PERSPECTIVES ON GLP-1 AGENTS FOR DIABETES

Varying signals for pancreatitis, hypersensitivity, and cancer
Three oral versus two injectable agents compared
Link to human and animal studies of the pancreas

Executive Summary

This issue focuses on five widely used drug treatments for Type 2 diabetes, exenatide (BYETTA), liraglutide (VICTOZA), sitagliptin (JANUVIA), saxagliptin (ONGLYZA), and linagliptin (TRADJENTA). These drugs are known as glucagon-like peptide-1 (GLP-1) agents because they mimic or increase the availability of GLP-1 in regulating blood sugar levels. Given emerging safety concerns about this increasingly prescribed class of drugs, we examined their safety profiles over 12 months of adverse drug event data.

The U.S. Food and Drug Administration (FDA) is changing the internal computer system that manages its adverse event report database, now called FAERS (FDA Adverse Event Reporting System). The agency released for public use reports from a partial quarter extending from July 1, 2012, through August 27, 2012. The partial-quarter data totaled 136,225 reports of all kinds, including 29,186 domestic, fatal, disabling, or serious events meeting the QuarterWatch criteria. Adjusted for partial reporting, it appears a full quarter total will be similar to recent previous quarters. Because examining a partial quarter of data has significant limitations, this issue will rely on the 12 months ending June 30, 2012.

QuarterWatch™ is an independent publication of the Institute for Safe Medication Practices (ISMP) that monitors all domestic, serious adverse drug events reported to the FDA. These case reports, best known as MedWatch reports, are a cornerstone of the nation’s system for monitoring the safety of prescription drugs after FDA marketing approval.

GLP-1 Agents’ Effects on Pancreas, Thyroid

The Agents and Their Mechanisms

Glucagon-like peptide-1 (GLP-1) is a hormone released from the gut when food is present that stimulates the release of insulin, slows gastric emptying, reduces appetite, and has other effects on the regulation of blood sugar. However, it is rapidly deactivated by an enzyme, dipeptidyl peptidase-4 (DPP-4). Two families of drugs have been developed to manipulate GLP-1 effects. Exenatide and liraglutide are longer-lived analogs of GLP-1 that are not inactivated by DPP-4, and are taken by injection. Sitagliptin, saxagliptin, and linagliptin are oral agents that prevent the rapid breakdown of GLP-1 by inhibiting DPP-4. All five agents have moved into clinical practice, accounting for 16.9 million prescriptions in the 4 quarters ending June 2012, according to data from IMS Health. The market thus far is dominated by sitagliptin, with 11.2 million dispensed outpatient prescriptions (66%) in the year period.
Safety Questions Arise

Concerns that the use of GLP-1 agents may be associated with pancreatitis have arisen through published studies of adverse drug event reports for sitagliptin and exenatide, and our own report about liraglutide. A recently published case control study in a large health insurance plan population reported a two-fold increased risk of pancreatitis for sitagliptin and exenatide. Pancreatitis, in turn, is a risk factor for pancreatic cancer, and one agent, liraglutide, has a Boxed Warning about the increased risk of thyroid cancer seen in a rodent carcinogenicity study.

Safety questions were recently amplified by some studies of human and animal pancreatic tissue. These tissue studies suggested that the more constant stimulation of GLP-1 receptors was leading to abnormal proliferation of tissue in the pancreas, possible activation of latent tumors, and alteration of the pancreatic ductal tissue.

In this setting we conducted a disproportionality analysis of domestic, serious adverse event reports for five GLP-1 agents from July 1, 2011, through June 30, 2012. As a comparator we combined the reports for three second generation sulfonylurea drugs with reports for metformin in a patient population with Type 2 diabetes.

