



HAL
open science

Incretin-based drugs and intestinal obstruction: A pharmacovigilance study

Bastien Gudin, Chayma Ladhari, Perrine Robin, Marie-Laure Laroche, Samy Babai, Dominique Hillaire-Buys, Jean-Luc Faillie

► **To cite this version:**

Bastien Gudin, Chayma Ladhari, Perrine Robin, Marie-Laure Laroche, Samy Babai, et al.. Incretin-based drugs and intestinal obstruction: A pharmacovigilance study. *Thérapie*, 2020, 75 (6), pp.641 - 647. 10.1016/j.therap.2020.02.024 . hal-03493460

HAL Id: hal-03493460

<https://hal.science/hal-03493460>

Submitted on 6 Apr 2022

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Incretin-based drugs and intestinal obstruction: a pharmacovigilance study

Running title: Incretin-based drugs and intestinal obstruction

Authors

Bastien Gudina, Chayma Ladhari^a, Perrine Robin^a, Marie-Laure Laroche^{b,c}, Samy Babai^d, Dominique Hillaire-Buys^a, Jean-Luc Faillie^{a,e}

Affiliations

^a Department of Medical Pharmacology and Toxicology, CHU Montpellier, Montpellier, France

^b Centre of Pharmacovigilance and Pharmacoepidemiology, CHU Limoges, Limoges, France

^c INSERM 1248, Faculty of Medicine, University of Limoges, Limoges, France

^d Department of Pharmacovigilance, Assistance Publique Hôpitaux de Paris, Creteil University Hospital, Creteil, France

^e EA 2415, IDESP, University of Montpellier, Montpellier, France

Corresponding author:

Pr Jean-Luc Faillie

Département de Pharmacologie Médicale et Toxicologie
CHU Montpellier, 371 avenue du Doyen Gaston Giraud,
34295 Montpellier, France

Tel.: +33 4 67 33 67 52

E-mail: jean-luc.faillie@umontpellier.fr

What is already known about this subject

- Incretin-based drugs induce a reduction in intestinal motility
- The risk of intestinal obstruction associated with incretin-based drugs is suspected from post-marketing data

What this study adds

- We identified a pharmacovigilance signal that suggests a risk of potentially serious intestinal obstruction associated with incretin-based drugs, as a class and with a greater signal for DPP4-i.

Introduction

Incretin-based drugs, which includes glucagon-like peptide 1 analogues (GLP-1a) and dipeptidyl peptidase 4 inhibitors (DPP-4i), are a class drugs marketed for the management of type 2 diabetes mellitus since 2007. They increase the action of the incretin hormones (especially GLP-1) which results in an increased glycaemic-dependent insulin secretion, but also in a reduction in intestinal motility.¹ These drugs are therefore frequently associated with constipation. A risk of more intense intestinal effects, such as potentially serious ileus or intestinal obstruction, is suspected from post-marketing data but has not yet been confirmed. In 2012, following a safety communication from the Japanese Medicines Agency reporting intestinal obstruction in three patients treated with GLP-1a, the European Medicine Agency (EMA) found 35 similar cases for exenatide and 24 for liraglutide (two GLP-1a) in the European pharmacovigilance database. Based on this signal, the term "intestinal obstruction" was added to the European summary of product characteristics (SPC) of liraglutide and exenatide as a rare event (<1/1000).² Similar case reports have been published with DPP-4i in Japan^{3,4} and in May 2015, the EMA reported 36 cases of intestinal stenosis and obstruction associated with sitagliptin and 8 with vildagliptin (two DPP-4i).⁵ European SPC of these drugs were not updated to include this adverse drug reaction (ADR). To note, the risk of intestinal obstruction is not mentioned in the U.S. Food and Drug Administration (FDA) medication information for any DPP-4i or GLP-1a except for alogliptin for which the term "ileus" is indicated.

The objective of this study was to investigate the risk of serious intestinal obstruction associated with incretin-based drugs and explore the potentiality of a class effect by performing a disproportionality analysis in a global pharmacovigilance database.

