Important Dosage and Administration Instructions
2.2 Initial Dosage
2.3 Titration and Maintenance of Therapy
2.4 Discontinuation of HYDEXOR
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Addiction, Abuse, and Misuse
5.2 Life-Threatening Respiratory Depression
5.3 Neonatal Opioid Withdrawal Syndrome
5.4 Hepatotoxicity
5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers
5.6 Risk of Medication Errors
5.7 CNS Depression
5.8 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients
5.9 Risks from Concomitant Use with Benzodiazepines or Other Central Nervous System Depressants
5.10 Concomitant Use with other Opioids
5.11 Severe Hypotension
5.12 Increased Risk of Seizures in Patients with Seizure Disorders
5.13 Bone-Marrow Depression
5.14 Neuroleptic Malignant Syndrome
5.15 Adrenal Insufficiency
5.16 Cholestatic Jaundice
5.17 Serious Skin Reactions
5.18 Hypersensitivity/Anaphylaxis
5.19 Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness
5.20 Risks of Use in Patients with Gastrointestinal Conditions
5.21 Withdrawal
5.22 Patients with Additional Risk Factors
5.23 Pediatric Use
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
7.1 Benzodiazepines and other CNS Depressants
7.2 Inhibitors of CYP3A4 and CYP2D6
7.3 CYP3A4 Inducers
7.4 Respiratory Depressants
7.5 Serotonergic Drugs
7.6 Monoamine Oxidase Inhibitors (MAOI)
7.7 Anticholinergics
7.8 Mixed Agonist/Antagonist Opioid Analgesics
7.9 Muscle Relaxants
7.10 Warfarin
7.11 Epinephrine
7.12 Laboratory Test Interference
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Hepatic Impairment
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WARNING: RISK OF LIFE-THREATENING RESPIRATORY DEPRESSION AND EXCESSIVE SEDATION; HYDEXOR REMS PROGRAM; ADDICTION, ABUSE, AND MISUSE, LIFE-THREATENING RESPIRATORY DEPRESSION, ACCIDENTAL INGESTION, NEONATAL OPIOID WITHDRAWAL SYNDROME, HEPATOTOXICITY, CYTOCHROME P450 3A4 INTERACTION, RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS, PEDIATRIC USE

Risk of Serious Harm Including Life-Threatening Respiratory Depression and Excessive Sedation Due to Additive Effects of HYDEXOR Components

Due to the risk of serious harm including life-threatening respiratory depression and falls or other accidents resulting from excessive sedation, HYDEXOR is limited to use in adult patients in certified, medically-supervised settings and should be used only when non-sedating alternatives are either not tolerated or ineffective. Discontinue use of HYDEXOR prior to discharge or transfer from the certified, medically-supervised setting [see Warnings and Precautions (5.1)].

Addiction, Abuse and Misuse

HYDEXOR exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient’s risk prior to prescribing HYDEXOR, and monitor all patients regularly for the development of these behaviors or conditions [see Warnings and Precautions (5.3)].

HYDEXOR Risk Evaluation and Mitigation Strategy (REMS) Program

Because of the potential for serious harm due to the additive effects of two central nervous system depressants in combination, HYDEXOR is only available through a restricted program called the HYDEXOR REMS [see Warnings and Precautions (5.1, 5.2)].

- HYDEXOR is limited to use in certified, medically-supervised healthcare settings such as hospitals and surgical centers.
- HYDEXOR should only be used when non-sedating alternatives are either not tolerated or ineffective.

Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression may occur with use of HYDEXOR. Monitor for respiratory depression, especially during initiation of HYDEXOR treatment or following an increase in dosing frequency [see Warnings and Precautions (5.4)].
HYDEXOR is contraindicated in pediatric patients of all ages due to the risk for fatal respiratory depression with promethazine, particularly in combination with an opioid [see Contraindications (4), Warnings and Precautions (5.4)].

Accidental Ingestion

Accidental ingestion of even one dose of HYDEXOR, especially by children, can result in a fatal overdose [see Warnings and Precautions (5.4)].

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see Warnings and Precautions (5.7), Drug Interactions (7.1)].

- Reserve concomitant prescribing of HYDEXOR and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation

Cytochrome P450 3A4 Interaction

The concomitant use of HYDEXOR with all cytochrome P450 3A4 inhibitors may result in an increase in hydrocodone plasma concentration, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression. In addition, discontinuation of a concomitantly used cytochrome P450 3A4 inducer may result in an increase in hydrocodone plasma concentration. Monitor patients taking HYDEXOR and any CYP3A4 inhibitor or upon discontinuation of a CYP3A4 inducer for signs and symptoms of respiratory depression and sedation [see Warnings and Precautions (5.5), Drug Interactions (7.2, 7.3)].

Hepatotoxicity

HYDEXOR contains hydrocodone bitartrate, acetaminophen and promethazine hydrochloride. Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4000 milligrams per day, and often involve more than one acetaminophen-containing product [see Warnings and Precautions (5.6)].

1 INDICATIONS AND USAGE

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 of 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. [see Warnings and Precautions (5.1)].

- Because of the risk for fatal respiratory depression, do not use in pediatric patients [see Contraindications (4), Warnings and Precautions (5.4)].

- 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

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Instructions

Due to excessive sedation that can result from the combination of hydrocodone and promethazine, patients may be at risks for increased falls [see Warnings and Precautions (5.1)]

HYDEXOR is only to be administered by a healthcare provider in a medically supervised healthcare setting, such as hospitals and surgical centers [see Warnings and Precautions (5.2)]. Hydexor should not be used in a skilled nursing facility where patients are likely to be older and more at risk for respiratory depression and falls due to excessive sedation.

HYDEXOR treatment must be discontinued prior to the patient leaving the medically supervised setting [see Warnings and Precautions (5.2)].

HYDEXOR is contraindicated in pediatric patients of all ages [see Contraindications (4), Warnings and Precautions (5.4)].

Use the lowest effective dosage for the shortest duration consistent with individual treatment goals not exceeding a 3 day time period. [see Warnings and Precautions (5)].

Initiate the dosing regimen for each patient individually; taking into account the patient's severity of pain, patient response, prior analgesic treatment experience, and risk factors for addiction, abuse, and misuse [see Warnings and Precautions (5.3)].

Monitor patients closely for respiratory depression, especially during initiation of therapy and following an increase in dosing frequency with HYDEXOR, and adjust the dosing frequency as appropriate [see Warnings and Precautions (5.1, 5.4)].

2.2 Initial Dosage

Initiate treatment with HYDEXOR in a dosing range of one tablet every four to six hours as needed for pain. The total daily dosage should not exceed 5 tablets.
2.3 Titration and Maintenance of Therapy
Individually adjust the HYDEXOR dosing frequency to provide adequate analgesia and adequate management of nausea and vomiting and to minimize adverse reactions. Do not dose HYDEXOR more frequently than every four hours.

2.4 Safe Discontinuation of HYDEXOR
Discontinue HYDEXOR as soon as the need for concomitant use of an analgesic and an antiemetic are no longer necessary, or after no longer than 3 days of use, whichever is sooner.

Discontinue use of HYDEXOR prior to discharge or transfer from the certified medically supervised healthcare setting. HYDEXOR is not for home or pediatric use [see Warnings and Precautions (5.1, 5.2, 5.4)].

When discontinuing HYDEXOR in a physically-dependent patient, switch the patient to a hydrocodone and acetaminophen containing product without promethazine and gradually taper the dosing frequency. Do not abruptly discontinue HYDEXOR in physically-dependent patients [see Warnings and Precautions (5.3), Drug Abuse and Dependence (9.3)].

3 DOSAGE FORMS AND STRENGTHS
HYDEXOR is a fixed-dose, immediate-release, white to off white, oval shaped, bi-layered tablet for oral administration containing 7.5 mg of hydrocodone bitartrate, 325 mg of acetaminophen and 12.5 mg of promethazine hydrochloride. Each tablet is debossed with BC 147 on both sides.

4 CONTRAINDICATIONS
HYDEXOR is contraindicated:
- In pediatric patients of all ages due to the potential for fatal respiratory depression from promethazine, particularly in combination with an opioid. [see Warnings and Precautions (5.43)].
- In patients with significant respiratory depression [see Warnings and Precautions (5.2)].
- In patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment [see Warnings and Precautions (5.8)].
- In patients with known or suspected gastrointestinal obstruction, including paralytic ileus [see Warnings and Precautions (5.20)].
- In patients with a known hypersensitivity to hydrocodone, acetaminophen, promethazine or any other component of HYDEXOR and in patients known to have had an idiosyncratic reaction to promethazine or to other phenothiazines. Patients known to be sensitive to other opioids may exhibit cross-sensitivity to hydrocodone [see Warnings and Precautions (5.18)].
5 WARNINGS AND PRECAUTIONS

5.1 Risk of Serious Harm including Life-Threatening Respiratory Depression and Excessive Sedation Due to Additive Effects of HYDEXOR Components

Because of the risk of serious harm, including life-threatening respiratory depression and falls or other accidents resulting from excessive sedation, [see 5.4, 5.7, 5.9, 5.10, 5.19, regarding other CNS and respiratory depression Warnings and Precautions] due to the additive effects of the two central nervous system depressants contained in HYDEXOR, HYDEXOR is limited to use in adult patients 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.

Use of HYDEXOR outside of a medically supervised healthcare setting can increase the risk of serious harm resulting from additive effects of respiratory depression and excessive sedation.

Discontinue use of HYDEXOR prior to discharge or transfer from the certified medically supervised healthcare setting. HYDEXOR is not for home or pediatric use.

5.2 HYDEXOR Risk Evaluation and Mitigation Strategy (REMS)

Because of the combined sedative effect resulting in respiratory depression and excessive sedation, HYDEXOR is only available through a restricted program called the HYDEXOR REMS. The goal of the HYDEXOR REMS is to 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.
- Hydexor should not be used in a skilled nursing facility where patients are likely to be older and more at risk for respiratory depression and falls due to excessive sedation.

Notable requirements of the HYDEXOR REMS include the following:

- Healthcare settings that dispense HYDEXOR must:
  - train all relevant staff that HYDEXOR must not be dispensed for use outside of the certified, medically-supervised healthcare setting, and
  - establish processes and procedures to verify that HYDEXOR is not dispensed for use outside of the certified, medically-supervised healthcare setting, and
  - establish processes and procedures to discontinue HYDEXOR after 3 days.
- Wholesalers and distributors must be registered in the program and must only distribute to certified healthcare settings.

Additional information is available at (add REMS website).
5.3 Addiction, Abuse, and Misuse

HYDEXOR contains hydrocodone, a Schedule II controlled substance. Because it contains an opioid, HYDEXOR exposes users to the risks of addiction, abuse, and misuse [see Warnings and Precautions (5.9) and Drug Abuse and Dependence (9)].

