

most private payers do not have sufficient market power to implement payment reforms if providers are reluctant to participate. However, a Medicare waiver could allow states such as Massachusetts, which has proposed moving toward a global payment system, to establish a uniform structure of incentives that reward organizations for becoming more integrated and more accountable for cost and quality.⁴ Under such a system, providers who were prepared to accept alternative payment models would see payments increase, though perhaps at a slower rate than the current trend. Others could remain in the fee-for-service system but would face diminishing financial prospects.

Although pilot projects will not have much effect on national health care spending in the short run, they can encourage innovation in health care delivery by reducing or eliminating the link between service volume and provider revenue. The congressional

proposals would reduce important historical barriers to innovation at the CMS, but success is ultimately about execution. The CMI would have to overcome a risk-averse CMS culture that promotes rigid adherence to rules. Although risk-averse behavior may be rational in a government bureaucracy, it often kills innovation.

What would it take to establish an effective innovation group within the CMS? The first step is to select a leadership team that understands health care delivery and federal government operations, thinks outside the box, and is willing to accept occasional failures as it pursues its objectives. The CMI will need a strategic plan with clear milestones and the ability to communicate skillfully with Congress. It will need to interact regularly with innovators and build on existing knowledge about what works. Regardless of the fate of national health care reform, Congress should try to enact some of the many good proposals de-

veloped over the past year that have bipartisan support. Successful innovation is essential to the long-term sustainability of Medicare and Medicaid. The CMI would cost relatively little in the context of the overall CMS budget, but if it were successful, the long-term effect on the U.S. health care system could be priceless.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Weighing Risks and Benefits of Liraglutide — The FDA's Review of a New Antidiabetic Therapy

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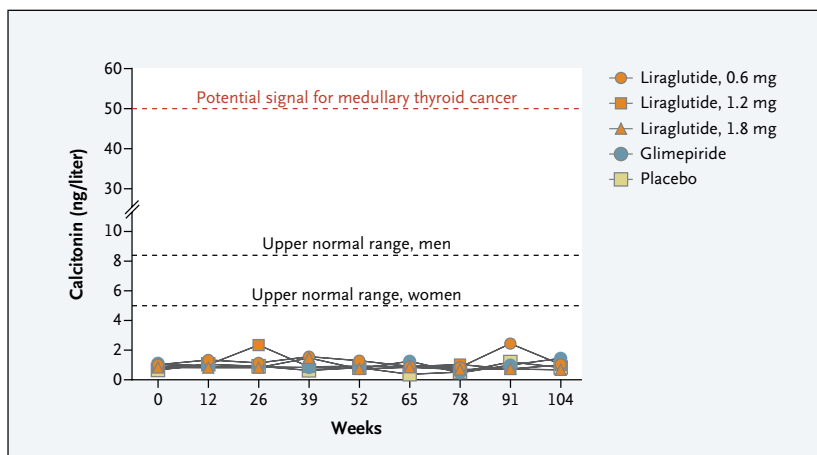
Type 2 diabetes mellitus affects approximately 24 million people in the United States, is the leading cause of kidney failure and blindness, and is associated with a doubling to quadrupling of the risk of death from cardiovascular causes. Furthermore, the prevalence of type 2 diabetes is expected to increase because of the obesity epidemic. Although many

antidiabetic therapies have been approved by the Food and Drug Administration (FDA), new therapies are needed to achieve glycemic goals, because beta-cell function declines over time in patients with diabetes.

On January 25, 2010, the FDA approved liraglutide, a glucagon-like-peptide-1 (GLP-1) receptor agonist that can be taken once

daily to improve glycemic control in adults with type 2 diabetes. We granted the approval on the basis of careful consideration of the drug's benefits, weighed against several complex safety-related concerns.

In clinical trials, when used in addition to other antidiabetic therapies, liraglutide resulted in reductions in the mean glycated



Geometric Mean Calcitonin Values in 1079 Patients in a 2-Year Trial in Which Liraglutide, Glimepiride, or Placebo Was Added to Metformin Therapy.

Data from weeks 0 through 52 are from the randomized, double-blind treatment period. Data after week 52 are from an open-label, voluntary extension period. Data are not available for all patients at every time point. Nonstimulated calcitonin values of 50 ng per liter or higher suggest a possible signal for medullary thyroid cancer.²

hemoglobin concentration of 0.8 to 1.4 percentage points as compared with placebo. When compared as monotherapy with a sulfonylurea, liraglutide was associated with a lower risk of hypoglycemia. Other potential benefits include greater weight loss than that achieved with some active controls and the absence of a need to adjust the dose for patients with renal impairment.

On the other hand, there are potentially serious safety concerns. First, data from studies in rodents suggested that liraglutide was associated with an increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. In rodents, C-cell hyperplasia is considered a preneoplastic lesion leading to medullary thyroid cancer.¹ Studies in rats and mice showed an increase in the occurrence of benign C-cell adenomas at liraglutide doses that resulted in plasma drug levels similar to those seen in humans at the ap-

proved doses. Malignant C-cell carcinomas were also observed in both rats and mice, and there was a statistically significant increase in incidence among male rats treated with liraglutide at doses resulting in plasma drug levels eight times those seen in humans receiving the maximum proposed dose. The incidence of liraglutide-induced medullary thyroid cancer did not affect the overall survival rate among either rats or mice.

