PharmaNote®

Volume 29, Issue 10 July 2014

Albiglutide: A New Treatment Option for Type II Diabetes

Bibidh Subedi, PharmD Candidate

Type II Diabetes Mellitus (T2DM) is a metabolic disorder characterized by decrease in insulin production, development of insulin resistance, or both, that leads to higher levels of glucose in the blood. Approximately 8.3% of the US population is diagnosed with diabetes and approximately 90-95% of these are type II.[1] Uncontrolled T2DM can lead to further complications such as heart disease, stroke, kidney disease, nervous system disease, and eye problems.[1]

Several types of pharmacological treatments are available to treat T2DM. Mainstay treatment options include biguanides (i.e., metformin), sulfonylureas (e.g., glyburide), meglitinides (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), and insulin. Newer options include the incretin mimetics, glucagon-like peptide-1 (GLP-1) agonists (e.g., exenatide), dipeptidyl peptidase-4 inhibitors (e.g., sitagliptin), and sodium-glucose cotransporter 2 (SGLT2) inhibitors (e.g., canagliflozin).[2]

Albiglutide (Tanzeum®), manufactured by GlaxoSmithKline LLC, was granted an FDA-approved indication in April 2014 for the treatment of T2DM. This agent is a GLP-1 agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.[3] The objective of this article is to review the pharmacology, pharmacokinetics, pharmacodynamics, clinical trials, adverse effects, precautions, and dosing and administration of albiglutide.

Pharmacology

As T2DM advances, patients have diminished insulin concentrations and decreased postprandial GLP-1 induced insulin secretion. Albiglutide is a GLP-1 agonist that increases glucose-dependent insulin secretion and slows gastric emptying, leading to the reduction of peak glucose absorption.[3] Albiglutide lowers both fasting and postprandial glucose in patients with T2DM. Reduction in fasting plasma glucose is observed after a single dose and reduction in postprandial glucose is seen at around week 16 of continuous therapy.[3] A single 50 mg subcutaneous dose (maximum recommended dose) does not impair glucagon response to low glucose concentrations.[3] Additionally, this maximum dose does not prolong QTc interval to any clinically relevant extent.[3]

Albiglutide, administered subcutaneously at a 30-mg dose, reaches its maximum concentration between 3 and 5 days.[3] Steady state is achieved after 4-5 weeks of once-weekly administration.[3] Albiglutide is metabolized primarily in vascular endothelium via catabolism by ubiquitous proteolytic enzymes and excreted via the kidneys.[3] No

Inside This Issue:

pharmacokinetic data are available in patients ≤18 years of age. A drug-drug interaction has been noted with simvastatin: the C_{max} of simvastatin and its active metabolite are increased by approximately 18% and 98%, respectively, when administered concurrently with albiglutide.[3] The pharmacokinetic profile of albiglutide is summarized in **Table 1**.

Table 1 | Pharmacokinetics of albiglutide.[3]

Parameter	Changes Observed
Absorption	
C_{max}[a]	1.74 mcg/mL
AUC[a]	465 mcg·h/mL
Distribution (V_d)	11 L
Metabolism	Catabolized by proteolytic enzymes in vascular endothelium
Elimination	
Clearance	67 mL/h
$t_{1/2}$	5 days

[a]After a single 30-mg dose.
AUC = area under the curve.