Although the risk of addiction in any individual is unknown, it can occur in patients appropriately prescribed HYDEXOR during hospitalization. Addiction can occur at recommended dosages and if the drug is misused or abused.

Assess each patient’s risk for opioid addiction, abuse, or misuse prior to prescribing HYDEXOR for use during hospitalization, and monitor all patients receiving HYDEXOR for the development of these behaviors or conditions. Risks are increased in patients with a personal or family history of substance abuse (including drug or alcohol abuse or addiction) or mental illness (e.g., major depression). The potential for these risks should not, however, prevent the proper management of pain in any given patient. Patients at increased risk may be prescribed opioids such as HYDEXOR, but use in such patients necessitates intensive counseling about the risks and proper use of HYDEXOR along with intensive monitoring for signs of addiction, abuse, and misuse.

Opioids are sought by drug abusers and people with addiction disorders and are subject to criminal diversion. Opioids in combination with other central nervous system depressants may be more attractive to some individuals who abuse opioid analgesics. Consider these risks when prescribing HYDEXOR for use during hospitalization. Strategies to reduce these risks include use of HYDEXOR only in hospitals and surgical centers and by not prescribing HYDEXOR for outpatient use [see Patient Counseling Information (17)]. Contact local state professional licensing board or state controlled substances authority for information on how to prevent and detect abuse or diversion of this product.

5.4 Life-Threatening Respiratory Depression

Serious, life-threatening, or fatal respiratory depression has been reported with the use of opioids, even when used as recommended. There is increased risk with HYDEXOR because it contains both an opioid, hydrocodone, and a phenothiazine, promethazine, and the effects can be additive. Respiratory depression, if not immediately recognized and treated, may lead to respiratory arrest and death. Management of respiratory depression may include close observation, supportive measures, and use of opioid antagonists, depending on the patient’s clinical status [see Overdosage (10)]. Carbon dioxide (CO₂) retention from opioid-induced respiratory depression can exacerbate the sedating effects of opioids.

While serious, life-threatening, or fatal respiratory depression can occur at any time during the use of HYDEXOR, the risk is greatest during the initiation of therapy or following an increase in dosing frequency. To reduce the risk of respiratory depression, proper dosing frequency adjustment of HYDEXOR is essential [see Dosage and Administration (2.1)]. Monitor patients closely for respiratory depression while on treatment with HYDEXOR.

Risk of Fatal Respiratory Depression in Pediatric Patients

HYDEXOR is contraindicated for use in pediatric patients of all ages because of the potential for fatal respiratory depression [see Contraindications (4)]. Postmarketing cases of respiratory
depression, including fatalities, have been reported with use of promethazine in pediatric patients less than 2 years of age. Respiratory depression and apnea, sometimes associated with death, are strongly associated with promethazine products and are not directly related to individualized weight-based dosing. A wide range of weight-based doses of promethazine have resulted in respiratory depression in these patients. Concomitant administration of promethazine products with other respiratory depressants is associated with respiratory depression, and death, in pediatric patients. Because HYDEXOR contains two respiratory depressants, i.e., an opioid, and a phenothiazine, HYDEXOR is contraindicated for use in pediatric patients of all ages [see Contraindications (4)].

Opioids can cause sleep-related breathing disorders including central sleep apnea (CSA) and sleep-related hypoxemia. Opioid use increases the risk of CSA in a dose-dependent fashion. In patients who present with CSA, consider decreasing the HYDEXOR dosing frequency using best practices for opioid taper and carefully monitor the patient for signs of respiratory depression [see Dosage and Administration (2.4)].

Accidental ingestion of even one dose of HYDEXOR, especially by children, can result in respiratory depression and death.

5.5 Risks of Concomitant Use or Discontinuation of Cytochrome P450 3A4 Inhibitors and Inducers

Concomitant use of HYDEXOR with a CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), may increase plasma concentration of hydrocodone and prolong opioid adverse reactions, which may cause potentially fatal respiratory depression [see Warnings and Precautions (5.2)], particularly when an inhibitor is added after a stable dose of HYDEXOR is achieved. Similarly, discontinuation of a CYP3A4 inducer, such as rifampin, carbamazepine, and phenytoin, in HYDEXOR-treated patients may increase hydrocodone plasma concentration and prolong opioid adverse reactions. When using HYDEXOR with CYP3A4 inhibitors or discontinuing CYP3A4 inducers in HYDEXOR treated patients, monitor patients closely at frequent intervals and consider reduction in dosing frequency of HYDEXOR until stable drug effects are achieved [see Dosage and Administration (2.1), Drug Interactions (7.2, 7.3)].

Concomitant use of HYDEXOR with CYP3A4 inducers or discontinuation of a CYP3A4 inhibitor could decrease hydrocodone plasma concentration, decrease opioid efficacy or, possibly, lead to a withdrawal syndrome in a patient who had developed physical dependence to hydrocodone. When using HYDEXOR with CYP3A4 inducers or discontinuing CYP3A4 inhibitors, monitor patients closely at frequent intervals and consider increasing the opioid dosing frequency if needed to maintain adequate analgesia or if symptoms of opioid withdrawal occur [see Dosage and Administration (2.4), Drug Interactions (7.2, 7.3)].

5.6 Hepatotoxicity

Acetaminophen has been associated with cases of acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury are associated with the use of acetaminophen at doses that exceed 4,000 milligrams per day, and often involve more than one acetaminophen containing product. The excessive intake of acetaminophen may be intentional to
cause self-harm or unintentional as patients attempt to obtain more pain relief or unknowingly take other acetaminophen-containing products.

The risk of acute liver failure is higher in individuals with underlying liver disease and in individuals who ingest alcohol while taking acetaminophen.

Healthcare providers should not prescribe more than one product that contains acetaminophen, due to potential for acetaminophen hepatotoxicity. Daily doses of more than 4,000 milligrams of acetaminophen per day should be avoided.

Because acetaminophen is extensively metabolized by the liver, the use of HYDEXOR in patients with hepatic impairment is not recommended.

5.7 Risks from Concomitant Use with Benzodiazepines or Other Central Nervous System Depressants

Profound sedation, respiratory depression, coma, and death may result from the concomitant use of HYDEXOR with benzodiazepines or other central nervous system (CNS) depressants (e.g., non-benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because HYDEXOR contains both an opioid, hydrocodone, and phenothiazine, promethazine this risk is increased. Therefore, reserve HYDEXOR for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioid analgesics alone. Because of similar pharmacological properties and the presence of promethazine in HYDEXOR, it is reasonable to expect greater risk with the concomitant use of additional CNS depressant drugs than with other opioid analgesics [see Drug Interactions (7.1)].

If the decision is made to prescribe a benzodiazepine or other CNS depressant concomitantly with HYDEXOR, prescribe the lowest effective dosages and minimum durations of concomitant use. In patients already receiving HYDEXOR, prescribe a lower initial dose of the benzodiazepine or other CNS depressant than indicated in the absence of an opioid and promethazine, and titrate based on clinical response. If HYDEXOR is initiated in a patient already taking a benzodiazepine or other CNS depressant, follow patients closely for signs and symptoms of respiratory depression and sedation.

Advise both patients and caregivers about the risks of respiratory depression and sedation when HYDEXOR is used with benzodiazepines or other CNS depressants (including alcohol and illicit drugs). Advise patients not to use HYDEXOR longer than 3 days or after they leave the hospital. Screen patients for risk of substance use disorders, including opioid abuse and misuse, and warn them of the risk for overdose and death associated with the use of additional CNS depressants including alcohol and illicit drugs [see Drug Interactions (7.1) and Patient Counseling Information (17)].

5.9 Risk of Central Nervous System Depression

Use of HYDEXOR may lead to CNS depression. There is increased risk because HYDEXOR contains both an opioid, hydrocodone, and phenothiazine, promethazine. HYDEXOR should not be prescribed for outpatient use as it may impair the mental and/or physical abilities required for
the performance of potentially hazardous tasks, such as driving a vehicle or operating machinery [see Warnings and Precautions (5.5)]. The impairment may be amplified by concomitant use of other central-nervous-system depressants such as alcohol, sedatives/hypnotics (including barbiturates), additional narcotics or narcotic analgesics, general anesthetics, tricyclic antidepressants, or tranquilizers; therefore such agents should either be eliminated or given in reduced dosage in the presence of HYDEXOR [see Warnings and Precautions (5.9), Patient Counseling Information (17), Drug Interactions (7.1)].

5.10 Life-Threatening Respiratory Depression in Patients with Chronic Pulmonary Disease or in Elderly, Cachectic, or Debilitated Patients

The use of HYDEXOR in patients with acute or severe bronchial asthma in an unmonitored setting or in the absence of resuscitative equipment is contraindicated.

Patients with Chronic Pulmonary Disease: HYDEXOR-treated patients with significant chronic obstructive pulmonary disease or cor pulmonale, and those with a substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression are at increased risk of decreased respiratory drive including apnea, even at recommended dosages of HYDEXOR [see Warnings and Precautions (5.2)].

Elderly, Cachectic, or Debilitated Patients: Life-threatening respiratory depression is more likely to occur in elderly, cachectic, or debilitated patients because they may have altered pharmacokinetics or altered clearance compared to younger, healthier patients [see Geriatric Use (8.5)].

Monitor such patients closely for signs of respiratory depression when prescribing HYDEXOR. Concomitant therapy with other drugs that depress respiration should be avoided [see Warnings and Precautions (5.2) and Drug Interactions (7.1, 7.4)]. Alternatively, consider the use of non-opioid analgesics in these patients.

5.11 Adrenal Insufficiency

Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use. Presentation of adrenal insufficiency may include non-specific signs and symptoms including nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. If adrenal insufficiency is suspected, confirm the diagnosis with diagnostic testing as soon as possible. If adrenal insufficiency is diagnosed, treat with physiologic replacement doses of corticosteroids. Wean the patient off of the opioid to allow adrenal function to recover and continue corticosteroid treatment until adrenal function recovers. Other opioids may be tried as some cases reported use of a different opioid without recurrence of adrenal insufficiency. The information available does not identify any particular opioids as being more likely to be associated with adrenal insufficiency.

5.12 Severe Hypotension

HYDEXOR may cause severe hypotension including orthostatic hypotension and syncope in ambulatory patients. There is increased risk because HYDEXOR contains both an opioid, hydrocodone, and phenothiazine, promethazine, and in patients whose ability to maintain blood pressure has already been compromised by a reduced blood volume or concurrent administration
of certain CNS depressant drugs (e.g., other phenothiazines or general anesthetics) [see Drug Interactions (7.1)]. Monitor these patients for signs of hypotension after initiating or changing the dosing frequency of HYDEXOR. In patients with circulatory shock, HYDEXOR may cause vasodilation that can further reduce cardiac output and blood pressure. Avoid the use of HYDEXOR in patients with circulatory shock.