Report Totals

We identified 1,723 serious adverse drug event reports for the five GLP-1 drugs in the 12-month study period. That total included 831 reported cases of pancreatitis, 105 cases of pancreatic cancer, 32 cases of thyroid cancer, and 101 cases indicating a hypersensitivity reaction. Exenatide, with 612, reports accounted for the most cases while saxagliptin, with 100 cases, the fewest.

Signals for Pancreatitis

We observed a marked signal for reported pancreatitis in all five GLP-1 agents compared to cases reported for the other diabetes drug controls. After adjusting for differences in report characteristics, the reporting odds ratio for the two injectable agents was 28.5 (95% CI 17.4-46.4) and for the three oral agents was 20.8 (95% CI 12.6-34.5). Examined individually in comparison to the other diabetes drug controls, the highest odds ratio was for sitagliptin and the lowest was for saxagliptin. Complete results appear in the full report.

Pancreatic Cancer Results

The 105 reported cases of pancreatic cancer among the five drugs varied from a high of 71 cases for exenatide to a single case for both saxagliptin and linagliptin. Among the comparator diabetes drugs, 2 cases were reported. The adjusted odds ratio for the GLP-1 group compared to the diabetes drug controls was OR 25.6 (95% CI 15.9-47.8).

Signal for Thyroid Cancer

The two injectable GLP-1 analogs, exenatide and liraglutide, were associated with reports of thyroid cancer, but the three oral agents were not. We identified 14 reported thyroid cancer cases for exenatide and 17 cases for liraglutide. One case was reported among the diabetes drug comparators and one case for sitagliptin.

* An odds ratio is the ratio of the odds of an event occurring in one group to the odds of it occurring in another group.
Hypersensitivity Signal

The newest oral agent, linagliptin, was associated with a marked signal for hypersensitivity reactions that included angioedema, urticaria, rashes, blisters, and skin exfoliation. While all the agents, including the diabetes comparators, had reports indicating hypersensitivity, the adjusted odds ratio for linagliptin was 7.7 (95% CI 4.2-13.8) compared to the diabetes controls, and was the only GLP-1 agent with a statistically significant difference with the comparators.

Results for Renal Failure

We also investigated reports of renal impairment and failure. One agent, exenatide, was identified in a 2009 FDA report as associated with a large number of adverse event reports for this condition. In these data, no statistically significant differences were seen in a comparison between the GLP-1 agents and the diabetes drug controls, and a trend suggested a lower reported risk for some GLP-1 agents.

Higher Reporting Rates for Three Drugs

Another approach to assessing the reported risks of GLP-1 agents is to examine report totals after adjusting for patient exposure, which varied widely among the five drugs. Notable differences emerged when we compared the total serious adverse event reports for the five GLP-1 agents with dispensed prescription volume over the 12-month study period. (See Figure 1) The adverse event reporting rate per 100,000 prescriptions for three drugs—exenatide, liraglutide and linagliptin—was approximately 10 times the rate for sitagliptin and saxagliptin. The evidence that two injectable agents may have higher risks of adverse events than two of the three oral agents is assessed in the full report.

Manufacturers Respond

We shared preliminary results of our study with the drug manufacturers of the five GLP-1 agents. Three manufacturers said that a causal relationship between drug treatment and pancreatic cancer was unproven, and noted various specific weaknesses in using adverse event reports to assess this risk. In addition, some manufacturers have sponsored and cited animal, epidemiological, and meta-analysis human studies that did not detect the risks explored here.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The FDA Adverse Event Reporting System (FAERS) data combine reports originated by drug manufacturers with cases submitted directly by consumers and health professionals through the agency’s MedWatch program. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. However, given numerous reports with credible detail, adverse event data may have important scientific weight in a broader assessment of causality. A majority of new warnings, restrictions, or other major actions to manage the risks of drugs are based on these data. The reporting rate for FAERS is unknown, and published
estimates in specific cases range from around 1% to 15%, and up to 30% in unusual cases of enhanced reporting. We use the term *signal* to mean evidence that, in our judgment, is substantial enough to warrant publication but requires further investigation to determine the frequency of occurrence and to establish a causal relationship to the suspect drug. More complete disclaimers and descriptions of our criteria are included in the methods summary section of this report. A disclosure statement at the end of this report expands our description of this project and its staff.