Clinical Trials

Multiple clinical trials have assessed the efficacy and adverse effects of albiglutide (**Table 2**). Pratley, et al., evaluated the efficacy of albiglutide once weekly versus liraglutide once daily.[5] This trial was a randomized non-inferiority study that enrolled 841 patients ≥18 years of age with inadequately controlled T2DM and a BMI of 20 to 45 kg/m^2. Participants were administered either albiglutide 30 mg once weekly, titrated to 50 mg at week 6, or liraglutide 0.6 mg once daily, titrated to 1.2 mg at week 1 and 1.8 mg at week 2. The primary outcome was change in HbA1c from baseline at week 32 for albiglutide versus liraglutide, with a 95% confidence interval (CI) non-inferiority upper margin of 0.3%. The secondary outcomes were HbA1c change from baseline over time (at weeks 4, 6, 12, 18, 26, and 32), change in fasting plasma glucose from baseline over time, the proportion of patients meeting HbA1c treatment goals of below 7.0% and below 6.5%, time to hyperglycemia rescue, and change in bodyweight from baseline. The study was powered at 93% with a significance level of 0.025 in order to prove non-inferiority. Mean HbA1c was reduced by 0.78% (95% CI -0.87 to -0.69) in the albiglutide group and 0.99% (95% CI -1.80 to -0.90) in the liraglutide group. The authors concluded that once-daily liraglutide had greater reduction in HbA1c than once-weekly albiglutide, with a treatment difference of 0.21% (95% CI 0.08 to 0.34; non-inferiority p- value=0.0846). Hence albiglutide did not meet the prespecified non-inferiority margin. Although albiglutide did not appear non-inferior to liraglutide, it showed a clinically significant reduction in HbA1c at 32 weeks relative to baseline. These data suggest that albiglutide may be a suitable alternative to liraglutide for patients who are candidates for GLP-1 agonist treatment and cannot tolerate liraglutide. Injection site reactions occurred more frequently in albiglutide- versus liraglutide-treated participants (12.9% vs. 5.4%, respectively), whereas gastrointestinal events occurred more frequently in liraglutide- versus albiglutide-treated participants (49% vs. 35.9%, respectively).

Rosenstock, et al., evaluated the efficacy and adverse effects of albiglutide in regards to several different dosages.[6] They performed a randomized double-blind study in which 356 subjects diagnosed with T2DM were randomly assigned to subcutaneous placebo or albiglutide (weekly [4 mg, 15 mg, or 30 mg], biweekly [15 mg, 30 mg, or 50 mg], or monthly [50 mg or 100 mg]) or exenatide twice daily (5 µg twice daily for 4 weeks followed by 12 weeks of 10 µg twice daily) as an open-label active reference over 16 weeks of treatment followed by a 11-week washout period. The exenatide-treated subjects were eligible to participate if they were treated with metformin, whereas metformin was not required for albiglutide-treated subjects. The primary outcome measure was change in HbA1c from baseline at week 16. The HbA1c reduction was similar between 30 mg weekly, 50 mg biweekly, and 100 mg monthly (reductions of 0.87%, 0.79%, and 0.87%, respectively) and greater than that seen in the placebo group (0.17% reduction) and exenatide-treated participants (0.54% reduction). The difference in mean HbA1c reduction between the albiglutide treatment groups and the placebo group was statistically significant: 30 mg weekly resulted in a 0.62% reduction (p<0.003 vs. placebo); 50 mg biweekly, a 0.57% reduction (p<0.003 vs. placebo); and 100 mg monthly, a 0.60% reduction (p<0.002 vs. placebo). No statistical comparisons were con-

ducted between albiglutide and exenatide treatment groups. Weight loss was similar comparing all 3 albiglutide doses (1.1 to 1.7 kg total weight loss) and gastrointestinal adverse events occurred less frequently in the 30 mg weekly regimen compared with the 50 mg every two weeks or 100 mg monthly albiglutide regimens or exenatide. The authors of this study concluded that weekly albiglutide significantly improved glycemic control and caused weight loss with an adverse effect profile similar to or better than placebo or exenatide.[6]

Adverse Events & Precautions

The most common adverse effects with albiglutide were gastrointestinal in nature, including diarrhea, nausea, vomiting, gastroesophageal reflux disease, and dyspepsia. Injection site reactions, including hematoma, erythema, rash, hypersensitivity, and hemorrhage, also occurred in patients treated with albiglutide, although all were considered mild in severity. Hypoglycemia was minimal and most frequently seen when albiglutide was added to sulfonylurea or insulin.[3]

Table 3 summarizes adverse effects documented in ≥5% of patients treated with albiglutide.