Because of the potential for promethazine hydrochloride to reverse epinephrine's vasopressor effect, epinephrine should not be used to treat hypotension associated with HYDEXOR overdose.

5.13 Increased Risk of Seizures in Patients with Seizure Disorders

HYDEXOR contains hydrocodone and promethazine, two drugs that may lower seizure threshold, increase the frequency of seizures in patients with seizure disorders, and may increase the risk of seizures occurring in other clinical settings associated with seizures. Consider the use of alternative analgesics in patients with a history of seizure disorders. If used in patients with a history of seizures, monitor patients for worsened seizure control during HYDEXOR therapy.

5.14 Bone Marrow Depression

HYDEXOR contains promethazine and should be used with caution in patients with bone marrow depression. Leukopenia and agranulocytosis have been reported with promethazine, usually when it has been used in association with other known marrow-toxic agents.

5.15 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with promethazine hydrochloride alone or in combination with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include immediate discontinuation of HYDEXOR, antipsychotic drugs, if any, and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

Since recurrences of NMS have been reported with phenothiazines, the reintroduction of HYDEXOR should be carefully considered.
5.16   **Cholestatic Jaundice**

Administration of promethazine hydrochloride has been associated with reported cholestatic jaundice.

5.17   **Serious Skin Reactions**

Rarely, acetaminophen may cause serious skin reactions such as acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. Patients should be informed about the signs of serious skin reactions and use of HYDEXOR should be discontinued at the first appearance of skin rash or any other sign of hypersensitivity.

5.18   **Hypersensitivity/Anaphylaxis**

There have been post-marketing reports of hypersensitivity and anaphylaxis associated with use of acetaminophen. Clinical signs included swelling of the face, mouth, and throat, respiratory distress, urticaria, rash, pruritus, and vomiting. There were infrequent reports of life-threatening anaphylaxis requiring emergency medical attention. HYDEXOR should be discontinued immediately and patients should seek medical care if they experience these symptoms. HYDEXOR should not be prescribed for patients with acetaminophen allergy.

5.19   **Risk of Use in Patients with Increased Intracranial Pressure, Brain Tumors, Head Injury, or Impaired Consciousness**

In patients who may be susceptible to the intracranial effects of CO₂ retention (e.g., those with evidence of increased intracranial pressure or brain tumors), HYDEXOR may reduce respiratory drive, and the resultant CO₂ retention can further increase intracranial pressure. Monitor such patients for signs of sedation and respiratory depression, particularly when initiating therapy with HYDEXOR.

Opioids may also obscure the clinical course in a patient with a head injury. Avoid the use of HYDEXOR in patients with impaired consciousness or coma.

5.20   **Risks of Use in Patients with Gastrointestinal Conditions**

HYDEXOR is contraindicated in patients with known or suspected gastrointestinal obstruction, including paralytic ileus.

HYDEXOR contains hydrocodone, an opioid, and promethazine, an anticholinergic phenothiazine. The concurrent use of anticholinergic drugs with opioids may produce paralytic ileus. The hydrocodone in HYDEXOR may cause spasm of the sphincter of Oddi. Opioids may cause increases in serum amylase. Monitor patients with biliary tract disease, including acute pancreatitis, for worsening symptoms.

5.21   **Withdrawal**

Do not abruptly discontinue HYDEXOR in a patient physically dependent on opioids. When discontinuing HYDEXOR in a physically-dependent patient switch patients to a hydrocodone and acetaminophen containing product without promethazine and gradually taper the dosing frequency. Rapid
tapering of [moiety] in a patient physically dependent on opioids may lead to a withdrawal syndrome and return of pain [see Dosage and Administration (2.4), Drug Abuse and Dependence (9.3)]

Additionally, avoid the use of mixed agonist/antagonist (e.g., pentazocine, nalbuphine, and butorphanol) or partial agonist (e.g., buprenorphine) analgesics in patients who are receiving a full opioid agonist analgesic, including HYDEXOR. In these patients, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect and/or precipitate withdrawal symptoms [see Drug Interactions (7.9)].

5.22 Increased Risk to Specific Populations Due to Anticholinergic Properties of Promethazine

Because of the anticholinergic properties of promethazine hydrochloride, HYDEXOR should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, stenosing peptic ulcer, pyloroduodenal obstruction, and bladder-neck obstruction. HYDEXOR should be used cautiously in persons with cardiovascular disease.

5.23 Neonatal Opioid Withdrawal Syndrome

Prolonged use of HYDEXOR during pregnancy can result in withdrawal in the neonate. Neonatal opioid withdrawal syndrome, unlike opioid withdrawal syndrome in adults, may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. Observe newborns for signs of neonatal opioid withdrawal syndrome and manage accordingly. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available [see Use in Specific Populations (8.1), Patient Counseling Information (17)].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the label:

- Life-Threatening Respiratory Depression and Excessive Sedation [see Warnings and Precautions (5.1, 5.4, 5.10)]
- Addiction, Abuse, and Misuse [see Warnings and Precautions (5.3)]
- Hepatotoxicity [see Warnings and Precautions (5.6)]
- Interactions with Benzodiazepines and Other CNS Depressants [see Warnings and Precautions (5.7)]
- CNS Depression [see Warnings and Precautions (5.1, 5.9)]
- Severe Hypotension [see Warnings and Precautions (5.12)]
- Seizures [see Warnings and Precautions (5.13)]
6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect rates observed in practice. Patients observed in a clinical setting, under direct physician supervision at the lowest effective dosage for the shortest duration is consistent with individual treatment goals.

A total of 725 subjects were exposed to one or more doses of HYDEXOR in 6 clinical studies, including 463 subjects who were treated with HYDEXOR in two placebo- and active-controlled multiple-dose trials in patients with moderate-to-severe pain following bunionectomy or dental extraction. The best treatment outcomes were observed during the first 3 days of therapy in clinical settings. In these two studies, there were 338 subjects who received HYDEXOR for at least five days.

Adverse events (except nausea and vomiting, which were OINV efficacy endpoints) were assessed in the two controlled studies in two ways, that is, routine patient reporting and prospective monitoring. The incidence and severity of nine prospectively monitored adverse events (AEs) were evaluated using the Opioid Symptoms Scales (OSS), including the nine AEs of confusion, constipation, difficulty concentrating, difficulty voiding, drowsiness, dry mouth, headache, itchiness, and lightheaded/dizziness. The severity of each of the nine opioid symptoms was evaluated and rated on a 0-to-10 point Likert scale. The most common adverse events observed in the pooled controlled studies through routine and prospective monitoring (i.e., greater than or equal to 1% in the HYDEXOR treatment group and greater than the placebo or active comparator groups) are listed in Table 1.

Table 1: Adverse Events Occurring in at least 1% of Patientsa in Dental and Bunionectomy Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>HYDEXOR (N=463)</th>
<th>Hydrocodone bitartrate / acetaminophen b (N=455)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness*</td>
<td>211 (46%)</td>
<td>131 (29%)</td>
<td>12 (12%)</td>
</tr>
<tr>
<td>Headache*</td>
<td>78 (17%)</td>
<td>69 (15%)</td>
<td>20 (20%)</td>
</tr>
<tr>
<td>Dry mouth*</td>
<td>71 (15%)</td>
<td>36 (8%)</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Lightheaded/Dizzy*</td>
<td>66 (14%)</td>
<td>61 (13%)</td>
<td>5 (5%)</td>
</tr>
</tbody>
</table>
The frequency of the central nervous system adverse events of confusion, difficulty concentrating, and drowsiness rated as severe on the OSS (i.e., ≥7 on 0-10 point scale) was higher for HYDEXOR compared to hydrocodone bitartrate/acetaminophen and placebo as shown in Table #1. Frequencies are displayed for 2 time periods: over Days 1-2 (when subjects in the dental study used study medication as needed for pain and subjects in the bunionectomy study used study medication on a fixed schedule every 4-6 hours) and over Days 3-5 (when subjects in both studies used study medication as needed for pain).

Table 2: Severe Solicited Opioid-Related Adverse Events on Days 1-2 and on Days 3-5 in Dental and Bunionectomy Studies

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Time Period</th>
<th>Hydexor (N=463)</th>
<th>hydrocodone bitartrate/acetaminophen b (N=455)</th>
<th>Placebo (N=100)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>Days 1-2</td>
<td>22 (4.8%)</td>
<td>17 (3.7%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>21 (4.5%)</td>
<td>16 (3.5%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Difficult concentration*</td>
<td>Days 1-2</td>
<td>21 (4.5%)</td>
<td>28 (6.2%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>41 (8.9%)</td>
<td>53 (11.6%)</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>Itchiness</td>
<td>Days 1-2</td>
<td>58 (12.5%)</td>
<td>29 (6.4%)</td>
<td>6 (6.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>39 (8.4%)</td>
<td>13 (2.9%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td>Lightheaded/Dizzy</td>
<td>Days 1-2</td>
<td>47 (10.2%)</td>
<td>49 (10.8%)</td>
<td>2 (2.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>36 (7.8%)</td>
<td>24 (5.3%)</td>
<td>3 (3.0%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Days 1-2</td>
<td>200 (43.2%)</td>
<td>122 (26.8%)</td>
<td>12 (12.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>96 (20.7%)</td>
<td>44 (9.7%)</td>
<td>6 (6.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>Days 1-2</td>
<td>55 (11.9%)</td>
<td>48 (10.5%)</td>
<td>16 (16.0%)</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>38 (8.2%)</td>
<td>29 (6.4%)</td>
<td>6 (6.0%)</td>
</tr>
<tr>
<td>Difficult to Pass Urine</td>
<td>Days 1-2</td>
<td>4 (0.9%)</td>
<td>2 (0.4%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Days 3-5</td>
<td>74 of 101</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 6.2 Postmarketing Experience

The following additional adverse reactions have been reported in postmarketing experience of the individual components of HYDEXOR. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Additionally, HYDEXOR is only intended to be used in a clinical setting under direct physician supervision where these situations can be closely monitored.

**Hydrocodone**

*Serotonin syndrome*: Cases of serotonin syndrome, a potentially life-threatening condition, have been reported during concomitant use of opioids with serotonergic drugs.

*Adrenal insufficiency*: Cases of adrenal insufficiency have been reported with opioid use, more often following greater than one month of use.

*Androgen deficiency*: Cases of androgen deficiency have occurred with chronic use of opioids [see Clinical Pharmacology (12.2)].

*Anaphylaxis*: Anaphylaxis, angioedema, and other hypersensitivity reactions have been reported with opioids.

**Acetaminophen**

*Anaphylaxis*: Anaphylaxis, angioedema, and other hypersensitivity reactions have been reported with acetaminophen.