**Conclusions**

These data and other recent studies establish the need to reassess the safety of this class of drugs. It underlines the truth of the observation that drugs have many effects and the measured benefit—in this case lowered blood sugar levels—is only one. Not enough is known about the long-term pathophysiological effects of these drugs on the pancreas and thyroid.

These results add additional scientific weight to the association of all five GLP-1 agents with reports of pancreatitis. However, the marked association in adverse event data does not indicate how frequently this adverse event might occur. While available studies suggest that severe cases of pancreatitis are relatively rare over the short term, they do not address the incidence of cumulative or subclinical injury suggested in human and animal studies of pancreatic tissue.

Considered as a group, these data provide a signal for pancreatic cancer substantial enough to warrant further investigation. As we have previously reported, links between drug treatments and increased cancer risk are difficult to measure in adverse event data. A relationship, however, is biologically plausible.

The two injectable agents had a signal for thyroid cancer. One, liraglutide, has a Boxed Warning about this risk derived from animal studies. However, the number of cases reported over 12 months was modest, and the difficulties in assessing cancer risk from adverse event reports also apply here.

It is clear from these data that linagliptin has a higher risk of reported hypersensitivity reactions. Better information about the incidence of the more severe hypersensitivity reactions should guide judgments about its place in diabetes treatment.

These data provide preliminary evidence that the toxicity of the injectable agents may be higher than that of the oral agents. The serious adverse event reporting rates for the two injectables were 10 times as high as those for the most widely prescribed oral agent, sitagliptin, and smaller differences were also seen in pancreatitis and pancreatic cancer. In addition, the association with reports of thyroid cancer was seen only for the injectable agents.

We recommended updating the prescribing information to include stronger alerts based on the adverse event data and new studies now available. Also, new studies of the long-term effects of GLP-1 agents on human and primate pancreatic and thyroid tissues should be a major priority.
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Methods Summary

QuarterWatch seeks to improve patient safety through publishing the results of our regular monitoring and analysis of serious adverse drug events reported to the FDA. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1]

Our publication examines domestic adverse drug events that are specifically coded as “serious,” which means under FDA regulation events that resulted in death, permanent disability, a birth defect, involved hospitalization, were life threatening, required intervention to prevent harm, or had other medically serious consequences.[2] We exclude reports from foreign sources, cases from clinical studies, which have different reporting requirements, and events in which the injuries were not coded as serious. We standardize drug names to an ingredient name based on the National Library of Medicine RxNorm project [3] and do not distinguish between different routes of administration or dosage forms unless otherwise stated.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[4] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events.[5] We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that also combine several related but more specific medical terms. The QuarterWatch database was updated in November 2012 to MedDRA version 15.1.

To provide a broader perspective on the adverse events reported, we assess patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

“The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2012 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities.”

Reported totals for any calendar quarter, specific drug, or adverse event may change over time because thousands of reports are revised, entered into the FDA system late, or subject to changes in the QuarterWatch or FDA coding or report criteria. To compensate, all historical comparisons and trends over time are recalculated every quarter and may differ from previously reported totals. The term signal as used in QuarterWatch means evidence of sufficient weight to justify an alert to the public and the scientific community, and to warrant further investigation.

In this issue, we compared the safety profiles of the five GLP-1 agents using a statistical technique called the reporting odds ratio.[6] To calculate an odds ratio, we compare the odds of the event of interest (such as pancreatitis) occurring in the reports for one drug to the odds of it occurring in comparator drugs. This approach avoids the problem that patient exposure and reporting rates may vary among drugs. In addition, we use logistic regression to adjust for other differences in reports that may be unrelated to the safety question under study.