Albiglutide is considered Pregnancy Category C and should not be used during pregnancy unless the expected benefit outweighs the potential risks. There are no adequate data to guide the use of albiglutide during lactation. Safety and effectiveness have not been established in pediatric patients ≤18 years of age.[3]

Dosing & Administration

Albiglutide is available in 30 mg and 50 mg subcutaneous injection doses. The recommended starting dose is 30 mg once weekly given as a subcutaneous injection in the abdomen, thigh, or upper arm region, at any time of the day without regard to meals. The dose may be titrated up to 50 mg once weekly if glycemic response is inadequate. Patients have up to 3 days to administer a dose if it is missed; afterwards, the dose should be skipped and the patient should administer the next usual dose. No dose adjustment is needed in patients with mild, moderate or severe renal impairment (eGFR 15-89 mL/min/1.73 m^2). Dose

Table 2 | Summary of albiglutide clinical trials.[3]

Study	Treatment Arms	Primary Endpoint	Results (% change in HbA1c)	Author's Conclusions
Pratley (2014)[5]	• Albiglutide 30 mg/week titrated to 50 mg at week 6 (n=422) • Liraglutide 0.6 mg/day titrated to 1.2 mg at week 1 and 1.8 mg at week 2 (n=419)	Change in HbA1c from baseline at week 32	• Albiglutide: -0.78% • Liraglutide: -0.99%	Once-daily liraglutide had greater reduction in HbA1c than once-weekly albiglutide
Rosenstock (2009)[6]	• Albiglutide weekly: ◆ 4 mg (n=36) ◆ 15 mg (n=35) ◆ 30 mg (n=31) • Albiglutide every 2 weeks: ◆ 15 mg (n=34) ◆ 30 mg (n=33) ◆ 50 mg (n=35) • Albiglutide monthly: ◆ 50 mg (n=35) ◆ 100 mg (n=35) • Exenatide 5 mcg twice daily for 4 weeks titrated to 10 mcg twice daily for 12 weeks (n=35) • Placebo (n=52)	Change in HbA1c from baseline at week 16	• Albiglutide: ◆ 30 mg weekly: -0.87% ◆ 50 mg every 2 weeks: -0.79% ◆ 100 mg monthly: -0.87% • Placebo: -0.17% • Exenatide: -0.54%	Weekly albiglutide significantly improved glycemic control with an adverse effect profile similar to or better than placebo or exenatide

Negative sign indicates reduction in HbA1c.

Table 3 | Adverse effects occurring in ≥5% of patients in albiglutide placebo-controlled trials.[3]

Adverse Effect	Albiglutide (n=923)	Placebo (n=468)
Injection site reaction	10.5	2.1
URTI	14.2	13.0
Diarrhea	13.1	10.5
Nausea	11.1	9.6
Cough	6.9	6.2
Back pain	6.7	5.8
Influenza	5.2	3.2
Arthralgia	6.6	6.4
Sinusitis	6.2	5.8

Data represent percent of patients experiencing the adverse event.
URTI = upper respiratory tract infection.

recommendations are not available for patients with eGFR <15 mL/min/1.73 m^2 due to lack of evidence. Hypoglycemia may occur when used in combination with sulfonylureas or insulin, therefore clinicians should consider lowering sulfonylurea or insulin dosage when starting albiglutide.[3]

Summary

Albiglutide is a new GLP-1 agonist with once-weekly dosing indicated for treatment of T2DM in adults. Currently available trial data suggest similar or better efficacy than exenatide twice daily, but modestly lower efficacy than liraglutide once daily. Adverse effects were generally similar between albiglutide and placebo with the exception of greater injection site reactions occurring in albiglutide-treated patients. As with other GLP-1 agonists, gastrointestinal adverse effects are relatively common. Albiglutide treatment should be initiated at 30 mg weekly and can be titrated up to 50 mg weekly if needed based on adequacy of HbA1c lowering. No dose adjustment is required for decreased renal function. The drug has not been studied in patients ≤18 years of age. Future studies are needed to further characterize the place of albiglutide among the GLP-1 agonists and other antidiabetic agents.