**Promethazine**

*Central Nervous System*: Blurred vision, disorientation, extrapyramidal symptoms including tardive dyskinesia, lassitude, tinnitus, incoordination, fatigue, euphoria, nervousness, diplopia, insomnia, tremors, convulsive seizures, excitation, catatonic-like states, hysteria, hallucinations.

*Cardiovascular*: Increased or decreased blood pressure, tachycardia, bradycardia, faintness.

*Hematologic*: Leukopenia, thrombocytopenia, thrombocytopenic purpura, agranulocytosis.

*Gastrointestinal System*: Nausea, vomiting, jaundice.
**Respiratory:** Asthma, nasal stuffiness, respiratory depression (potentially fatal) and apnea (potentially fatal) [see Warnings and Precautions (5.2, 5.8)].

**Dermatological:** Dermatitis, photosensitivity, urticaria.

**Other:** Angioneurotic edema. Neuroleptic malignant syndrome (potentially fatal) [see Warnings and Precautions (5.1)].

**Paradoxical Reactions:** Hyperexcitability and abnormal movements have been reported in patients following a single administration of promethazine hydrochloride. Respiratory depression, nightmares, delirium, and agitated behavior have also been reported in some of these patients.

7 **DRUG INTERACTIONS**

No drug interaction studies have been conducted with HYDEXOR, although studies have been conducted with individual components.

**Table 1: Clinically Significant Drug Interactions with HYDEXOR**

<table>
<thead>
<tr>
<th>Benzodiazepines and other Central Nervous System (CNS) Depressants</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Impact:</strong> Due to additive pharmacologic effect, the concomitant use of benzodiazepines or other CNS depressants, including alcohol, can increase the risk of hypotension, respiratory depression, profound sedation, coma, and death.</td>
</tr>
<tr>
<td><strong>Intervention:</strong> Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients closely for signs of respiratory depression and sedation. HYDEXOR contains promethazine. When given concomitantly with promethazine containing products, the dose of barbiturates should be reduced by at least one-half. Dosage must be individualized. Excessive amounts of promethazine hydrochloride relative to a narcotic may lead to restlessness and motor hyperactivity in the patient with pain; these symptoms usually disappear with adequate control of the pain [see Warnings and Precautions (5.1)].</td>
</tr>
<tr>
<td><strong>Examples:</strong> Benzodiazepines and other sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol.</td>
</tr>
</tbody>
</table>

**Serotonergic Drugs**

| **Clinical Impact:** The concomitant use of opioids with other drugs that affect the serotonergic neurotransmitter system has resulted in serotonin syndrome. HYDEXOR contains an opioid, hydrocodone, and a phenothiazine, promethazine, which have serotonergic effects. |

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**Intervention:** Avoid the use of additional serotonergic drugs. Discontinue HYDEXOR if serotonin syndrome is suspected

**Examples:** Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), triptans, 5-HT3 receptor antagonists, drugs that effect the serotonin neurotransmitter system (e.g., mirtazapine, trazodone, tramadol), certain muscle relaxants (i.e., cyclobenzaprine, metaxalone), monoamine oxidase (MAO) inhibitors (those intended to treat psychiatric disorders and also others, such as linezolid and intravenous methylene blue).

**Inhibitors of CYP3A4 and CYP2D6**

**Clinical Impact:** The concomitant use of HYDEXOR and CYP3A4 inhibitors, can increase the plasma concentration of hydrocodone, resulting in increased or prolonged opioid effects. These effects could be more pronounced with concomitant use of HYDEXOR and CYP2D6 and CYP3A4 inhibitors, particularly when an inhibitor is added after a stable dose of HYDEXOR is achieved [see Warnings and Precautions (5.5)]. After stopping a CYP3A4 inhibitor, as the effects of the inhibitor decline, the hydrocodone plasma concentration will decrease [see Clinical Pharmacology (12.3)], resulting in decreased opioid efficacy or a withdrawal syndrome in patients who had developed physical dependence to HYDEXOR.

**Intervention:** Consider reduction in dosing frequency of HYDEXOR until stable drug effects are achieved. Monitor patients for respiratory depression and sedation at frequent intervals. If a CYP3A4 inhibitor is discontinued, consider an increase in dosing frequency of HYDEXOR until stable drug effects are achieved. Monitor for signs of opioid withdrawal.

**Examples:** Macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g. ketoconazole), protease inhibitors (e.g., ritonavir)

**CYP3A4 Inducers**

**Clinical Impact:** The concomitant use of HYDEXOR and CYP3A4 inducers can decrease the plasma concentration of hydrocodone, resulting in decreased efficacy or onset of a withdrawal syndrome in patients who have developed physical dependence to hydrocodone [see Warnings and Precautions (5.5)].

After stopping a CYP3A4 inducer, as the effects of the inducer decline, the hydrocodone plasma concentration will increase, which could increase or prolong both the therapeutic effects and adverse reactions and may cause serious respiratory depression.

**Intervention:** Consider an increase in dosing frequency of HYDEXOR until stable drug effects are achieved. Monitor for signs of opioid withdrawal. If a CYP3A4 inducer is
**Examples:** Rifampin, carbamazepine, and phenytoin.

### Monoamine Oxidase Inhibitors (MAOIs)

**Clinical Impact:** MAOI interactions with opioids may manifest as serotonin syndrome or opioid toxicity (e.g., respiratory depression, coma). If urgent use of an opioid is necessary, use test doses and frequent titration of small doses to treat pain while closely monitoring blood pressure and signs and symptoms of CNS and respiratory depression.

**Intervention:** The use HYDEXOR is not recommended for patients taking MAOIs or within 14 days of stopping such treatment.

**Examples:** Phenelzine, tranylcypromine, and linezolid.

### Anticholinergic Drugs

**Clinical Impact:** The concomitant use of anticholinergic drugs may increase risk of urinary retention and/or severe constipation, which may lead to paralytic ileus.

**Intervention:** Monitor patients for signs of urinary retention or reduced gastric motility when HYDEXOR is used concomitantly with anticholinergic drugs.

### Mixed Agonist/Antagonist and Partial Agonist Opioid Analgesics

**Clinical Impact:** May reduce the analgesic effect of HYDEXOR and/or precipitate withdrawal symptoms.

**Intervention:** Avoid concomitant use.

**Examples:** Butorphanol, nalbuphine, pentazocine, and buprenorphine.

### Muscle Relaxants

**Clinical Impact:** Hydrocodone may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

**Intervention:** Monitor patients for signs of respiratory depression that may be greater than otherwise expected and decrease the dosage of HYDEXOR and/or the muscle relaxant as necessary.

### Warfarin

**Clinical Impact:** Post-marketing surveillance of acetaminophen individual products has revealed rare reports of alteration of warfarin effect, including elevation of prothrombin times.
**Intervention:** HYDEXOR contains acetaminophen as an active ingredient, monitor the prothrombin time of patients on warfarin also receiving HYDEXOR for signs of an interaction and adjust the dosage of warfarin as needed.

### Epinephrine

**Clinical Impact:** Promethazine hydrochloride has the potential to reverse epinephrine's vasopressor effect.

**Intervention:** Epinephrine should not be used to treat hypotension associated with HYDEXOR overdose.

### Diuretics

**Clinical Impact:** Opioids can reduce the efficacy of diuretics by inducing the release of antidiuretic hormone.

**Intervention:** Monitor patients for signs of diminished diuresis and/or effects on blood pressure and increase the dosage of the diuretic as needed.

### Laboratory Test Interference

**Clinical Impact:** HYDEXOR contains promethazine hydrochloride which may affect the following laboratory tests:

- **Pregnancy Tests**
  Diagnostic pregnancy tests based on immunological reactions between HCG and anti-HCG may result in false-negative or false-positive interpretations in patients receiving promethazine hydrochloride.

- **Glucose Tolerance Test**
  An increase in blood glucose has been reported in patients receiving promethazine hydrochloride.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Risk Summary**

Prolonged use of opioid analgesics during pregnancy may cause neonatal opioid withdrawal syndrome [see Warnings and Precautions (5.23), Clinical Considerations]. There are no available data on HYDEXOR use in pregnant women to evaluate for a drug-associated risk of
major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published studies on the association between hydrocodone, promethazine, and acetaminophen and fetal outcomes have reported inconsistent findings and have important methodological limitations (see Data).

No reproductive or developmental toxicology studies in animals have been conducted to evaluate Hydexor or its hydrocodone bitartrate component.

Reproductive and developmental studies in rats and mice from the published literature identified adverse events at clinically relevant doses with acetaminophen and promethazine. Treatment of pregnant rats with doses of acetaminophen approximately equal to the recommended maximum human daily dose (MHDD) showed evidence of fetotoxicity and increases in bone variations in the fetuses. In another study, necrosis was observed in the liver and kidney of both pregnant rats and fetuses at doses approximately equal to the MHDD. In mice treated with acetaminophen at doses within the clinical dosing range, cumulative adverse effects on reproduction were seen in a continuous breeding study. A reduction in numbers of litters of the parental mating pair was observed as well as retarded growth and abnormal sperm in their offspring and reduced birth weight in the next generation. In rats, female fertility was decreased following in utero exposure to acetaminophen. Increased resorptions of fetuses in pregnant mice and rats and skeletal fragility, decreased pup weight, and developmental delays were reported in rat pups born to dams treated with promethazine during gestation at doses within the human dosing range [see Data].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Prolonged use of opioid analgesics during pregnancy for medical or nonmedical purposes can result in physical dependence in the neonate and neonatal opioid withdrawal syndrome shortly after birth.

Neonatal opioid withdrawal syndrome presents as irritability, hyperactivity and abnormal sleep pattern, high pitched cry, tremor, vomiting, diarrhea and failure to gain weight. The onset, duration, and severity of neonatal opioid withdrawal syndrome vary based on the specific opioid used, duration of use, timing and amount of last maternal use, and rate of elimination of the drug by the newborn. Observe newborns for symptoms of neonatal opioid withdrawal syndrome and manage accordingly [see Warnings and Precautions (5.23)].

Due to the promethazine component, HYDEXOR administered to a pregnant woman within two weeks of delivery may inhibit platelet aggregation in the newborn. The effect on later growth and development of the newborn is unknown.

Labor or delivery

Opioids cross the placenta and may produce respiratory depression and psycho-physiologic effects in neonates. An opioid antagonist, such as naloxone, must be available for reversal of opioid-induced respiratory depression in the neonate. HYDEXOR is not recommended for use in pregnant women during or immediately prior to labor, when other analgesic techniques are more
appropriate. Opioid analgesics, including HYDEXOR, can prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation, which tends to shorten labor. Monitor neonates exposed to opioid analgesics during labor for signs of excess sedation and respiratory depression.

Data

Human Data

Hydrocodone

A limited number of pregnancies have been reported in published observational studies describing hydrocodone use during pregnancy. However, these data cannot definitively establish or exclude any drug-associated risk during pregnancy. Methodological limitations of these observational studies include small sample size and lack of details regarding dose, duration, and timing of exposure.