The QuarterWatch master database of all adverse event reports submitted to the FDA is maintained on a MySQL open source database (http://www.mysql.com/) and analyzed with the R Package for Statistical Computing (http://www.r-project.org/). A full technical description of our methodology can be found on the QuarterWatch web pages (http://www.ismp.org/quarterwatch/detailedmethods.aspx).
Results

This issue of QuarterWatch provides limited insight into reporting trends because the FDA released only a partial data set for the third quarter of 2012, extending from July 1, 2012, through August 27, 2012. The reason was the agency’s transition to a new computer system used to receive, analyze, and release adverse event reports from consumers, health professionals, and drug manufacturers.

In the partial results for the third quarter, the FDA received 29,186 reports of fatal, disabling, or serious adverse drug events in the United States. This included 4,293 cases with a death outcome, 1,097 cases with permanent disability or a birth defect, and 23,796 cases with other serious outcomes, including hospitalization, life-threatening events, and events requiring medical intervention to prevent harm. Adjusted for the partial quarter, the case totals showed no unusual changes from previously reported event totals.

The other data cited in this issue of QuarterWatch are for the 12 months ending June 30, 2012, and exclude the partial quarter. Full quarter data and annual results for 2012 will appear in the next issue of QuarterWatch.

Perspectives on GLP-1 Agents for Diabetes

We identified signals for pancreatitis for all five GLP-1 agents and for reported pancreatic cancer for three of five agents. In addition, signals were seen for reported thyroid cancer for the two injectable agents and for hypersensitivity for one oral agent. Safety concerns about this growing class of agents for Type 2 diabetes drugs have arisen from several different sources: adverse drug event reports, an epidemiological study, animal studies of drug effects, and a new study of human pancreatic tissue from organ donors. Taken together, these data raise, but do not resolve, significant safety questions that could affect the future of the entire class. The agents are shown in Table 1. (No data were available for a sixth agent, alogliptin (NESINA), which was approved in January, 2013.)

Table 1. GLP-1 agents for diabetes

<table>
<thead>
<tr>
<th>Injectable agents</th>
<th>Brand name</th>
<th>Year approved</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>2005</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td>2010</td>
<td>Novo Nordisk</td>
</tr>
<tr>
<td>Oral agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia</td>
<td>2006</td>
<td>Merck</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza</td>
<td>2009</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Tradjenta</td>
<td>2011</td>
<td>Boehringer Ingelheim</td>
</tr>
</tbody>
</table>

These drugs were developed and became popular because they offered benefits in lowering blood sugar levels in Type 2 diabetes and appeared to avoid the problems of many existing drugs.[7] The earliest oral drugs were sulfonylureas, which directly stimulated the release of insulin. Their limitations were twofold: treatment could result in hypoglycemia or excessively low blood sugar, and in longer term clinical trials no agents successfully documented the primary benefit sought from treatment: lower risks of heart attack and strokes. A second major class, commonly called the glitazones, had other evident shortcomings. The first, troglitazone (REZULIN), was withdrawn because of potentially fatal liver toxicity. The second, rosiglitazone (AVANDIA), was heavily restricted when studies accumulated suggesting it increased rather than reduced the risk of serious cardiovascular events.[8] The third and last agent in the class, pioglitazone (ACTOS), has been associated with an increased risk of reported bladder cancer in this publication and in epidemiological studies. [9] [10] All three glitazones had additional significant disadvantages. They lowered blood sugar levels by inducing adipose tissue to absorb more glucose. This led to increased risk of weight gain and edema.

