



# The Pharmacist Activist

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Editorial

## Hydrocodone, Zohydro ER, Pain Relief, Addiction, and Death— What Are Our Priorities?

**F**ollowing decades of debate, the Drug Enforcement Administration (DEA), on August 22, published in the Federal Register its Final Rule that moves hydrocodone combination products (HCPs) from Schedule III to Schedule II. The debate of this question has been particularly intensive during the past year. The DEA received 573 comments on the proposed rule to schedule HCPs from a wide range of organizations of health professionals, government agencies, patient advocates, and individuals. And this followed a process conducted by the Food and Drug Administration (FDA) in which 768 comments were submitted. The Final Rule occupies 22 pages in the Federal Register and can be summarized in the statement, “Hydrocodone combination products are now in Schedule II.” The national pharmacy organizations demonstrated self-inflicted impotence by supporting both possibilities—1) continued placement of HCPs in Schedule III and 2) moving them to Schedule II.

My initial response to this situation is this: WHAT A WASTE of time, expertise, effort, and resources! The only consolation is that the best decision was made—HCPs should be in Schedule II. However, I contend that this decision could have been made by addressing just 2 questions that can be answered in less than 2 minutes, rather than the more than 2 decades that it has taken. The two questions are the following:

- 1) **When comparing HCPs and oxycodone combination products (OCPs), is there a clinically important difference in their analgesic effectiveness, and in their potential/risk for causing dependence, addiction, and death?**

It is my expectation that “No” would be the almost unanimous response to this question. If you respond “Yes,” please provide me with the information to support that response so that I may learn more.

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Assuming almost complete agreement that HCPs and OCPs have very similar properties, actions, and risks, it seems logical to expect that these products should be in the same Schedule of the Controlled Substances Act, rather than continue their classification in Schedules III and II, respectively. That brings us to the second question:

**2) Should these two very similar groups of products be placed in the more restrictive Schedule II or the less restrictive Schedule III?**

In view of the extensive abuse and the very large number of deaths resulting from overdoses of these products, I would anticipate that there would be almost complete agreement that the products be classified in Schedule II.

### **Zohydro ER**

Zohydro ER is an extended-release formulation of hydrocodone as a single agent that is classified in Schedule II. The approval of this product by the FDA earlier this year sparked an outcry of concern and predictions that it would be widely abused because of the larger amount of hydrocodone included because the extended-release formulation is administered less frequently, and that the formulation is not “abuse-deterrent.” Some have demanded that such formulations must be abuse-deterrent so that the risks of addiction and overdose deaths can be reduced. However, the extent to which these formulations deter abuse is often misunderstood and the rhetoric often obscures attention to even more important issues. I would suggest that the most important question to be asked about Zohydro ER is:

**Does Zohydro ER provide any advantage for patients experiencing severe pain that can't be provided by morphine extended-release or oxycodone extended-release formulations?**

I will defend the right of the company (in this case Zogenix) to develop a formulation, conduct clinical studies, and request and receive approval from the FDA to market Zohydro ER in a formulation that is not abuse-deterrent. However, I also exercise my right

to conclude and provide my opinion that Zohydro ER has no advantage over similar available products and there is not a need to prescribe it.

### **Different opinions are well-intentioned**

Although I do not agree with certain of the opinions that have been voiced regarding the scheduling of HCPs and the availability of Zohydro ER, I respect the fact that these positions are well-intentioned. The position that the HCPs should continue to be classified in Schedule III is based on the concern that patients with needs for these medications will have greater difficulty in obtaining them on a timely basis if they were placed in Schedule II. Those with concerns that the Zohydro ER formulation is not abuse-deterrent are trying to avoid an even larger number of overdose tragedies with these products.

The debate and rhetoric regarding certain of the pertinent issues delay or prevent us from identifying strategies that offer the hope of greater effectiveness. We should first respond by agreeing that 1) many patients suffer from severe pain that can be managed more effectively and 2) much more must be done to prevent drug abuse and overdose deaths. We can agree further that our highest priority should be to relieve pain experienced by patients to the extent possible.

### **Better strategies are needed**

In recent years there has been a proliferation of new products containing an opioid analgesic. Confusion and numerous errors have occurred because of differences among products, questions regarding equivalency of dosages when switching or adding products, etc. Valid questions exist as to whether the new products offer any advantage over previous options. As one example, do extended-release formulations of hydrocodone and oxycodone have any advantages over extended-release formulations of morphine that could not be effectively addressed by closer monitoring and dosage adjustment of the morphine-containing formulation? I do not think so. Are we ready for a recommendation (and formulary

*(Continued on Page 4)*

# New Drug Review

## Albiglutide (Tanzeum – GlaxoSmithKline)

### Antidiabetic Agent

**New Drug Comparison  
Rating (NDCR) = 3**

*(no or minor advantages/  
disadvantages)  
in a scale of 1 to 5 with 5  
being the highest rating*

#### Indication:

Administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

#### Comparable drugs:

Exenatide (Byetta), exenatide extended-release (Bydureon), liraglutide (Victoza).

#### Advantages:

- Less frequent administration (once a week; compared with liraglutide [once a day] and exenatide [twice a day]; exenatide extended-release is also administered once a week).