References

1. Diabetes Public Health Resource. Available at: http://www.cdc.gov/diabetes/pubs/factsheet11.htm?loc=diabetes-statistics. Accessed May 15, 2014.
2. American Diabetes Association: Standards of Medical Care in Diabetes-2014. Diabetes Care 2014; 37(Suppl 1):S14-S80.
3. Tanzeum® [package insert]. Wilmington, DE: GlaxoSmithKline LLC; 2014.
4. Diabetes Basics. Available at: http://www.diabetes.org/diabetes-basics/. Accessed May 15, 2014.
5. Pratley, RE, Nauck MA, Barnett AH, et al. Once-weekly albiglutide versus once-daily liraglutide in patients with type 2 diabetes inadequately controlled on oral drugs (HARMONY 7): A randomized, open-label, multicentre, non-inferiority phase 3 study. Lancet Diabetes Endocrinol 2014;2(4):289-97.
6. Rosenstock, J, Reusch J, Bush M, et al. Potential of albiglutide, a long-acting GLP-1 receptor agonist, in type 2 diabetes: A randomized controlled trial exploring weekly, biweekly, and monthly dosing. Diabetes Care 2009;32 (10):1880-6.

Zohydro®: Extended-release Hydrocodone: A Review

Danielle Cheek, PharmD Candidate

Chronic pain is a debilitating condition affecting over 100 million Americans, or approximately one-third of America's adult population. The annual cost, in 2010, of chronic pain in the United States, including medical costs and costs related to disability, lost wages, and productivity was approximately $600 billion dollars.[1] Opioids are one of the most widely used treatments for pain. Because of their high abuse potential, opioids are often combined with nonopioids to allow for lower opioid consumption — a so-called "opioid-sparing" strategy.[2] One very common example of an opioid/nonopioid combination is hydrocodone/acetaminophen (Vicodin®, Lortab®). This medication has been the most commonly prescribed drug since 1997.[3-5] One concern, is that the nonopioid component, acetaminophen, can be highly toxic if taken in high quanti-

ties. In some instances, high acetaminophen doses may lead to serious liver damage or death. Despite efforts being taken to reduce acetaminophen toxicity, it continues to be a concern.[5] For this reason, many have considered the need for a formulation containing hydrocodone alone.

On October 25, 2013, hydrocodone extended-release (HC-ER), marketed under the brand name Zohydro ER®, was granted an FDA-approved indication for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which alternative treatment options are inadequate.[6] HC-ER is an extended release, single entity hydrocodone product formulated by Zogenix.[7] This article will outline the pharmacology and pharmacokinetics, clinical trials, adverse effects, dosing and administration, use in special populations, cost, and controversies surrounding the FDA approval of HC-ER.

Pharmacology/Pharmacokinetics

Hydrocodone is a semi-synthetic opioid agonist that is relatively selective for mu-opioid receptors; however, at higher doses it may interact with other opioid receptors. Hydrocodone acts as an analgesic by binding to opioid receptors in the peri-aquaductal and peri-ventricular gray matter, the ventro-medial medulla and the spinal cord.

HC-ER is primarily metabolized into norhydrocodone via CYP3A4 mediated N-demethylation. Therefore coadministration with drugs inhibiting CYP3A4 may cause increased hydrocodone plasma concentration and increase the risk of respiratory depression and sedation. To a lesser extent, hydrocodone is metabolized via CYP2D6 mediated O-demethylation into hydromorphone which may contribute to it's analgesic effect. Hydrocodone and its metabolized are eliminated primarily in the kidneys. Patients with -to-moderate hepatic dysfunction will not require dosage adjustment, but those with severe hepatic dysfunction or renal impairment should be initiated at the lowest dose of 10 mg and monitored closely for adverse events such as respiratory depression and sedation.[6]

Unlike conventional hydrocodone combination products, HC-ER was formulated with a prolonged absorption allowing for a longer duration of action. Peak plasma concentration occurs ~5 hours after administration. Food has a limited effect on the extent of absorption, but a 27% increase in peak plasma concentration was observed when HC-ER was administered with a high fat meal. The extent of plasma protein binding is unknown; however, HC-ER likely exhibits similar protein binding as other opioids and is believed to fall within the range 19% to 45%, similar to hydromorphone and oxycodone respectively.[6]