GLP-1 agents had a completely different mechanism of action, did not lead to the weight gain seen with the glitazones, and had lower rates of hypoglycemia compared to sulfonylureas. All these agents
focused on glucagon-like peptide-1 (GLP-1) one of the many hormones involved in the complex process of regulating blood sugar levels. Human GLP-1 is released from the gut in the presence of food and stimulates the release of insulin, reduces appetite, and slows gastric emptying.[11] However, once present, it is quickly inactivated by an enzyme, dipeptidyl peptidase-4 (DPP-4). The new agents deployed two different strategies to increase levels of GLP-1. The two injectable agents, exenatide and liraglutide, are synthetic analogs of GLP-1 that are not inactivated by DPP-4. The oral agents work indirectly, inhibiting DPP-4 so they were less effective in quickly inactivating the naturally present GLP-1. As shown in Figure 2, patient exposure to the five drugs has increased steadily in the seven quarters ending December 31, 2012, according to data from IMS Health.

**Figure 2. GLP-1 dispensed prescription growth & year approved**

Safety Questions Arise

The problem with GLP-1 agents flows from a fundamental issue with many drugs: while one effect is of medical interest (in this case lowering blood sugar), drugs have many effects, and some untoward effects may raise safety issues. GLP-1 receptors are located in many tissues of the body—in the heart, kidneys, thyroid, and exocrine pancreas. Furthermore, the drugs make GLP-1 more continuously available, while normally the GLP-1 peptide is quickly inactivated.[12]Early in development of GLP-1 agents it was recognized that the hormone stimulated cellular proliferation and inhibited programmed cell death.[13] Of greater concern, premalignant pancreatic lesions also had GLP-1 receptors, and therefore, the agents might be cancer promoters. In addition, animal studies showed that GLP-1 agents stimulated cell division in the pancreas, both in ducts and in insulin-producing beta cells.[14] A study in rats and mice reported that a GLP-1 agent showed abnormal cell growth in the pancreas.[15] However, a Novo Nordisk study of liraglutide reported no abnormal pancreatic tissue or pancreatitis in mice, rats, or monkeys.[16] Animal studies for
liraglutide, however, had shown increased risk of thyroid cancer, resulting in a Boxed Warning on the product label.[17]

Study results in humans are now becoming available. The first major study came from a research team at the University of California at Los Angeles (UCLA) in July 2011 and relied on FDA adverse event data. It reported increased risk for reported pancreatitis and pancreatic cancer with sitagliptin and exenatide.[18] QuarterWatch reported on a signal for pancreatitis for the newer liraglutide in May 2011.[19] Next, in February 2013, a case control study using insurance claims data from seven states' Blue Cross/Blue Shield health plans showed a 2.2-fold increased risk of hospitalization for pancreatitis among patients treated with the two GLP-1 agents studied, sitagliptin and exenatide. [20] The most direct evidence, however, came in March 2013, when investigators at UCLA and the University of Florida examined the pancreatic tissue of recent organ donors, comparing those who had taken GLP-1 agents (N=8) with those taking other diabetes drugs (N=12), and controls without diabetes (N=14).[21] Investigators reported that the pancreatic mass of those taking GLP-1 patients was 40% increased compared to that of the other diabetes drugs or non-diabetic controls. The study also identified precancerous growths in the pancreas of those who had been treated with GLP-1 agents and a six-fold increase in beta cells compared to the diabetes comparators. One might discount a human study with a small number of subjects were it not the case that a high-dose toxicology study of liraglutide in cynomolgus monkeys revealed a 65% increase in exocrine pancreatic tissue.[22] The UCLA pancreas study also spurred the FDA to announce in March 2013 that it was conducting a new investigation of the issue.[23] In the presence of these rising safety concerns, we used the most recent 12 months of serious adverse event data to investigate the safety profile of five GLP-1 agents.

**Methods for GLP-1 Assessment**

We selected all domestic, serious adverse drug event reports for the five GLP-1 drugs for the one-year period July 1, 2011, through June 30, 2012. For diabetes drug controls, we combined the reports for three second-generation sulfonylureas (glipizide, glimepiride, glyburide) with cases for metformin, the most widely used oral agent for diabetes. For random comparators, we selected cases among all other drugs but in the same age range (20-85). We excluded two types of patient death reports identified as problematic in earlier QuarterWatch studies: completed suicides and death cases that had no other event term to indicate why death occurred. Overall 92.3% of excluded cases were in the two controls, and the exclusions had the effect of lowering the odds ratios for the five study drugs in comparison with controls.