#### Disadvantages:

- Less reduction in glycosylated hemoglobin (HbA1c) and fasting plasma glucose (FPG) (compared with liraglutide; comparative studies with exenatide have not been conducted);
- Less weight loss (compared with liraglutide);
- More likely to cause injection site reactions (compared with exenatide and liraglutide);
- Formulation requires reconstitution (compared with exenatide and liraglutide; exenatide extended-release also requires reconstitution).

#### Most important risks/adverse events:

Thyroid C-cell tumors have been reported in rodents (boxed warning; contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with Multiple Endocrine Neoplasia syndrome type 2); pancreatitis (treatment should be discontinued if pancreatitis is suspected; other antidiabetic therapies should be considered in patients with a history of pancreatitis); hypersensitivity reactions; hypoglycemia (when used concomitantly with insulin or an insulin secretagogue [e.g., a sulfonylurea]); risk in patients with severe gastrointestinal disease including severe gastroparesis (use is not recommended in patients with pre-existing severe GI disease; renal function should be monitored in patients with renal impairment experiencing severe GI adverse events); slows gastric emptying and may alter absorption of concomitantly administered oral medications.

#### Most common adverse events:

Upper respiratory tract infection (14%), diarrhea (13%), nausea (11%), injection-site reaction (11%).

#### Usual dosage:

Administered subcutaneously in the abdomen, thigh, or upper arm; 30 mg once a week on the same day each week; dosage may be increased to 50 mg once a week if the glycemic response is not adequate; if a dose is missed, the patient should administer it as soon as possible within 3 days after the missed dose; thereafter, doses should be administered on the usual day of administration.

#### Products:

Pen-injectors – 30 mg, 50 mg of lyophilized powder that is reconstituted with diluent included in the pen device (should be stored in a refrigerator).

#### Comments:

Albiglutide is the third glucagon-like peptide-1 (GLP-1) receptor agonist, joining exenatide (marketed initially in an immediate-release formulation and subsequently in an additional extended-release formulation) and liraglutide. The new drug is a recombinant fusion protein comprised of two tandem copies of modified human GLP-1 genetically fused in tandem to human albumin. A human GLP-1 fragment sequence has been modified to confer resistance to dipeptidyl peptidase 4 (DPP-4) mediated proteolysis. The human albumin moiety of the protein, together with the DPP-4 resistance, provides a longer half-life that permits administration of doses just once a week.

The effectiveness of albiglutide was demonstrated in 8 clinical trials that included more than 2,000 patients with type 2 diabetes. Albiglutide was evaluated as a stand-alone therapy, as well as in combination with metformin, glimepiride, pioglitazone, or insulin (but not prandial insulin). Its use resulted in reduction of HbA1c and FPG concentrations. In a study in which albiglutide was compared with liraglutide, the new drug provided less of an HbA1c reduction (0.8%) than liraglutide (1.0%), and the between-treatment difference did not meet the pre-specified, non-inferiority margin.

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restrictions) that morphine be identified as the opioid analgesic of first choice and that other opioids only be considered when efforts to use a morphine-containing formulation have not provided optimum pain relief and safety? In addition to morphine, I would include fentanyl as a choice, primarily to increase options with respect to routes of administration.

The education of health professionals regarding pain management includes coverage of many different but very similar opioids and their formulations. However, this may result in insufficient attention being devoted to the principles of pain management and strategies to use analgesics as safely and as effectively as possible. It is better to learn how to use one or two of these agents very well than to have just adequate knowledge about all of them.

Because of the concerns relating to the abuse of opioids, some patients with severe pain associated with cancer and other medical problems have encountered difficulties and/or delays in obtaining prescriptions for analgesics. There is an unacceptable irony that some patients with important medical needs can experience suspicion and denial or delay in obtaining a prescription for an opioid analgesic, whereas drug abusers can quickly purchase heroin that is not legally available.

## Drug abuse and overdose deaths

Pharmacists, physicians, and other health professionals have no control over the access to and use of drugs that are smuggled into the country or obtained through illicit channels. However, a substantial percentage of the supply of medications that have been abused and have been the cause of overdose deaths have been prescribed by physicians and dispensed by pharmacists.

The professions of pharmacy and medicine have traditionally deferred to legislators, government agencies, insurance companies, and healthcare benefit programs to establish laws, policies, and procedures that will assure the integrity of the drug prescribing and distribution system. The current system has failed to deter the experimentation and abuse of drugs, and the number of overdose deaths has sharply increased.

I do not have the answers for the dilemma of drug abuse that faces our health professions and society. However, I am confident that within pharmacy and the other health professions we have individuals who have the abilities, ideas, and experience to design a program/system that will be much more effective in preventing drug abuse than our present systems. Our health professions must accept much greater responsibility for the part of the drug distribution and use system for which we have control. We must make it clear to health care professionals that intentional betrayal of patients, society, and our professions with respect to matters associated with drug abuse will not be tolerated. The consequences will be license revocation and a prison sentence.

In a positive direction, our health professions organizations must identify and convene members who are best prepared to contribute expertise and ideas in the establishment of a program/system that will be more effective in preventing/reducing drug abuse. This can't be an initiative that is dependent on the extent to which participants can serve as volunteers. They should be compensated for their expertise and time. With respect to the outcomes and benefits anticipated, it will be the best investment our professions can make.

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