Clinical Trials

The safety and efficacy of HC-ER was evaluated in a randomized, double blind, placebo-controlled, multicenter, phase 3 clinical trial.[8] The study consisted of a screening phase (≤2 weeks) an open-label conversion/titration phase (≤6 weeks), and a treatment phase (12 weeks), followed by a follow-up phone call 2 weeks after treatment phase completion. Inclusion was limited to males and nonpregnant, nonlactating females, aged 18-75 years, with moderate-to-severe chronic low back pain (CLBP) for ≥3 months. Participants were required to be candidates for around-the-clock opioid therapy, with an average pain score of ≥4 on the Numeric Rating Scale (NRS) in the past 4 weeks. Participants must have been using opioids equivalent to ≥30 mg of hydrocodone (≥45 mg of oral morphine) at least 5 days per week for the past 4 weeks. Participants were excluded from the study if they had a clinically significant condition that could interfere with pain assessment or increase the risk of treatment related adverse events, any chronic pain condition other than CLBP, a history of opioid abuse, a score of > 12 on the depression or anxiety subscales of the Hospital Anxiety and Depression Scale, or a history of major depressive disorder which was poorly controlled with medication.[8]

Participants were switched from their current opioid to a starting dose of HC-ER equivalent to 20% to 30% lower than their current opioid medication (refer to **Table 1** for conversion). During the conversion/titration phase of the study, patients were allowed to use 1-2 tablets every 4-6 hours of hydrocodone bitartrate 5 mg/ acetaminophen 500 mg for breakthrough pain. For participants whose pain was not well controlled at their given dose, HC-ER was titrated up by 10 mg per dose (or 20 mg per day) every 3-7

days until the patient was stabilized or until they were taking 200 mg/day.[8]

Patients were required to be stabilized on a HC-ER dose between 20 and 100 mg twice daily before they could be entered into the treatment phase. Of the 510 patients enrolled at the beginning of the study, 302 met these requirements and were selected to continue with the trial. These patients were then randomized to receive either HC-ER at their current dose or placebo. Those assigned to placebo were tapered off HC-ER over 2-10 days in a blinded fashion. Patients were allowed to use 2 doses per day of hydrocodone bitartrate 5 mg/acetaminophen 500 mg for breakthrough pain during the treatment phase.[8]

The primary efficacy endpoint was a change from baseline until the last day of treatment in average pain intensity (PI) on the 11-NRS pain scale. Secondary endpoints included response rates at 30% improvement level, 50% improvement level, subject global assessment of medication (SGAM) ratings, additional NRS measures for pain, use of rescue medication, Oswestry Disability Inventory scores, safety, and tolerability.[8]

Among the 510 subjects in the conversion titration phase, average age was 49 years, 54% were women, 79% were white, and the average pain score was 7 out of 10 at baseline.[8] In the treatment phase, the baseline demographics were similar between both the HC-ER group and the placebo group in the areas of age, race, BMI, average PI score at screening (before titration), prestudy opioid usage, and baseline average PI score (after titration). However, sex distribution between the groups varied, with a proportion of women in the HC-ER group (61.6%) versus the placebo group (49%; p=0.028).[8]

Table 1 | Conversion factor for oral opioids to HC-ER.[7]

Prior Oral Opioid	Approximate Oral Conversion Factor
Hydrocodone	1
Oxycodone	1
Methadone	1
Oxymorphone	2
Hydromorphone	2.67
Morphine	0.67
Codeine	0.10

Note: This table does not indicate equianalgesic dosing and therefore should not be used to convert from HC-ER to other opioids.

The authors concluded that HC-ER was significantly better than placebo in the areas of change in average PI of the 11-NRS pain scale, 30% improvement level, Subject Global Assessment of Medication (SGAM) score, 50% improvement level, Increase in Average Pain Intensity Score, and rescue medication use. Details of the primary and secondary endpoints are summarized in **Table 2**. HC-ER did not show a significant benefit in comparison to placebo in the Oswestry Disability Inventory scores.[8]

Adverse Reactions

In a Phase 3 efficacy and safety study, the most common adverse events occurring with HC-ER were constipation, nausea, somnolence, vomiting, and urinary tract infections.[8] In a phase 3 long-term safety study, the most common adverse events were constipation, nausea, back pain, vomiting, arthralgia, headache, urinary tract infections, fall, upper respiratory tract infections, nasopharyngitis, anxiety, sinusitis, and insomnia.[10] The most common adverse events seen in both studies