The study endpoints were as follows: For pancreatitis we selected any report with any of 12 Preferred Terms (PTs) grouped into the High Level Term (HLT) Acute and chronic pancreatitis. Cases of pancreatic cancer were selected if the case contained any of 13 PTs grouped in the HLT Pancreatic neoplasms malignant (excl islet cell and carcinoid). Reported thyroid cancers were identified with any one of eight PTs falling in the HLT Thyroid neoplasms malignant. Hypersensitivity was defined as any case report containing any of 221 PT terms grouped in the HLT Dermal and epidermal conditions, or Angioedema and urticaria. Renal adverse effects cases were defined as any of 16 PT terms grouped in the HLT Renal failure and impairment.

To compare drugs, which differed in patient exposure, report source, number of total cases, and number of years on the market, we calculated the reporting odds ratio for each drug and study endpoint compared to the diabetes drug comparator group. We used logistic regression to adjust for differences in report source (health professional or consumer) and report type (direct to FDA or manufacturer originated). The full data for analysis are shown in Table 2.
Table 2. Serious adverse drug event reports for GLP-1 agents and diabetes drugs comparator

<table>
<thead>
<tr>
<th>Injectable</th>
<th>Oral (DPP-4)</th>
<th>Diabetes Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Liraglutide</td>
<td>Sitagliptin</td>
</tr>
<tr>
<td>Cases, N</td>
<td>612</td>
<td>587</td>
</tr>
</tbody>
</table>

Report Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Injectable</th>
<th>Oral (DPP-4)</th>
<th>Diabetes Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>58 (11.3)</td>
<td>57.3 (10.7)</td>
<td>66.8 (12.6)</td>
</tr>
<tr>
<td>Male, pct*</td>
<td>39%</td>
<td>44%</td>
<td>46%</td>
</tr>
<tr>
<td>HP vs Consumer, pct</td>
<td>37%</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>MFR vs Direct, pct</td>
<td>95%</td>
<td>94%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Adverse Events

<table>
<thead>
<tr>
<th></th>
<th>Injectable</th>
<th>Oral (DPP-4)</th>
<th>Diabetes Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis HLT</td>
<td>263</td>
<td>326</td>
<td>177</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td>71</td>
<td>14</td>
<td>18</td>
</tr>
<tr>
<td>Thyroid Cancer HLT</td>
<td>14</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hypersensitivity HLGTs</td>
<td>27</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Renal failure HLT</td>
<td>95</td>
<td>23</td>
<td>16</td>
</tr>
</tbody>
</table>

*Percent calculations omit missing values

HP = Health professional; MFR = manufacturer; HLT = High Level Term

Report Totals

The five agents accounted for 1,723 domestic, serious adverse events in the 12-month period ending June 30, 2012. The total included 831 reported cases of pancreatitis, 152 cases of renal failure/impairment, 105 cases of pancreatic cancer, 32 cases of thyroid cancer, and 101 cases indicating a hypersensitivity reaction. The five study drugs had many similarities: all were brand name GLP-1 agents for Type 2 diabetes, with the overwhelming majority of reports collected and submitted by manufacturers. The diabetes drug comparators differed in having a smaller proportion of case reports from manufacturers (76%) compared to the GLP-1 agents (93%). Exenatide had two differences with the other drugs. It was the only drug with a majority of reports from consumers (63%) rather than health professionals and a large number of legal cases. While we excluded identifiable legal cases, drugs that are a litigation target may have a higher reporting rate because of publicity and advertising for clients. We excluded 159 legal cases for exenatide, 2 for sitagliptin, and none for the other agents. Linagliptin differed in having been approved just prior to the study period, and these data capture the first group of reports. Because of these factors, and different patient exposure explored below, simple drug-to-drug comparisons of the raw numbers of events are of limited value.