Methods

Data source

Data were extracted from Vigibase, a global database of spontaneous reports of ADR managed by the World Health Organization. Vigibase is the largest pharmacovigilance database and records more than 20 million anonymous reports from over 130 countries.⁶ The following data were retrieved from the database: patient's age and gender, country of origin, type of reporter (healthcare professionals or not), dates of

drug exposure, and description, seriousness, onset date and evolution of ADR. An ADR is considered serious when it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect.⁷ Drugs are coded using the ATC (Anatomical Therapeutic Chemical) classification⁸ and adverse reactions are coded according to the MedDRA classification (Medical Dictionary for Regulatory activities, version 18.1).⁹

Study population

We extracted from VigiBase all the reports of adverse drug reaction of patients exposed to at least one diabetes drug (ATC class A10) registered between January 2007 (the first year of marketing of an incretin-based drug) and January 2018.

Study design

The disproportionality of reports for intestinal obstruction associated with incretin-based drugs was studied by performing a case-non case study. This design allows the calculation of reporting odds ratio (ROR), which compares the exposure to incretin-based drugs between cases and non-cases to detect pharmacovigilance signals in ADR databases.¹⁰ Cases were defined as patients with adverse reaction coded with the MedDRA High Level Group Term (HLGT) "Gastrointestinal stenosis and obstruction", non-cases were all other reactions recorded.

Exposure definition

Exposure to incretin-based drugs was defined by the mention in the report of an exposure to one GLP-1 analogue (ATC code A10BJ) or one DPP-4 inhibitor (ATC code A10BH). Analysis according to each class of incretin-based drugs used the specific ATC codes.

Statistical analysis

The main analysis studied the disproportionate reporting of intestinal obstructions associated with incretin-based drugs and each class of incretin-based drugs compared to all other diabetes drugs in the full database during the study period. Temporal analyses were also performed to study the effect of safety communications. A secondary analysis focused on serious reactions and used the same methodology in a narrowed population which included only serious adverse drugs reactions reported in patient over 40 years old during a restricted period from January 2013 to March 2016. Narrowing the study population limited the sample size and allowed the extraction of individual data from VigiBase which was necessary to access to the

information on seriousness but not possible in the full database. RORs and their 95% confidence interval were computed according to the usual methods.^{10,11}

Results

Characteristics of cases of intestinal obstruction exposed to incretin-based drugs

Between January 2007 and January 2018, 501,244 adverse reactions reported with diabetes drugs were recorded in VigiBase. We identified 698 cases of intestinal obstruction, among which 452 cases involved an incretin-based drug: 258 (57.1%) a DPP-4 inhibitor, 216 (47.8%) a GLP-1 analogue, and 11 (2.5%) both classes of drugs. Table 1 presents the characteristics of cases of intestinal obstruction exposed to incretin-based drugs. Exposed cases were mainly reported by healthcare professionals (71.9%) and mainly originated from United States and Japan (54% and 35.2%, respectively). The most frequent incretin-based drugs involved were sitagliptin (33.4%), exenatide (25.4%), liraglutide (14.6%), vildagliptin (8.8%), and dulaglutide (7.5%). Intestinal obstructions induced by incretin-based drugs were generally considered serious (92.9%) and 11 cases resulted in death (4.3% of cases with available evolution). The frequency for the different types of intestinal obstruction was similar for GLP-1a and DPP-4i.

Disproportionality analyses of intestinal obstructions associated with incretin-based drugs

In our main analysis, intestinal obstructions were more than 4.5 times more frequently reported with incretin-based drugs than with other diabetes drugs (ROR 4.52, 95%CI: 3.87–5.28). The disproportionate reporting was statistically significant for all incretin-based drugs individually (except for albiglutide, lixisenatide and semaglutide for which the ROR was not computable because of too few exposed cases) with a greater signal for DPP-4i (ROR 8.66, 95%CI: 7.27–10.32) compared to GLP-1a (ROR 3.05, 95%CI: 2.54–3.66) (Table 2).

