Generic Insulin, HGH Approval Guidelines Sought

BY JOYCE FRIEDEN
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The Food and Drug Administration plans to hold off on issuing approval guidelines for generic insulin and human growth hormones, despite pressure from congressional leaders.

Instead, the agency will offer broader guidance on follow-on proteins in general, Patrick Rowan, FDA associate commissioner for legislation, wrote to Sen. Orrin Hatch (R-Utah) and Rep. Henry Waxman (D-Calif.), in response to their letter.

"FDA expects that this approach will provide useful guidance to the industry, while ensuring that we do not stifle innovation and the utilization of state-of-the-art technologies," Mr. Rowan wrote. "FDA's consideration of regulatory requirements for these products has not stalled and … we are moving ahead as quickly as resources will allow." He pointed out that the agency already has approved several follow-on protein products that meet FDA criteria, including human recombinant hyaluronidase (Hylenex), calcitonin-salmon recombinant (Fortical Nasal Spray), and glucagon recombinant (GlucaGen).

In their letter, Sen. Hatch and Rep. Waxman noted that the agency has been working on guidance documents for generic insulin and human growth hormone for 4 years.

"In 2002, FDA officials drafted guidance documents providing the requirements for approval of generic forms of insulin and human growth hormone," they wrote. "Since that time, the agency has held public workshops and public meetings on various issues pertaining to generic biologics, but it apparently decided to defer the release of the guidance documents for insulin and HGH until it had resolved issues pertaining to the entire class of biologics.

'It is time for FDA to clarify what data it will require that manufacturers provide when seeking to market a generic insulin or HGH product.'

"Now, several years later, the effort to develop the appropriate regulatory requirements for generic biologics appears to be at a complete standstill," the legislators wrote. "It is time for FDA to clarify what data it will require that manufacturers provide when seeking to market a generic insulin or HGH product."

Rather than waiting for guidance on the broader category to emerge, Sen. Hatch and Rep. Waxman argue that generic insulin and human growth hormone are simpler than other follow-on protein products and therefore should have guidance documents issued for them now.

Insulin and human growth hormone "have relatively simple structures with a long history of safe use by millions of people," they wrote. "Moreover, because both of these products currently are regulated under the federal Food, Drug, and Cosmetic Act, establishing the approval requirements for their generic forms does not raise the legal issues that exist with approval of generic forms of [other follow-on protein] products. The legal framework for such approval already exists."

Dr. Bill Law Jr., president of the American Academy of Clinical Endocrinologists, said that waiting for more general guidance would not be such a bad idea.

"Obviously, having less expensive biologicals would make it easier for patients to afford to actually purchase and administer them when prescribed, so it would be good for both patients and their physicians," Dr. Law said in an interview. "However, an inexpensive product that is either unsafe or ineffective is not a good bargain."

He noted that he talks every day with patients who are concerned about difficulty in paying for biologicals and other medications.

"However, I'm sure that they would rather continue to pay for a branded product that has proved to be safe and effective in human clinical trials than to be included later as a subject in a scientific article documenting major safety and/or efficacy deficiency problems in a generic biological product that was approved for use in humans based on poorly thought-out requirements created urgently because of political pressure by well-intentioned but scientifically naïve legislators," he said. ■

Drug Noncompliance Rampant In Diabetics, Targets Often Missed

BY BRUCE JANCIN
Denver Bureau

ATLANTA — More than one in five diabetic patients are nonadherent to their key medications—and the consequences soon show up in increased rates of hospitalization and mortality, Dr. P. Michael Ho said at the annual meeting of the American College of Cardiology.

Given this high rate of nonadherence and its marked negative impact, it seems appropriate to incorporate routine assessment of medication adherence into the clinical care of patients with diabetes, added Dr. Ho of the University of Colorado, Denver.

"Once medication nonadherence is identified, physicians should approach it similar to an elevated systolic blood pressure reading or a high LDL value; that is, it's a risk marker for adverse outcomes which requires treatment and follow-up," he said.