Signals for Pancreatitis

All five agents were strongly associated with reports of pancreatitis when compared to the other diabetes drug controls. The adjusted odds ratio of serious reports indicating pancreatitis was 25.8 times higher for the GLP-1 agents, compared to the diabetes controls. The adjusted OR was 25.8 (95% CI 15.9-41.8). Both the diabetes controls and the GLP-1 agents had higher odds of pancreatitis reports compared to the randomly selected cases, indicating a higher risk of pancreatitis across the diabetes patient population. The results for the five agents compared to the diabetes controls are shown in Figure 3. Similar results were
seen in a sensitivity analysis that also adjusted for differences in age and gender but included fewer cases because of missing values.

### Signals for Pancreatic Cancer

Case totals for pancreatic cancer were fewer and the results more mixed than for the pancreatitis endpoint. The two injectables and the three oral agents all had greatly increased adjusted odds of reported pancreatic cancer cases compared to the diabetes controls. For the injectables, the adjusted OR was 23.3 (95% CI 5.7-95.1) and for the combined oral agents, the adjusted OR was 13.5 (95% CI 3.11-58.5). However, examined individually, both linagliptin and saxagliptin had just a single reported case, with an increased odds ratio that was not statistically significant. These two drugs were also the most recently approved and had the fewest number of overall serious case reports of the group.

### Thyroid Cancer Results

The reported thyroid cancer cases were largely limited to the two injectable GLP-1 analogs, exenatide and liraglutide. Overall there were 32 reported thyroid cancer cases for the five drugs, with 14 cases for exenatide and 17 cases for liraglutide. One case was reported for saxagliptin and 1 case for the diabetes comparators. Grouped together, the two injectable agents had an adjusted odds ratio of 15.2 compared to the diabetes controls, and while statistically significant, the confidence intervals were very wide (95% CI 2.0-111.7). Thyroid cancer is a biologically plausible adverse event for the injectable GLP-1 analogs, given evidence for one agent in animal studies, and the fact that thyroid tissues have GLP-1 receptors.

### Renal Failure and Impairment

With 152 cases for the five GLP-1 agents, reports of renal failure or impairment were more numerous than all other adverse events studied except pancreatitis. One agent, exenatide, was identified in an FDA drug safety notice in 2009 for large numbers of such cases.[24] Renal failure can also be a complication of Type 2 diabetes. However, compared to the diabetes controls, the odds ratio for each of the five agents was lower or not statistically significantly different. Two GLP-1 drugs, liraglutide and sitagliptin, had significantly
lower odds of a reported case of renal failure and impairment. Exenatide showed a trend toward a higher risk, but was not significantly different from the diabetes controls. Further evidence that renal failure and impairment was likely attributable to the underlying patient population was seen in a comparison with random selected controls. Compared to randomly selected controls, the odds ratio for the diabetes controls was 4.0 (95% CI 2.8-6.3) and for the GLP-1 agents together was 2.6 (95% CI 1.8-3.6).

Higher Reporting Rates for Three Drugs

Figure 1 (reprinted from the Executive Summary) and Figure 1a provide a richer perspective on the number of serious adverse event reports for each of the five drugs by comparing report totals to patient exposure during the period, measured by total of dispensed outpatient prescriptions. In Figure 1 we calculated the number of serious adverse event reports per 100,000 dispensed outpatient prescriptions. While sitagliptin had a substantial number of reports (n=115) these data, adjusted for patient exposure, show the lowest reporting rate. The newcomer linagliptin had the smallest absolute number of reports, but one of the highest rates after adjusting for patient exposure.