Promethazine

The majority of studies examining the use of promethazine in pregnancy did not find an association with an increased risk of congenital anomalies. In the few studies reporting an association, no consistent pattern of malformations was noted. Most of the studies, both positive and negative, were limited by small sample size, recall bias and lack of information regarding dose and timing of exposure.

Acetaminophen

Published epidemiological studies with oral acetaminophen use during pregnancy have not reported a clear association with acetaminophen use and birth defects, miscarriage, or adverse maternal or fetal outcomes. The results from a large population-based prospective cohort, including data from 26,424 women with live born singletons who were exposed to oral acetaminophen during the first trimester, indicate no increased risk for congenital malformations, compared to a control group of unexposed children. The rate of congenital malformations (4.3%) was similar to the rate in the general population. A population-based, case-control study from the National Birth Defects Prevention Study showed that 11,610 children with prenatal exposure to acetaminophen during the first trimester had no increased risk of major birth defects compared to 4,500 children in the control group. Other epidemiological data showed similar results. However, these studies cannot definitively establish the absence of any risk because of methodological limitations, including recall bias.

Animal Data

No reproductive or developmental studies were conducted with Hydexor or its hydrocodone bitartrate component. The following data are based in findings from studies that evaluated acetaminophen or promethazine alone.

Studies in pregnant rats that received oral acetaminophen during organogenesis at doses up to 0.88 times the MHDD (3.9 grams/day, based on body surface area comparison) showed evidence of fetotoxicity (reduced fetal weight and length) and a dose-related increase in bone variations (reduced ossification and rudimentary rib changes). Offspring had no evidence of external, visceral, or skeletal malformations. When pregnant rats received oral acetaminophen throughout gestation at doses of 1.2 times the MHDD (based on a body surface area comparison), areas of necrosis occurred in both the liver and kidney of pregnant rats and fetuses. These effects did not
occur in animals that received oral acetaminophen at doses of 0.3 times the MHDD, based on a body surface area comparison.

In a continuous breeding study, pregnant mice received 0.25, 0.5, or 1.0% acetaminophen via the diet (357, 715, or 1430 mg/kg/day). These doses are approximately 0.45, 0.89, and 1.8 times the MHDD, respectively, based on a body surface area comparison. A dose-related reduction in body weights of fourth and fifth litter offspring of the treated mating pair occurred during lactation and post-weaning at all doses. Animals in the high dose group had a reduced number of litters per mating pair, male offspring with an increased percentage of abnormal sperm, and reduced birth weights in the next generation pups.

Teratogenic effects have not been demonstrated in rat-feeding studies at doses of 6.25 and 12.5 mg/kg of promethazine hydrochloride (0.15 and 0.30 times lower than the MHDD of 400 mg/day based on body surface area). Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats (0.6 times higher than the MHDD based on body surface area).

No evidence of embryotoxicity or malformation were reported in a published study in which pregnant rats were treated with promethazine hydrochloride from Gestation Day 1 to 15 or Gestation Day 10 through 15 via oral gavage doses of 50 to 250 mg/kg/day (1.2 to 6.1 times the MHDD of 400 mg/day based on body surface area).

Increased resorptions were reported in a published study in which pregnant rats were treated orally from Gestation Day 5 to 16 with 20 mg/kg promethazine hydrochloride (0.5 times the MHDD of 400 mg).

Increased resorptions were reported in a published study in which pregnant mice were treated intraperitoneally from Gestation Day 1 to 5 with 1 mg/kg promethazine hydrochloride (0.01 times the MHDD of 400 mg/day based on body surface area).

Skeletal fragility of pups was reported in a published study in which pregnant Lister Hooded rats were treated orally from Gestation Day 7 to 13 with 5 or 10 mg/kg promethazine hydrochloride (0.12 or 0.24 times the MRHD of 400 mg based on body surface area). No malformations or maternal toxicity were reported. Subsequent studies suggested that the effect was most prominent when treated on Days 10 to 12 of gestation.

Decreased pup weight and delays in initial occurrence of behavioral/reflex responses in pups were reported in a published study in which pregnant rats were treated orally from Gestation Day 10 to 12 with 10 mg/kg promethazine hydrochloride (0.24 times the MHDD of 400 mg based on body surface area).

### 8.2 Lactation

**Risk Summary**

There are no data on the presence of HYDEXOR in human milk, the effects on the breastfed infant, or the effects on milk production. However, data are available on the individual components (hydrocodone, promethazine, acetaminophen) (*see Data*). Because of the potential for serious adverse reactions in the breastfed infant, including excess sedation and respiratory depression, breastfeeding is not recommended during treatment with HYDEXOR. Consider alternative therapies.

**Clinical Considerations**
Infants exposed to HYDEXOR through breast milk should be monitored for excess sedation and respiratory depression. Withdrawal symptoms can occur in breastfed infants when maternal administration of an opioid analgesic is stopped, or breastfeeding is stopped.

Data

**Hydrocodone**

Hydrocodone is transferred into human milk. Published cases report variable concentrations of hydrocodone and hydromorphone (an active metabolite) in breast milk with administration of immediate-release hydrocodone to nursing mothers in the early postpartum period with relative infant doses of hydrocodone ranging between 1.4 and 3.7%. There are reports of excessive sedation and respiratory depression in breastfed infants exposed to hydrocodone. However, there is no information on the effects of hydrocodone on milk production.

**Promethazine**

There are no data on the presence of promethazine in human milk. However, direct oral administration of promethazine has been associated with respiratory depression, including fatalities, in pediatric patients [see Warnings and Precautions (5.4)]. Promethazine has been shown to decrease basal prolactin levels in non-nursing women, and therefore may affect milk production.

**Acetaminophen**

Limited published studies report that orally administered acetaminophen passes rapidly into human milk with similar levels in the milk and plasma. Average and maximum neonatal doses of 1% and 2%, respectively, of the weight-adjusted maternal dose are reported after a single oral administration of 1 gram of acetaminophen. There is one well-documented report of a rash in a breast-fed infant that resolved when the mother stopped acetaminophen use and recurred when she resumed acetaminophen use.

### 8.3 Females and Males of Reproductive Potential

**Infertility**

Chronic use of opioids may cause reduced fertility in females and males of reproductive potential. It is not known whether these effects on fertility are reversible [see Adverse Reactions (6.2), Clinical Pharmacology (12.2)].

Published animal studies report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on body surface area comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. Additional published animal studies indicate that acetaminophen exposure in utero adversely impacts reproductive capacity of both male and female offspring at clinically relevant exposures [see Nonclinical Toxicology (13.1)].

### 8.4 Pediatric Use

HYDEXOR is contraindicated in all pediatric patients due to the risk of fatal respiratory depression. The safety and effectiveness of HYDEXOR have not been established in pediatric patients. [see Boxed Warning and Warnings and Precautions (5.23)].
8.5 Geriatric Use

The safety and effectiveness of HYDEXOR have not been studied in geriatric patients [see Boxed Warning and Warnings and Precautions (5.7)].

Clinical studies of HYDEXOR did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In an open-label safety study in patients with acute flares of osteoarthritis, the overall safety profile in patients aged ≥ 65 (n =65) was consistent with that of patients aged < 65.

Elderly patients (aged 65 years or older) may have increased sensitivity to hydrocodone and promethazine. In general, use caution when selecting a dosage for an elderly patient, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other drug therapy.

Respiratory depression is the chief risk for elderly patients treated with opioids, and has occurred after large initial doses were administered to patients who were not opioid-tolerant or when opioids were co-administered with other agents that depress respiration. Titrate the dosage of HYDEXOR slowly in geriatric patients and monitor closely for signs of central nervous system and respiratory depression [see Warnings and Precautions (5.X)].

This drug is known to be substantially excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

8.6 Hepatic Impairment

The safety and effectiveness of HYDEXOR have not been studied in patients with impaired hepatic function.

Because hydrocodone, acetaminophen and promethazine are extensively metabolized by the liver, the use of HYDEXOR in patients with hepatic impairment is not recommended [see Boxed Warning, Warnings and Precautions (5.6)].

8.7 Renal Impairment

The safety and effectiveness of HYDEXOR have not been studied in patients with impaired renal function.

Patients with renal impairment may have higher hydrocodone plasma concentrations than those with normal function. The use of HYDEXOR in patients with renal disease is not recommended [see Clinical Pharmacology (12.3)].

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

HYDEXOR contains hydrocodone, a Schedule II controlled substance.
9.2 Abuse

HYDEXOR contains hydrocodone, a substance with a high potential for abuse similar to other opioids including codeine, hydromorphone, morphine, and oxycodone. HYDEXOR can be abused and is subject to misuse, addiction, and criminal diversion [see Warnings and Precautions (5.3)].

All patients treated with opioids require careful monitoring for signs of abuse and addiction, since use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of a prescription drug, even once, for its rewarding psychological or physiological effects.

Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

“Drug-seeking” behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other treating health care provider(s). “Doctor shopping” (visiting multiple prescribers) to obtain additional prescriptions is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Health care providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

HYDEXOR, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of HYDEXOR

Abuse of HYDEXOR poses a risk of overdose and death. The risk is increased with concurrent abuse of HYDEXOR with alcohol and other central nervous system depressants [see Warnings and Precautions (5.9)].

Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

Human Abuse Potential Study
A randomized, double-blind, placebo- and active-controlled, crossover human abuse potential study in opioid-experienced, non-dependent recreational drug users (n = 37) was conducted to determine the abuse potential of two single oral doses of HYDEXOR (3 tablets containing 22.5 mg hydrocodone/975 mg acetaminophen/37.5 mg promethazine and 5 tablets containing 37.5 mg hydrocodone/1625 mg acetaminophen/62.6 mg promethazine) compared to single oral doses of hydrocodone/acetaminophen (3 tablets containing 22.5 mg hydrocodone/975 mg acetaminophen, 5 tablets containing 37.5 mg hydrocodone/1625 mg acetaminophen) and placebo. There were no statistically significant differences on the subjective measures Drug Liking or Take Drug Again when the two identical doses of hydrocodone/acetaminophen, with or without promethazine, were compared.

9.3 Dependence

Both tolerance and physical dependence can develop during chronic opioid therapy. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia (in the absence of disease progression or other external factors). Tolerance may occur to both the desired and undesired effects of drugs and may develop at different rates for different effects.

Physical dependence results in withdrawal symptoms after abrupt discontinuation or a significant dosage reduction of a drug. Withdrawal also may be precipitated through the administration of drugs with opioid antagonist activity (e.g., naloxone, nalmefene), mixed agonist/antagonist analgesics (pentazocine, butorphanol, nalbuphine), or partial agonists (buprenorphine). Physical dependence may not occur to a clinically significant degree until after several days to weeks of continued opioid usage.