Dr. Ho presented a retrospective cohort study of 11,532 diabetic patients at a large Denver-area nonprofit integrated managed care plan. The rate of nonadherence to oral hypoglycemic, statin, and antihypertensive therapies—all of which are recommended as core components of diabetes care in national guidelines based upon level I evidence—was 21% during the assessment year of 2003.

Nonadherence was defined as having filled prescriptions for these medications on less than 80% of days of follow-up. The lowest nonadherence rate was with antihypertensive medications (19%) while the highest (25%) was with statin therapy.

Outcomes were assessed during 2004 and the first one-third of 2005. Unadjusted all-cause mortality was 4% in adherent and 6% in nonadherent patients, a significant difference. The rate of all-cause hospitalization was 19% in the adherent group and 23% in nonadherent patients.

The mean LDL level in adherent patients was 85.5 mg/dL, compared with 98.2 mg/dL in the nonadherent subjects. Systolic and diastolic blood pressures and mean hemoglobin A_{1c} values were also higher in the nonadherent cohort.

Nonadherent patients were significantly more likely to be female, younger, and had fewer comorbidities. Upon adjustment for these and other variables in a multivariate logistic regression analysis, medication nonadherence was associated with an 81% increase in the relative risk of all-cause mortality and a 58% increase in all-cause hospitalization. Each 25% increment in medication adherence was associated with a 25% relative risk reduction in mortality and a 17% decrease in hospitalization risk.

It's known from other studies that fewer than 50% of adults with diabetes achieve targets for LDL, blood pressure, and HbA_{1c}. These data suggest medication nonadherence may be the explanation, Dr. Ho continued.

In terms of potential remedies for the poor rate of medication adherence, Dr. Ho said this problem deserves to be a high-priority research area. He noted there are encouraging reports out of Stanford (Calif.) University regarding the use of interactive voice-response technology when applied to groups of diabetic patients.

This system is similar to the automated telephone technology the airlines use when customers call in to make a reservation. The diabetic patient can phone in to the interactive system, or the system can phone the patient. Studies to date have shown this telephone-based strategy results in improved medication adherence and intermediate outcomes, according to Dr. Ho. ■

Metabolic Syndrome's Associated CHD Risk Varies Substantially

BY BRUCE JANCIN
Denver Bureau

ATLANTA — The majority of the estimated 40 million Americans with the metabolic syndrome are at very low or low calculated 10-year risk for coronary heart disease, Dr. Khiet Hoang reported at the annual meeting of the American College of Cardiology.

On the other hand, more than half of all men with the metabolic syndrome are at intermediate or high risk for CHD, as is also true for African Americans, both male and female, according to Dr. Hoang of the Heart Disease Prevention Program at the University of California, Irvine.

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These findings underscore the wide spectrum of cardiovascular risk encompassed by the term metabolic syndrome. And that, in turn, reinforces the importance of individualized formal global risk assessment of patients with metabolic syndrome in order to more appropriately target intensity of treatment, the physician added.

Dr. Hoang and coworkers estimated the prevalence of metabolic syndrome by applying the National Cholesterol Education Program criteria to adults aged 20-79 in the National Health and Nutrition Examination Survey database for 2001-2002. They then applied the Framingham risk algorithms to calculate 10-year CHD risk in individuals with metabolic syndrome. Patients with diabetes or preexisting CHD were automatically classified as high risk.

The prevalence of the metabolic syndrome was 27.5% in men and 28.6% among women. Of individuals with the syndrome, 15% were at intermediate CHD risk (their 10-year calculated risk was 10%-20%) and 41% were at very low risk (their 10-year risk was less than 6%).

Fully one-third of all persons with the metabolic syndrome were deemed at high risk for a future CHD event, meaning their 10-year risk exceeded 20%. A particularly striking finding was that roughly 90% of these individuals were high risk by virtue of having diabetes or preexisting CHD; only 3.1% of all adults with metabolic syndrome were high risk on the basis of a calculated Framingham 10-year risk greater than 20%.

The proportion of individuals with metabolic syndrome at high CHD risk was 47% among African Americans, 32% in Hispanics, and 31% in whites. ■

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