To provide context we compared these reporting rates to those in an ongoing study of 77 outpatient drugs in 2011. The serious adverse event reporting rate for the two injectable drugs (exenatide = 42.6, liraglutide = 33.9) was higher than for 90% of the entire brand name group in the 2011 study. The rate for the two most widely prescribed oral agents (sitagliptin = 2.8, saxagliptin = 4.4) was around the median for brand name drugs in 2011. Brand name drugs in the 2011 study spanned a full spectrum of inherent toxicity, ranging from potent drugs for metastatic cancer to topical preparations. We noted that the number of years on the market didn’t appear to affect the reporting rate. The two oldest drugs (sitagliptin, approved 2005, and exenatide, 2006) accounted for both the lowest and highest reporting rate, respectively.

The overall results support the proposition that the toxicity of the injectable GLP-1 analogs may be higher than that of the oral DPP-4 inhibitors, linagliptin excepted. The serious event reporting rate was higher, as were the adjusted odds ratios for pancreatitis. The results for pancreatic cancer, however, were more mixed, and the number of case relatively few. However, future research could provide important insights into whether there are differences between the orals and injectables or among individual drugs.

Hypersensitivity Signal

All five GLP-1 agents have been previously associated with a risk of hypersensitivity in prescribing information,[25] [26] [27] [28] [22] with the two injectables that are GP-1 analogs also causing antibody formation. However, a marked signal was seen for linagliptin, with an adjusted OR of 7.7 (95% CI 4.2-13.8) compared to the diabetes drug controls. Hypersensitivity reactions are seen in many classes of drugs, and when compared to the randomly selected controls there were no statistically significant increases for either
the GLP-1 agents or the diabetes drug controls. These data set linagliptin apart in a group of diabetes drugs already known to share the adverse effect of hypersensitivity reactions.

While the hypersensitivity contraindication for linagliptin was routine in the prescribing information for physicians, the risk of allergic reactions was clearly and prominently featured as the first item in the Patient Information leaflet, including a description of common symptoms.

**Manufacturer Comments**

We received comments from Bristol-Myers Squibb (exenatide and saxagliptin), Boehringer Ingelheim (linagliptin), and Merck & Co. (sitagliptin). None of the companies identified any unusual factors that could have led to abnormal increases in the rates of voluntary reporting.

Pancreatitis risk: Bristol-Myers Squibb confirmed that exenatide was associated with pancreatitis in postmarket adverse event reporting, but added “evaluation of these reports has not established a causal relationship.” Boehringer Ingelheim noted pancreatitis was reported at a higher rate for linagliptin in clinical trials compared to both placebo and a sulfonylurea comparator. Merck, however, said it had not observed an increased risk of pancreatitis in two pooled studies of its clinical trials and noted, “The existence of postmarketing reports describing this event does not establish the presence of an association with sitagliptin.”

Pancreatic cancer risk: All three manufacturers denied an association between the drug and pancreatic cancer. Bristol-Myers Squibb reported neither a safety signal in all Phase2b/3 trials of saxagliptin, nor any signal detected in carcinogenicity studies in the mouse and rat. Merck said no increased risk of pancreatic cancers was identified in its pooled clinical studies or in its preclinical tests for damage to DNA and carcinogenicity studies in rodents. Boehringer Ingelheim reported “available evidence does not indicate an increased risk of pancreatic cancer.”

Comments on adverse event reports: Boehringer Ingelheim identified seven different limitations on adverse event report analysis that compared drugs, including variation in time on the market, media coverage, potential confounders from underlying conditions, preferential prescribing patterns for certain patient groups, and differences between new users and longer-term users. Merck stated that with voluntary reports, “It is generally not possible to reliably establish the frequency of such events or to establish a causal relationship….” Merck safety surveillance officials attributed the increased reports to “stimulated reporting” triggered by FDA safety communications and media coverage of studies identifying possible risks.
QuarterWatch Team and Funding Sources

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