Although these findings are troubling, their relevance to humans is unknown. The incidence of medullary thyroid cancer in the United States is approximately 600 cases per year — making it infeasible to conduct a clinical trial to detect an increased risk of this type of cancer associated with liraglutide exposure. However, calcitonin, a hormone secreted by thyroid C cells, is used clinically as a biomarker for the detection of medullary thyroid

cancer; calcitonin levels were routinely monitored in clinical trials and could be a useful indicator. Serum calcitonin levels below 10 pg per milliliter are considered to be evidence of the absence of medullary thyroid cancer, whereas levels above 100 pg per milliliter are highly predictive of medullary thyroid cancer.² In the controlled clinical trials, increases in calcitonin levels occurred in a slightly higher percentage of the patients treated with liraglutide than in control patients; although the increases represented shifts from below to slightly above the assay's detection limit (0.7 ng per liter), calcitonin levels were still within normal ranges. Furthermore, data from a long-term study did not reveal any notable difference in mean calcitonin levels between liraglutide and control groups over 2 years of follow-up (see graph).

The FDA concluded that increases in the incidence of carcinomas among rodents translated into a low risk for humans, because statistically significant increases occurred only at drug-exposure levels many times those anticipated in humans, and the increase in cancers did not affect overall survival rates. However, it is difficult to extrapolate findings from studies in animals to humans. To further explore possible associations between medullary thyroid cancer and liraglutide use, the FDA exercised its authority under the Food and Drug Administration Amendments Act to require additional studies in animals and the establishment of a cancer registry to monitor the annual incidence of medullary thyroid cancer over the next 15 years.

Another safety concern is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway. This concern arises from post-marketing reports submitted to the FDA Adverse Event Reporting System regarding pancreatitis associated with the use of exenatide and sitagliptin, both of which act through this pathway. Limitations of postmarketing reporting (e.g., incomplete data), coupled with the possibility that baseline rates of pancreatitis in patients with diabetes may be as high as three times those among people without diabetes,³ have made it difficult to determine whether the spontaneous reports indicate that use of these drugs was the cause of increased risk. Despite this uncertainty, we required the manufacturers of exenatide and sitagliptin to prominently address the possible increased risk of pancreatitis in the drugs' labeling and to conduct additional studies in animals.

In the phase 2 and phase 3 trials of liraglutide, there were seven cases of pancreatitis reported among the 4257 patients treated with liraglutide and only one case in the 2381 patients in the comparator group. After adjustment for more patient-years of exposure to liraglutide, this finding of pancreatitis represented a 4:1 imbalance between the liraglutide and comparator groups. The small number of events makes it difficult to draw conclusions about causation, but this imbalance, along with concerns about exenatide and sitagliptin, led the FDA to require the sponsor to perform postapproval mechanistic studies in animals and to conduct an epidemiologic evaluation

using a large insurance-claims database. Prescribers and patients should be aware that the common side effects of liraglutide include nausea and vomiting, but persistent or severe nausea and vomiting should be carefully evaluated, since they may be early manifestations of pancreatitis and therefore warrant prompt discontinuation of liraglutide treatment.

A final question is whether it is possible to rule out increased risks of cardiovascular events from antidiabetic therapies. In December 2008, the FDA published industry guidelines outlining recommendations for assessing any cardiovascular risk conferred by new antidiabetic drugs.⁴ To gain approval for such drugs, sponsors would have to compare the incidence of cardiovascular events in the group receiving the agent under investigation with that in comparator groups and demonstrate that the upper bound of the two-sided 95% confidence interval for the estimated risk ratio was less than 1.8. Drugs meeting this standard could be approved for marketing, with more stringent evaluation of cardiovascular risk (resulting in an upper confidence limit of less than 1.3) required after approval.

The clinical development program for liraglutide was completed before that guideline was issued, but analyses of cardiovascular events from the combined phase 2 and phase 3 trials showed that this drug met the standard for ruling out an unacceptable increase in cardiovascular risk. The overall rates of cardiovascular events in the pre-approval clinical trials were low, however, and the more stringent criteria outlined for postapproval

evaluations were not met. The FDA is therefore requiring a postapproval study of cardiovascular safety.

In approving liraglutide, the FDA recognized that it may benefit patients who have inadequate diabetes control despite their use of another antidiabetic therapy. Improved glycemic control significantly reduces the risk of microvascular complications from diabetes and is a cornerstone of diabetes treatment. The FDA also recognizes that all products approved for treating type 2 diabetes, including long-marketed products, carry risks. Several of liraglutide's potential safety problems will be studied further. A risk evaluation and mitigation strategy is required that includes a medication guide and a communication plan for educating prescribers about the drug's risks and benefits and the fact that it is not recommended as first-line therapy for patients whose diabetes has not proven controllable with diet and exercise. The FDA expects to learn more about liraglutide's safety from the required postapproval studies and clinical trials. In the interim, physicians will need to carefully review the prescribing information and decide whether the benefit-risk profile is favorable for each individual patient.

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