Table 2 | Primary and secondary endpoints in a phase 3 efficacy and safety study of HC-ER.[8]

Treatment Group (N)	Change in average NRS PI scores (mean ± SD)	Achieved ≥30% Improvement	SGAM score	Achieved ≥50% Improvement	Increase in Average Pain Intensity Score (mean ± SD)	Rescue Medication Use (mean ± SD)	ODI
Placebo (n=151)	0.96 ± 1.55	31%	0	23%	0.83 ±1.84	7.5 ± 3.9	57.6
HC-ER (n=151)	0.48 (± 1.56)*	68**	0.8**	48**	1.68 (±2.12)**	6.0 (±3.4)	53.2†

Table compares date of screening to Day 85.
*p<0.01 for comparison between groups.
**p<0.001 for comparison between groups.
†p<0.05 for comparison between groups.
NRS = Numeric Rating Scale; **SGAM =** Subject Global Assessment of Medication; **ODI =** Oswestry Disability Inventory; **PI =** pain intensity.

Table 3 | Treatment-emergent adverse events (TEAEs) that occurred in ≥5% of patients.[8,10]

Adverse Event	During Open-Labeled Titration Period in Phase 3 Study	During the Double-Blind Treatment Period in Phase 3 Study	During Conversion/Titration Phase in Safety Study	During the Treatment Phase in Safety Study	Increase in Average Pain Intensity Score
	Treatment				
	HC-ER (n=510)	HC-ER (n=151)	Placebo (n=151)	HC-ER (n=638)	HC-ER (n=424)
Constipation	56 (11)	12 (8)	0 (0)	72 (11.3)	53 (12.5)
Nausea	50 (10)	11 (7)	5 (3)	68 (10.7)	42 (9.9)
Somnolence	24 (5)	1 (1)	0 (0)	49 (7.7)	18 (4.2)
Headache	19 (4)	0 (0)	2 (1)	48 (7.5)	29 (6.8)
Vomiting	14 (3)	7 (5)	1 (1)	26 (4.1)	41 (9.7)
URTI	7 (1)	5 (3)	1 (1)	7 (1.1)	25 (5.9)
UTI	4 (1)	8 (5)	3 (2)	6 (0.9)	28 (6.6)
Back Pain	4 (1)	6 (4)	5 (3)	9 (1.4)	47 (11.1)
Arthralgia	NR	NR	NR	9 (1.4)	33 (7.8)
Fall	NR	NR	NR	8 (1.3)	25 (5.9)
Nasopharyngitis	NR	NR	NR	11 (1.7)	24 (5.7)
Anxiety	NR	NR	NR	8 (1.3)	23 (5.4)
Sinusitis	NR	NR	NR	9 (1.4)	23 (5.4)
Insomnia	NR	NR	NR	24 (3.8)	21 (5.0)

Data represent n (%).
NR = data not reported; **URI =** upper respiratory tract infection; **UTI =** urinary tract infection

are summarized in **Table 3**. Both trials suggest HC-ER has a similar side effect profile as other opioid analgesics.

Dosing & Administration

Zohydro ER® is to be taken orally, and is available as 10, 20, 30, 40, and 50 mg extended-release tablets. The recommended starting dose should be individualized based on patient factors. Elderly patients, those with concomitant diseases, or hepatic or renal dysfunction, should be started on lower doses. In patients with risk factors for addiction, abuse, and misuse, this medication should only be used if alternate treatment options are ineffective, not tolerated, or insufficient for managing pain. Most opioid naïve patients should be started on 10 mg every 12 hours. In phase 3 clinical trials, **Table 1** was used to convert patients from previous opioids to Zohydro ER®. This table does not represent equailanalgesic dosing and has not been approved to convert from Zohydro ER® to other opioids.[7]

Special Populations

The safety and efficacy of HC-ER has not been well established in pediatric populations, pregnant women, or nursing mothers. HC-ER has been classified as a pregnancy category C. There are no well-controlled studies in pregnant women, and animal studies have only showed fetal malformations at doses of 15 times an equivalent human dose. Nonetheless, HC-ER should only be used in these populations if the benefit outweighs the risk.[7]

