Testimony Before the FDA's Drug Safety and Risk Management & Anesthetic and Analgesic Drug Products Advisory Committees regarding

HYDEXOR

hydrocodone/acetaminophen/promethazine

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I have no financial conflicts of interest.

Today's main focus is to decide whether previous safety concerns would be adequately addressed through labeling/REMS?

- **Review of safety concerns from February 2018 AC Meeting**
- **Company response to the 19 to 2 AC vote against Hydexor approval, and FDA response to company's criticism**
- **Current FDA Comments**
- **Would the proposed labeling and REMS alter the inherent, previously documented harm/benefit ratio of Hydexor?**

Review of safety concerns from February 2018 AC Meeting

- **Most 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 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.**
- **The majority agreed that Hydexor poses greater risks than currently marketed hydrocodone-acetaminophen products. Some added that the proposed fixed-dose combination includes 7.5 mg of hydrocodone, which is higher than the usual starting dose of this drug.**

Review of safety concerns from February 2018 AC Meeting (cont'd)

- **Dr. Steve Maisel: "We're asking people to take a drug to prevent the side effect of another drug, but in itself is causing more side effects. And pretty soon we'll have another drug proposed to us that will mitigate the adverse effect of the second drug and so on. That's not the way to practice medicine or do business here. That's a very dangerous slope."**

Olas' response to the 19 to 2 AC vote against Hydexor approval as discussed in 7/19 FDA Letter to the company denying its appeal

"The negative vote was largely the result of a 'philosophical bias against fixed-dose combinations' and did not constitute a 'significant scientific development' with selected quotes of committee members who voted against approval. The quotes you provided…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… [S]elective highlighting of texts from the transcript can result in different conclusions on the rationale behind a vote… [F]inally, 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."

FDA Denial Letter (cont'd)

"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."

Current FDA Comments

From Director's memo for this meeting: "**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… [A]lthough the Phase 3 clinical trials were enriched to enroll a population at risk for OINV [opioid-induced nausea and vomiting], a substantial number of patients treated with the hydrocodone/acetaminophen comparator did not develop OINV."**

Can 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.

Would the proposed labeling and REMS alter the inherent, previously documented harm/benefit ratio of Hydexor?

<u>Labeling change</u>: The FDA accurately states: "We regulate drugs, not doctors." Even if companies do not violate prohibitions on off-label advertising, it is likely—if not certain—that off-label prescribing will occur, as with all opioids and many other drugs. Given the increased harms of adding promethazine and failure to 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, overuse is guaranteed.

Would the proposed labeling and REMS alter the inherent, previously documented harm/benefit ratio of Hydexor? (cont'd)

<u>Proposed REMS</u>—This optimistic program to mitigate risks has not been successful, as evaluated by the FDA for another opioid. During an August 3, 2018 meeting of your two committees, data presented by the FDA revealed the failure of the transmucosal immediate-release fentanyl (TIRF) REMS, the most rigorous such opioid REMS safety program created to date. The TIRF REMS was created to provide safe use of TIRF products by limiting prescribing of them to breakthrough pain in cancer patients, and to ensure that, because of the inherent risks of these potent drugs, only opioid-tolerant patients would be prescribed these products. Subsequent FDA analysis demonstrated that this REMS risk mitigation had been ineffective.

Summary

- **It is highly unlikely that previously documented safety concerns can be alleviated by more limited labeling and a REMS program.**
- **The combination of hydrocodone with another central nervous system depressant, promethazine, being prescribed for large numbers of people who will not get any benefit from promethazine, guarantees a serious risk of harm without any advantage for such patients.**
- **I am hopeful that your advisory committees, in coordination with the ever-increasing public health focus of the FDA, will make the right decision.**