Infants born to mothers physically dependent on opioids will also be physically dependent and may exhibit respiratory difficulties and withdrawal signs [see Use in Specific Populations (8.1)].

10 OVERDOSAGE

The clinical presentation of acute overdosage from HYDEXOR may include signs and symptoms of hydrocodone toxicity, acetaminophen toxicity or promethazine toxicity, or a combination of these. A single or multiple drug overdose with HYDEXOR is a potentially lethal polydrug overdose, and consultation with a regional poison control center is recommended. There is no information available on overdosage with HYDEXOR in humans. However, information is available on the individual components:

Hydrocodone bitartrate

Acute overdose with HYDEXOR can be manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, in some cases, pulmonary edema, bradycardia, hypotension, partial or complete airway obstruction, atypical snoring, and death. Marked mydriasis rather than miosis may be seen with hypoxia in overdose situations [see Clinical Pharmacology (12.2)].

In case of overdose, priorities are the reestablishment of a patent and protected airway and institution of assisted or controlled ventilation, if needed. Employ other supportive measures (including oxygen and vasopressors) in the management of circulatory shock and pulmonary edema as indicated. Cardiac arrest or arrhythmias will require advanced life-support techniques.
The opioid antagonists, naloxone or nalmefene, are specific antidotes to respiratory depression resulting from opioid overdose. For clinically significant respiratory or circulatory depression secondary to hydrocodone overdose, administer an opioid antagonist. Opioid antagonists should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to hydrocodone overdose.

Because the duration of opioid reversal is expected to be less than the duration of action of hydrocodone in HYDEXOR, carefully monitor the patient until spontaneous respiration is reliably re-established. If the response to an opioid antagonist is suboptimal or only brief in nature, administer additional antagonist as directed by the product’s prescribing information.

In an individual physically dependent on opioids, administration of the recommended usual dosage of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal symptoms experienced will depend on the degree of physical dependence and the dose of the antagonist administered. If a decision is made to treat serious respiratory depression in the physically dependent patient, administration of the antagonist should be begun with care and by titration with smaller than usual doses of the antagonist.

**Acetaminophen**

In acetaminophen overdose dose-dependent, potentially fatal hepatic necrosis is the most serious adverse effect. Renal tubular necrosis, hypoglycemic coma, and coagulation defects may also occur. The initial symptoms seen within the first 24 hours following an acetaminophen overdose are: anorexia, nausea, vomiting, malaise, pallor and diaphoresis. Clinical and laboratory evidence of hepatic toxicity may not be apparent until 48 to 72 hours post-ingestion.

In the treatment of acetaminophen overdose, gastric decontamination with activated charcoal should be administered just prior to N-acetylcysteine (NAC) to decrease systemic absorption if acetaminophen ingestion is known or suspected to have occurred within a few hours of presentation. Serum acetaminophen levels should be obtained immediately if the patient presents 4 hours or more after ingestion to assess potential risk of hepatotoxicity; acetaminophen levels drawn less than 4 hours post-ingestion may be misleading. To obtain the best possible outcome, NAC should be administered as soon as possible where impending or evolving liver injury is suspected. Intravenous NAC may be administered when circumstances preclude oral administration. Vigorous supportive therapy is required in severe intoxication. Procedures to limit the continuing absorption of the drug must be readily performed since the hepatic injury is dose dependent and occurs early in the course of intoxication.

**Promethazine hydrochloride**

Signs and symptoms of overdosage with promethazine hydrochloride range from mild depression of the central nervous system and cardiovascular system to profound hypotension, respiratory depression, unconsciousness, and sudden death. Other reported reactions include hyperreflexia, hypertonia, ataxia, athetosis, and extensor-plantar reflexes (Babinski reflex). Stimulation may be evident, especially in children and geriatric patients. Convulsions may rarely occur. A paradoxical-type reaction has been reported in children receiving single doses of 75 mg to 125 mg orally, characterized by hyperexcitability and nightmares. Atropine-like signs and symptoms-dry mouth, fixed, dilated pupils, flushing, as well as gastrointestinal symptoms-may occur.
Treatment of overdosage is essentially symptomatic and supportive. Activated charcoal orally or by lavage may be given, or sodium or magnesium sulfate orally as a cathartic. Attention should be given to the reestablishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Diazepam may be used to control convulsions. Acidosis and electrolyte losses should be corrected. Note that any depressant effects of promethazine hydrochloride are not reversed by naloxone. Avoid analeptics which may cause convulsions.

The treatment of choice for resulting hypotension is administration of intravenous fluids, accompanied by repositioning if indicated. In the event that vasopressors are considered for the management of severe hypotension which does not respond to intravenous fluids and repositioning, the administration of norepinephrine or phenylephrine should be considered. Epinephrine should not be used because its use in patients with partial adrenergic blockade may further lower the blood pressure [see Drug Interactions (7.11)]. Extrapyramidal reactions may be treated with anticholinergic antiparkinsonian agents, diphenhydramine, or barbiturates. Oxygen may also be administered. Limited experience with dialysis indicates that it is not helpful.

11 DESCRIPTION

HYDEXOR (hydrocodone bitartrate, acetaminophen, promethazine HCl) tablets, for oral use is a fixed-dose, immediate-release bi-layered tablet with one layer containing 12.5 mg of promethazine hydrochloride (equivalent to Promethazine 11.08 mg) and a second layer containing 7.5 mg of hydrocodone bitartrate (equivalent to hydrocodone 5 mg) and 325 mg of acetaminophen. HYDEXOR is a white to off white, oval, uncoated tablet debossed with BC 147 on both sides.

Hydrocodone bitartrate is a semisynthetic and centrally acting opioid analgesic. Its chemical name is: 4,5 α-epoxy-3-methoxy-17-methylmorphinan-6-one tartrate (1:1) hydrate (2:5). It has the following structural formula:

![Structure of Hydrocodone Bitartrate](image1.png)

The molecular formula of hydrocodone bitartrate is \( \text{C}_{18}\text{H}_{21}\text{NO}_3\cdot\text{C}_4\text{H}_6\text{O}_6\cdot2\frac{1}{2}\text{H}_2\text{O} \) and its molecular weight is 494.50.

Acetaminophen, N-acetyl-p-aminophenol, is a non-opioid, non-salicylate analgesic and antipyretic agent. It has the following structural formula:

![Structure of Acetaminophen](image2.png)

The molecular formula of acetaminophen is \( \text{C}_8\text{H}_9\text{NO}_2 \) and its molecular weight is 151.16.
Promethazine hydrochloride, a phenothiazine derivative, is a H₁ receptor antagonist and is designated chemically as 10H-Phenothiazine-10-ethanamine, N,N,α-trimethyl-, monohydrochloride, (±)- with the following structural formula:

![ Structural formula of Promethazine hydrochloride ]

Promethazine hydrochloride is a racemic compound; the molecular formula is C₁₇H₂₀N₂S·HCl and its molecular weight is 320.88.

Each HYDEXOR tablet contains:

- Hydrocodone bitartrate............7.5 mg (equivalent to hydrocodone 5 mg)
- Acetaminophen.........................325 mg
- Promethazine hydrochloride....12.5 mg (equivalent to Promethazine 11.08 mg)

In addition, each tablet contains the following inactive ingredients: Silicified microcrystalline cellulose, hydroxypropylmethyl cellulose, croscarmellose sodium, magnesium stearate and stearic acid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of HYDEXOR is derived from its 3 individual components: hydrocodone, acetaminophen, and promethazine.

**Hydrocodone**

Hydrocodone is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of hydrocodone is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with hydrocodone. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug.

**Acetaminophen**

Acetaminophen is a non-opioid and non-salicylate analgesic. The site and mechanism for the analgesic effect of acetaminophen has not been determined but is thought to primarily involve central actions.
Promethazine

The mechanism(s) mediating the antiemetic effect of promethazine is not entirely clear. Promethazine is primarily a H1 histamine receptor antagonist; however, at higher concentrations promethazine is also a dopamine receptor antagonist and muscarinic receptor antagonist.

12.2 Pharmacodynamics

Cardiac electrophysiology

No studies were conducted with HYDEXOR to evaluate its effect on QTc. Based on available in-vitro data from the hERG test of promethazine, a measure of its potential QT prolongation, the safety margin in this test was estimated to be 13-fold higher than that of promethazine known plasma concentration at the maximum recommended human clinical dose. The clinical relevance of these data has not been determined.

Effects on the Central Nervous System

Hydrocodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to both increases in carbon dioxide tension and electrical stimulation. Hydrocodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic (e.g., pontine lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Effects on the Gastrointestinal Tract and Other Smooth Muscle

Hydrocodone causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased to the point of spasm, resulting in constipation. Other opioid-induced effects may include a reduction in biliary and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Effects on the Cardiovascular System

Hydrocodone produces peripheral vasodilation, which may result in orthostatic hypotension or syncope. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Effects on the Endocrine System

Opioids inhibit the secretion of adrenocorticotropic hormone (ACTH), cortisol, and luteinizing hormone (LH) in humans [see Adverse Reactions (6.2)]. They also stimulate prolactin, growth hormone (GH) secretion, and pancreatic secretion of insulin and glucagon. Chronic use of opioids may influence the hypothalamic-pituitary-gonadal axis, leading to androgen deficiency that may manifest as low libido, impotence, erectile dysfunction, amenorrhea, or infertility. The causal role of opioids in the clinical syndrome of hypogonadism is unknown because the various medical, physical, lifestyle, and psychological stressors that may influence gonadal hormone levels have not been adequately controlled for in studies conducted to date [see Adverse Reactions (6.2)].
Effects on the Immune System

Opioids have been shown to have a variety of effects on components of the immune system in both in vitro and animal models. The clinical significance of these findings is unknown. Overall, the effects of opioids appear to be modestly immunosuppressive.

Concentration-Efficacy Relationships

The minimum effective analgesic concentration will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. The minimum effective analgesic concentration of hydrocodone for any individual patient may increase over time due to an increase in pain, the development of a new pain syndrome, and/or the development of analgesic tolerance [see Dosage and Administration (2.1)].

Concentration-Adverse Reaction Relationships

There is a relationship between increasing hydrocodone plasma concentration and increasing frequency of dose-related opioid adverse reactions such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation may be altered by the development of tolerance to opioid-related adverse reactions [see Dosage and Administration (2.1)].

12.3 Pharmacokinetics

Absorption

Following single oral administration of one HYDEXOR tablet under fasted conditions, peak plasma concentrations (Cmax) of hydrocodone, acetaminophen and promethazine are achieved at 1.5, 0.8 and 4 hours, and the mean Cmax are 20 ng/mL, 4.7 mcg/mL and 4.8 ng/mL, respectively.

Following single oral administration of one HYDEXOR tablet under fed conditions, peak plasma concentrations (Cmax) of hydrocodone, acetaminophen, and promethazine are achieved at 3, 2.8, and 6 hours, and the mean Cmax are 18 ng/mL, 3.3 mcg/mL and 3.7 ng/mL, respectively.