Clinical studies did not include enough subjects over the age of 65 to determine if they would respond differently to HC-ER than younger patients. However, the elderly are more susceptible to side effects of hydrocodone such as confusion, sedation, and respiratory depression. Therefore, geriatric patients should be initiated on a low dose and closely observed for adverse events.[7]

Cost

The average price for Zohydro ER® is approximately $428.30 for a 30-day retail supply. Cost varies based on pharmacy and dose and may range from approximately $375.73 to $472.54 (**Table 4**).[9]

Controversy

Since its FDA approval, Zohydro ER® has sparked considerable controversy in the medical community. Despite FDA advisory council voting

11-2 not to release Zohydro ER®, the FDA did grant the agent an approved indication for pain.[11] Acetaminophen toxicity scares have been a leading reason for Zohydro's approval. Hydrocodone/acetaminophen combination products have been reformulated to include lower doses of the acetaminophen. The manufacturer claims that Zohydro ER®'s acetaminophen-free formulation offers a distinct advantage to patients with liver disease who may be unable to tolerate long-term use of hydrocodone/acetaminophen combination products.[12] However, many argue, that while removing acetaminophen from these combination products will certainly decrease their potential for liver toxicity, HC-ER comes with its own risks. For one, unlike many extended-release opioid formulations, Zohydro ER® is not formulated with abuse-deterrent properties. This has been a great concern to many, including the state of Massachusetts, who has banned the sale of Zohydro ER® until it has been formulated to be crush-resistant.[13] Lack of abused-deterrent properties, along with its increased mg per tablet strength, and abuse potential has led many health care professionals to request the FDA pull Zohydro ER® off the market. Another plea came in the form of a letter signed by the attorneys general of 29 states. They petitioned the FDA to reconsider their approval of Zohydro ER until it could be reformulated with abuse-deterrent properties.[14] This letter was soon followed by another letter signed by 40 individuals from the Fed-Up Coalition Steering Committee comprised of doctors, abuse experts, and public health officials with similar concerns of Zohydro ER® and its threat to public safety.[15]

Summary

Zohydro ER® is the first single-entity hydrocodone approved by the FDA. Despite its similarity to other opioids, it has only been granted an approved indication for treatment in patient's requiring around-the-clock opioid therapy for which other treatment options are unavailable. In a phase 3 clinical trial, it was shown to be more effective than placebo at controlling pain. Its adverse effects are similar to other opioids with constipation, nausea, and somnolence being the most significant. Due to its high abuse potential and overdose risk, it has sparked much controversy since its approval.

References

1. Institute of Medicine Report from the Committee on Advancing Pain Research, Care, and Education: *Relieving Pain in America, A Blueprint for Transforming Prevention, Care, Education and Research*. The National Academies Press, 2011.
2. Berry, Patricia, Jeffrey Katz, et al, ed. *Pain: Current Understanding of Assessment, Management, and Treatments*. 2001. Web. 23 Mar. 2014.
3. IMS Health, National Prescription Audit, Dec 2012
4. IMS Health, IMS National Sales Perspectives TM, Year 2005, Extracted 9/06.
5. U.S. Food and Drug Administration. *Acetaminophen Overdose and Liver Injury — Background and Options for Reducing Injury* . 2009. Web.
6. Zohydro ER (hydrocodone bitartrate) package insert. San Diego, CA: Zogenix Inc.; 2013 Oct.
7. United States Food and Drug Administration. *FDA News Release*. Silver Springs, MD: , 2013. Web. Accessed 2014, March, 09)
8. Rauck RL, Nalamachu S, Wild JE, Walker GS, Robinson CY, Davis CS, Farr SJ. Single-Entity Hydrocodone Extended-Release Capsules in Opioid-Tolerant Subjects with Moderate-to-Severe Chronic Low Back Pain: A Randomized

Table 4 | Cost of 30-day retail supply of Zohydro ER®.[9]

Strength	Walgreeens	Walmart	CVS	Mean	Range
10 mg	$387.71	$375.73	$379.19	$380.87	$375.73 - $387.71
20 mg	$426.86	$413.75	$417.44	$419.22	$413.75 - $426.86
30 mg	$439.91	$426.42	$430.19	$432.17	$426.42 - $439.91
40 mg	$452.96	$439.10	$442.94	$445.00	$439.96 - $452.96
50 mg	$472.54	$458.11	$462.06	$464.24	$458.11 - $472.54