There is no effect of food on the bioavailability of hydrocodone and promethazine from HYDEXOR. The presence of food decreases the peak plasma concentration (Cmax) of acetaminophen by approximately 31% but has no effect on the total exposure (AUC) of acetaminophen.

Distribution

Although the extent of protein binding of hydrocodone in human plasma has not been fully determined, structural similarities to related opioid analgesics suggest that hydrocodone is not extensively protein bound. As most agents in the 5-ring morphinan group of semi-synthetic opioids bind plasma protein to a similar degree (range 19% [hydromorphone] to 45% [oxycodone]), hydrocodone is expected to fall within this range.

Acetaminophen appears to be widely distributed throughout most body tissues except fat. Its apparent volume of distribution is about 0.9 L/kg. A relative small portion (~20%) of acetaminophen is bound to plasma protein.

The extent of distribution, e.g., protein binding, of promethazine has not been fully determined.

Elimination
The mean plasma half-life of hydrocodone, acetaminophen and promethazine is 4.9, 4.6 and 17.5 hours respectively, following a single oral administration of HYDEXOR to healthy adult subjects.

**Metabolism**

Hydrocodone exhibits a complex pattern of metabolism, including O-demethylation, N-demethylation, and 6-keto reduction to the corresponding 6-α-and 6-β-hydroxy metabolites. Hydromorphone, a potent opioid, is formed from the O-demethylation of hydrocodone and contributes to the total analgesic effect of hydrocodone. The O- and N- demethylation processes are mediated by separate P-450 isoenzymes: CYP2D6 and CYP3A4, respectively.

Acetaminophen is primarily metabolized in the liver by first-order kinetics and involves three principal separate pathways: conjugation with glucuronide, conjugation with sulfate and oxidation via the cytochrome, P450-dependent, mixed-function oxidase enzyme pathway to form a reactive intermediate metabolite, which conjugates with glutathione and is then further metabolized to form cysteine and mercapturic acid conjugates. The principal cytochrome P450 isoenzyme involved appears to be CYP2E1, with CYP1A2 and CYP3A4 as additional pathways. In adults, the majority of acetaminophen is conjugated with glucuronic acid and, to a lesser extent, with sulfate. These glucuronide-, sulfate-, and glutathione-derived metabolites lack biologic activity. In premature infants, newborns, and young infants, the sulfate conjugate predominates.

Promethazine is metabolized by the liver to a variety of compounds; the sulfoxides of promethazine and N-demethylpromethazine are the predominant metabolites.

**Excretion**

Hydrocodone and its metabolites are eliminated primarily in the kidneys. Acetaminophen is eliminated from the body primarily by formation of glucuronide and sulfate conjugates in a dose-dependent manner. Less than 9% of acetaminophen is excreted unchanged in the urine. The sulfoxides of promethazine and N-demethylpromethazine are excreted in the urine.

**Specific Populations**

**Geriatric**

For hydrocodone, no significant pharmacokinetic differences based on age have been demonstrated.

A population pharmacokinetic analysis of data obtained from a clinical trial in patients with chronic pain showed no significant changes in the pharmacokinetics of acetaminophen in elderly patients (55 patients between 65 and 75 years of age and 19 patients over 75 years of age) with normal renal and hepatic function.

**Pediatric**

The pharmacokinetics, tolerability, and safety of HYDEXOR have not been studied.

**Sex**

For hydrocodone, no significant pharmacokinetic differences based on sex have been demonstrated.
Renal Impairment
The effect of renal insufficiency on the pharmacokinetics of HYDEXOR has not been studied.

Hepatic Impairment
The effect of hepatic insufficiency on the pharmacokinetics of HYDEXOR has not been studied.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenicity, mutagenicity, and reproductive studies have not been conducted with HYDEXOR or its hydrocodone bitartrate component.

Carcinogenesis

Acetaminophen
Long-term studies in mice and rats have been completed by the National Toxicology Program to evaluate the carcinogenic potential of acetaminophen. In 2-year feeding studies, F344/N rats and B6C3F1 mice were fed a diet containing acetaminophen up to 6000 ppm. Female rats demonstrated equivocal evidence of carcinogenic activity based on increased incidences of mononuclear cell leukemia at 0.8 times the maximum human daily dose (MHDD) of 3.9 grams/day, based on a body surface area comparison. In contrast, there was no evidence of carcinogenic activity in male rats that received up to 0.7 times or mice at up to 1.3 to 1.5 times the MHDD, based on a body surface area comparison.

Promethazine
No evidence of carcinogenic potential was noted in long-term studies in rats and mice treated with oral promethazine hydrochloride doses up to 33 and 45 mg/kg (0.8 and 0.5 times the MHDD of 400 mg/day on a body surface area comparison).

Mutagenesis

Acetaminophen
Acetaminophen was not mutagenic in the bacterial reverse mutation assay (Ames test). In contrast, acetaminophen tested positive for induction of sister chromatid exchanges and chromosomal aberrations in in vitro assays using Chinese hamster ovary cells.

In the published literature, acetaminophen has been reported to be clastogenic when administered at 1500 mg/kg/day to the rat model (3.7 times the MHDD, based on a body surface area comparison). In contrast, no clastogenicity was noted at a dose of 750 mg/kg/day (1.9 times the MHDD, based on a body surface area comparison), suggesting a threshold effect.

Promethazine
Promethazine tested positive in the presence of metabolic activation and negative in the absence of it in the in vitro sister chromatid exchange assay. Negative results were reported in the in vitro bacterial reverse mutation assay and the in vitro chromosome aberration assay.

Impairment of Fertility
Acetaminophen

In studies conducted by the National Toxicology Program, fertility assessments with acetaminophen have been completed in Swiss CD-1 mice via a continuous breeding study. There were no effects on fertility parameters in mice consuming up to 1.8 times the MHDD of acetaminophen, based on a body surface area comparison. Although there was no effect on sperm motility or sperm density in the epididymis, there was a significant increase in the percentage of abnormal sperm in mice consuming 1.8 times the MHDD (based on a body surface comparison) and there was a reduction in the number of mating pairs producing a fifth litter at this dose, suggesting the potential for cumulative toxicity with chronic administration of acetaminophen near the upper limit of daily dosing.

Published studies in rodents report that oral acetaminophen treatment of male animals at doses that are 1.2 times the MHDD and greater (based on body surface comparison) result in decreased testicular weights, reduced spermatogenesis, reduced fertility, and reduced implantation sites in females given the same doses. These effects appear to increase with the duration of treatment.

In a published mouse study, oral administration of 50 mg/kg acetaminophen to pregnant mice from Gestation Day 7 to delivery (0.06 times the MHDD) reduced the number of primordial follicles in female offspring and reduced the percentage of full-term pregnancies and number of pups born to these females exposed to acetaminophen in utero.

In a published study, oral administration of 350 mg/kg acetaminophen to pregnant rats (0.9 times the MHDD) from Gestation Day 13 to 21 (dams), reduced the number of germ cells in the fetal ovary and decreased ovary weight and reduced the number of pups per litter in F1 females as well as reduced ovary weights in F2 females.

Promethazine

Daily doses of 25 mg/kg intraperitoneally have been found to produce fetal mortality in rats.

14 CLINICAL STUDIES

The efficacy and safety of HYDEXOR for the relief of moderate-to-severe pain while preventing opioid-induced nausea and vomiting (OINV) in patients deemed to be at high risk for OINV associated with hydrocodone-containing products was evaluated in two randomized, double-blind, multiple-dose, placebo- and active-controlled clinical trials, one in a bunionectomy population and one in a dental extraction population.

14.1 Bunionectomy Study – NCT02462811

A total of 552 patients who underwent bunionectomy surgery and experienced a sufficient degree of post-surgical pain the day following surgery (pain rated as moderate or severe plus a score of 4 or more on an 11-point numerical rating scale [0-10]) were randomized in a 5:5:1 ratio to receive either HYDEXOR, hydrocodone bitartrate 7.5 mg/acetaminophen 325 mg (HB/APAP) or a matched placebo, respectively. The objectives of the study were to evaluate the analgesic effect of HYDEXOR compared to placebo and to evaluate rates of OINV compared to hydrocodone bitartrate/acetaminophen.
This study attempted to enroll patients more likely to experience OINV by asking them if they had ever experienced nausea or vomiting following exposure to any opioid medication or if they experience nausea or vomiting in response to any of the following: the sight of blood, bad smell, when riding in a car, when riding backwards in a train, on a roller-coaster, when spun around, when bending over, when just thinking about it, or with headaches. Most patients (69%) reported nausea or vomiting following exposure to an opioid medication. The remaining patients (31%) were enrolled based on reporting nausea based on the other listed items (24%) or based on investigator discretion (7%).

The median age of patients in the study was 42 years old, 88% of patients were female, 88% white and 6% black or African American, 3% Asian, 0.7% Native Hawaiian or other Pacific Islander, and 0.5% American Indian or Alaska Native.

The analgesic effect was measured by a Summed Pain Intensity Difference over 48 hours of treatment (SPID48) on a 0-10 numerical rating scale. Patients receiving HYDEXOR had a statistically significantly higher SPID48 than patients receiving placebo. Baseline and hourly post-treatment pain intensity ratings over the 48-hour treatment observation period are shown for each treatment group in Figure # 1 #. Prevention of OINV was evaluated based on the percentage of patients with complete response (no vomiting or use of rescue antiemetic medication [indicative of nausea]). The results of the comparison between HYDEXOR and hydrocodone bitartrate/acetaminophen are shown in Table 3. Complete response rates were significantly greater for HYDEXOR than for hydrocodone bitartrate/acetaminophen.

Figure 1:
Table 2: Prevention of OINV efficacy results for the bunionectomy study.

<table>
<thead>
<tr>
<th>Bunionectomy study</th>
<th>HYDEXOR (N=252)</th>
<th>HB/APAP&lt;sup&gt;a&lt;/sup&gt; (N= 250)</th>
<th>Placebo (N= 50)</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OINV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Complete Response&lt;sup&gt;b&lt;/sup&gt; over 48 hours, n (%)</td>
<td>222 (88)</td>
<td>137 (55)</td>
<td>47 (94)</td>
<td></td>
</tr>
<tr>
<td>Difference in Complete Response, Hydexor vs HB/APAP (95% CI)</td>
<td></td>
<td></td>
<td>33 (26, 41)</td>
<td></td>
</tr>
<tr>
<td>Patients with no vomiting over 48 hours, n (%)</td>
<td>237 (94)</td>
<td>194 (78)</td>
<td>50 (100)</td>
<td></td>
</tr>
<tr>
<td>Patients with no rescue anti-emetic usage over 48 hours, n (%)</td>
<td>225 (89)</td>
<td>144 (58)</td>
<td>47 (94)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI: Confidence interval
<sup>a</sup> Hydrocodone bitartrate 7.5 mg/acetaminophen 325 mg
<sup>b</sup> Complete Response is defined as no vomiting episode and no use of rescue antiemetic medication in the 0 to 48 hours post randomization.
Study drug use and OINV (using the two-component complete response definition) by study day are summarized in Table 4. For the first 48 hours, patients were dosed on a fixed schedule every 4 to 6 hours followed by 3 days of as needed dosing.