Double-Blind, Placebo-Controlled Study. Pain Med. 2014 Feb 12. doi: 10.1111/pme.12377. [Epub ahead of print] PubMed PMID: 24517082.
9. "Zohydro ER." Accessed.*GoodRx.* Web. 28 Mar 2014.
10. Rauck RL, Hale ME, Nalamachu S, Robinson CY, Farr SJ, Single-entity Hydrocodone extended release for chronic pain. Poster presented at: 23rd Annual Clinical Meeting of the American Academy of Pain Management (AAPM); September 20-23, 2012; Phoenix, Ariz.
11. Azad, Sonia, dir. "New painkiller Zohydro ER comes with big controversy." ABC Local News: KTRK-TV, Houston, Texas, 20 Mar 2014. Web. 23 Mar 2014.
12. Jakobson Ramin, Cathryn. "Why Did the F.D.A. Approve a New Pain Drug?." *New Yorker*. 03 Dec 2013: n. page. Web. 23 Mar. 2014.
13. Andersen, Travis. "State says it can ban painkiller Zohydro." *Boston Globe* [Boston] 12 Apr 2014, n. pag. Web. 12 Apr. 2014
14. Jeffrey, Susan. "Attorneys General Ask FDA to Rethink Zohydro ER Approval." (2013): n.pag. *Medscape*. Web. 23 Mar 2014.
15. Alexander, Caleb, Carol Bowman, et al. "New Drug Application NDA 202880, Zohydro ER." *Fed Up! Coalition Steering Committee*.

Clinical Trial Update

Nonsteroidal Anti-Inflammatory Drugs and Cardiovascular Outcomes in Women: Results from the Women's Health Initiative (Circ Cardiovasc Qual Outcomes. 2014;7:603-610.)

Nonsteroidal anti-inflammatory drugs (NSAIDs) all carry a warning for increased cardiovascular (CV) events. This warning is primarily based on observational data and has been seen most among agents that are relatively more COX-2 selective (i.e., celecoxib, diclofenac). Based on other observational data and meta-analyses, naproxen has generally been considered to have the least harmful CV profile.

This study examined data from 161,808 postmenopausal women aged 50 to 79 years in the Women's Health Initiative (WHI) from 1993 to 1998. The study sought to assess CV risk associated with NSAID use and adjusted for CV risk factors. The primary outcome was CV mortality, nonfatal MI, or nonfatal stroke.

Key findings:

Agent	Adjusted Hazard Ratios
Any NSAID	1.10 (95% CI, 1.06–1.15; P<0.001)
Celecoxib-only	1.13 (95% CI, 1.01–1.27; P=0.031)
Naproxen-only	1.22 (95% CI, 1.12–1.34; P<0.001)
Ibuprofen-only	1.00 (95% CI, 0.93–1.07; P=0.996)

One of the limiting factors of this study is that NSAID dosage was not available. The authors hypothesis that differing doses could be responsible for the disparate finding relating to naproxen safety. The authors state that the most likely dosage used in WHI patients was 220 mg twice daily, and that the higher dose, 500 mg twice daily, has a greater potential to inhibit platelet activity via a mechanism similar to aspirin, potentially resulting relatively less CV risk.

While this study is not conclusive, it highlights that any NSAID may have the potential to cause harm and the importance of limiting NSAID use as possible, especially in patients at risk for cardiovascular events.

UPCOMMING ARTICLES:

Dalbavancin: A Novel Treatment for Acute Bacterial Skin and Skin-Structure Infections

Tedizolid Phosphate: A New Antimicrobial Agent Against MRSA

The PharmaNote is Published by:
The Department of Pharmacy Services, UF Family Practice Residency Program, Departments of Community Health and Family Medicine and Pharmacotherapy and Translational Research University of Florida

John G. Gums, PharmD, FCCP	Editor-in-chief
Steve Smith, PharmD, MPH, BCPS	Editor
R. Whit Curry, MD	Associate Editor
Nicholas Carris PharmD, BCPS	Assistant Editor