Table 3: Summary of Study Drug Usage and OINV by Study Day

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Proportion of Patients with OINV (%)</th>
<th>Study Drug Usage, Expressed as Mean Number of Tablets</th>
<th>Proportion of Patients Using Study Drug (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HB/APAP</td>
<td>HYDEXOR</td>
<td>HB/APAP</td>
</tr>
<tr>
<td>1</td>
<td>32.0</td>
<td>8.3</td>
<td>4.12</td>
</tr>
<tr>
<td>2</td>
<td>36.0</td>
<td>7.9</td>
<td>4.33</td>
</tr>
<tr>
<td>3</td>
<td>22.4</td>
<td>6.4</td>
<td>3.70</td>
</tr>
<tr>
<td>4</td>
<td>8.0</td>
<td>0.8</td>
<td>2.39</td>
</tr>
<tr>
<td>5</td>
<td>6.4</td>
<td>1.2</td>
<td>2.04</td>
</tr>
</tbody>
</table>

a OINV was defined as any vomiting episode or use of rescue antiemetic medication on the calendar day of the study.

Although an OINV treatment effect for HYDEXOR appears to persist compared to hydrocodone bitartrate/acetaminophen over the five-day study period, most patients treated with hydrocodone bitartrate/acetaminophen did not develop OINV despite the trial having enrolled an enriched population more likely to experience OINV. Furthermore, the proportion of hydrocodone bitartrate/acetaminophen-treated patients experiencing OINV decreased over the study period at a faster rate than the proportion of patients using study drug, with only 6.4% of hydrocodone bitartrate/acetaminophen-treated patients developing OINV on Day 5. These data suggest that an antiemetic requirement does not persist in patients on continued opioid therapy who experienced OINV with initiation of the treatment.

14.2 Dental Study - NCT01780428

A total of 466 patients who underwent third molar removal and experienced a sufficient degree of post-surgical pain within four hours following surgery (pain rated as moderate or severe plus a pain score of 50 mm or more on a 100 mm visual analog scale) were randomized in a 4:4:1 ratio to receive either HYDEXOR, hydrocodone bitartrate 7.5 mg/acetaminophen 325 mg (HB/APAP) or a matched placebo, respectively. The objectives of the study were to evaluate the analgesic effect for HYDEXOR compared to placebo and to evaluate rates of OINV compared to hydrocodone bitartrate/acetaminophen.

This study attempted to enroll patients more likely to experience OINV using two different assessments. The first was a hydrocodone challenge where subjects were given a single dose of hydrocodone/acetaminophen and asked to report if they experienced any nausea or vomiting. The second was a survey where they were asked to report if they had ever experienced nausea or vomiting following exposure to any opioid medication or if they experience nausea or vomiting in response to any of the following: sight of blood, bad smell, when riding in a car, when riding backwards in a train, on a roller-coaster, when spun around, when bending over, when just thinking about it, or with headaches. The majority of patients in the study (79%) either reported nausea or vomiting following previous exposure to an opioid medication or reported nausea or vomiting on the hydrocodone challenge. The remaining patients (21%) were enrolled based on reporting nausea based on the other listed items (17%) or based on investigator discretion (5%).
The median age of patients in the study was 21 years old, 72% of patients were female, 80% white, 10% black or African American, 6% Asian, and 5% multi-racial or other races.

The analgesic effect was measured by a Summed Pain Intensity Difference over 24 hours of treatment (SPID24) based on a 0-3 categorical rating scale. Patients receiving HYDEXOR had a statistically significantly higher SPID24 than patients receiving placebo. [insert text] Baseline and hourly post-treatment pain intensity ratings over the 24-hour treatment observation period are shown for each treatment group in Figure 2. #. Prevention of OINV was evaluated based on the percentage of patients with complete response (no vomiting or use of rescue antiemetic medication [indicative of nausea]). The results of the comparison between HYDEXOR and hydrocodone bitartrate/acetaminophen are shown in Table 5. Complete response rates were significantly greater for HYDEXOR than for hydrocodone bitartrate/acetaminophen.

Figure 2:

Mean (SEM) Pain Intensity Ratings over 24 hours in CLCT-002

![Graph showing pain intensity ratings over 24 hours for HYDEXOR, Norco, and Placebo groups.]

SEM: Standard error of mean.
Table 4: Prevention of OINV efficacy results for the dental study.

<table>
<thead>
<tr>
<th>Dental study</th>
<th>HYDEXOR (N=211)</th>
<th>HB/APAPa (N=205)</th>
<th>Placebo (N=50)</th>
<th>Estimated Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OINV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with Complete Responseb over 48 hours, n (%)</td>
<td>187 (89)</td>
<td>140 (68)</td>
<td>48 (96)</td>
<td></td>
</tr>
<tr>
<td>Difference in Complete Response, Hydexor vs HB/APAP (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td>20.3 (12.2, 28.5)</td>
</tr>
<tr>
<td>Patients with no vomiting over 48 hours, n (%)</td>
<td>190 (90)</td>
<td>162 (79)</td>
<td>48 (96)</td>
<td></td>
</tr>
<tr>
<td>Patients with no rescue anti-emetic usage over 24 hours, n (%)</td>
<td>203 (96)</td>
<td>169 (82)</td>
<td>50 (100)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI: Confidence interval  

a Hydrocodone bitartrate 7.5 mg/acetaminophen 325 mg  
b Complete Response is defined as no vomiting episode and no use of rescue antiemetic medication in the 0 to 48 hours post randomization.  
c The study was not designed to compare the analgesic efficacy of HYDEXOR to hydrocodone bitartrate/acetaminophen.

The study drug usage and OINV by day in the dental study follow a similar trend as the bunionectomy study (Table 4). Although an OINV treatment effect for HYDEXOR appears to persist compared to hydrocodone bitartrate/acetaminophen over the five-day study period, the majority of patients treated with hydrocodone bitartrate/acetaminophen did not develop OINV despite the trial having enrolled an enriched population more likely to experience OINV. Furthermore, the proportion of hydrocodone bitartrate/acetaminophen-treated patients experiencing OINV decreased over the study period at a faster rate than does the proportion of patients using study drug, with only 2.54% of hydrocodone bitartrate/acetaminophen-treated patients developing OINV on Day 5. The data suggest that an antiemetic requirement does not persist in patients on continued opioid therapy who experienced OINV with initiation of the treatment.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

HYDEXOR is supplied as a white to off white, oval shaped, bi-layer tablet containing, hydrocodone bitartrate 7.5 mg, acetaminophen 325 mg and promethazine hydrochloride 12.5 mg. Each tablet is debossed with BC 147 on both sides and are packaged in bottles of 10 and 100 tablets.

<table>
<thead>
<tr>
<th>Bottle</th>
<th>NDC Number</th>
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<tbody>
<tr>
<td>10</td>
<td>72212-147-01</td>
</tr>
<tr>
<td>100</td>
<td>72212-147-10</td>
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</tbody>
</table>
16.2 Storage and Disposal

Store at 20°C - 25°C (68° - 77° F), excursions permitted to 15°C - 30°C (59°F - 86° F) [See USP Controlled Room Temperature]. Store in original container until dispensed, in a secure, limited access location, in accordance with institutional procedures for CII products.

Store HYDEXOR securely and dispose of properly [see Patient Counseling Information (17)].

17 PATIENT COUNSELING INFORMATION

Addiction, Abuse, and Misuse

Inform patients that the use of HYDEXOR, even when taken as recommended, can result in addiction, abuse, and misuse, which can lead to overdose and death [see Warnings and Precautions (5.1)]. Instruct patients not to share HYDEXOR with others and to take steps to protect HYDEXOR from theft or misuse.

Life-Threatening Respiratory Depression

Inform patients of the risk of life-threatening respiratory depression, including information that the risk is greatest when starting HYDEXOR or when the dosing frequency is increased, and that it can occur even at recommended dosages [see Warnings and Precautions (5.2)]. Advise patients how to recognize respiratory depression and to seek medical attention if breathing difficulties develop.

CNS Depression

Advise patients that HYDEXOR is not for use outside of the hospital due to the risk for drowsiness. Advise patients that HYDEXOR may cause marked drowsiness and may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. Advise patients to avoid alcohol and other CNS depressants as they may produce an additive CNS depression, when taken with HYDEXOR [see Warnings and Precautions (5.9) and Drug Interactions (7.1)].

Risks from Concomitant Use with Benzodiazepines or Other Central Nervous System Depressants

Inform patients that profound sedation, respiratory depression, coma, and death may result from the concomitant use of HYDEXOR with benzodiazepines or other central nervous system (CNS) depressants (e.g., non-benzodiazepines, sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, other opioids, alcohol). Because HYDEXOR contains both an opioid, hydrocodone, and phenothiazine, promethazine this risk is increased.

Hypotension

Inform patients that HYDEXOR may cause orthostatic hypotension and syncope. Instruct patients how to recognize symptoms of low blood pressure and how to reduce the risk of serious consequences should hypotension occur (e.g., sit or lie down, carefully rise from a sitting or lying position) [see Warnings and Precautions (5.11)].
Serotonin Syndrome
Inform patients that HYDEXOR could cause a rare but potentially life-threatening condition resulting from concomitant administration of serotonergic drugs. Warn patients of the symptoms of serotonin syndrome and to seek medical attention right away if symptoms develop. Instruct patients to inform their physicians if they are taking, or plan to take serotonergic medications. [see Drug Interactions (7.5)].

Adrenal Insufficiency
Inform patients that HYDEXOR could cause adrenal insufficiency, a potentially life-threatening condition. Adrenal insufficiency may present with non-specific symptoms and signs such as nausea, vomiting, anorexia, fatigue, weakness, dizziness, and low blood pressure. Advise patients to seek medical attention if they experience a constellation of these symptoms [see Warnings and Precautions (5.15)].

Anaphylaxis
Inform patients that anaphylaxis has been reported with ingredients contained in HYDEXOR. Advise patients how to recognize such a reaction and when to seek medical attention [see Contraindications (4)]

Pregnancy
Embryo-Fetal Toxicity
Inform female patients of reproductive potential that HYDEXOR can cause fetal harm and to inform the prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Lactation
Advise female patients not to breastfeed during treatment with HYDEXOR [see Use in Specific Populations (8.2)].

Involuntary Muscle Movements
Advise patients to report any involuntary muscle movements.

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