Figure 1 presents the evolution of the ROR for both classes of incretin-based drugs by reporting year. Analysis of the possible impact of the safety communications about GLP-1a (which begun in June 2012 with the alert from the Japanese medicines agency) showed that the disproportionality signal for GLP-1a was significantly present before the safety alerts (pooled ROR 1.69, 95% CI: 1.24–2.30) and did not substantially increased after June 2012. Regarding DPP-4i, the disproportionality signal became

statistically significant in 2013, peaked in 2015 (ROR 25.50, 95%CI: 18.32–35.55) which was the year the EMA reported several cases of intestinal obstruction associated with sitagliptin and vildagliptin, and decreased afterwards.

Our secondary analysis restricted to serious adverse reactions only, based on 125 exposed cases, showed even higher ROR for incretin-based drugs with, similarly, a more important signal for DPP-4i (ROR 12.67, 95%CI: 8.99–17.65) (Table 3).

Discussion

Our study demonstrated that intestinal obstructions were significantly more frequently reported with incretin-based drugs than with other treatments of diabetes, with a higher signal for serious cases and for DPP-4i compared to GLP-1a.

The risk of intestinal obstruction suggested by post-marketing data has been taken into account for GLP-1a by the EMA and added as a rare event in the European SPC of these drugs. However, regarding DPP-4 inhibitors, intestinal stenosis and obstruction are not currently mentioned. In February 2015, the EMA published a report presenting 36 cases of gastrointestinal stenosis and obstruction possibly related with the use of sitagliptin: 33 (91.7%) required hospitalization, time to onset varied between a few days up to 7 months, discontinuation of the drug resulted in an improvement in 23 cases (63.9%) and rechallenge of sitagliptin aggravated the digestive symptoms in 4 cases (11.1%).¹² The EMA concluded that there was no sufficient information to support a causal relationship between gastrointestinal stenosis/obstruction and sitagliptin.¹³

In the literature, nine case reports of ileus or intestinal obstruction associated with the use of DPP-4i in Japanese diabetic patients have been published.^{3,4} A retrospective cohort conducted by the manufacturer of alogliptin (a DPP-4i) in Japanese patients with type 2 diabetes did not find an increased risk of ileus with alogliptin but the study only compared alogliptin with other DPP-4i or with voglibose, an α -glucosidase inhibitor which has been associated with ileus.¹⁴

Potential mechanisms

GLP-1 plays an important role in gastrointestinal secretion and motility acting via a complex mechanism involving ascending vagal afferents to the central nervous system.¹ Exogenous GLP-1 has been shown to decrease the antro-duodeno-jejunal motility and inhibit intestinal contractions (migrating motor complexes) in a dose-

dependent manner in healthy subjects and patients with irritable bowel syndrome.¹⁵ Contrary, exendin(9–39), an inverse agonist of GLP-1, increases antro-pyloro-duodenal motility in human.¹⁶ Interestingly, a woman with a neuroendocrine tumor showing GLP-1 and 2 levels 300 to 400 times higher than normal presented delayed oro-cecal transit with residues found in the colon 14 days post ingestion.¹⁷ In another case of neuroendocrine tumor secreting GLP-1, glucagon-like peptide-2 (GLP-2) and peptide YY (PYY) and presenting with chronic constipation, octreotide administration decreased GLP-1 and GLP-2 levels and reduced intestinal transit time from 150 to 50 minutes.¹⁸ Nakatani *et al.* evaluated the effects of the GLP-1 analogue liraglutide on residue levels and gastrointestinal transit time using capsule endoscopy in 14 type 2 diabetes patients: liraglutide significantly increased the rate of gastrointestinal residues and, in patients without diabetic neuropathy, the intestinal transit time.¹⁹

Our results showed a more important disproportionality signal for DPP-4i. Dipeptidylpeptidase-4 is an enzyme that degrades GLP-1 but also numerous peptides such as PYY, a distal gut inhibitory peptide, and GLP-2 which is considered as an intestinotrophic peptide showing growth-promoting and cytoprotective effects in the gastrointestinal tract.²⁰ Hence, unlike GLP-1a, DPP-4i enhance GLP-2 and PYY which could also have a significant importance in occurrence of gastrointestinal obstruction. Indeed, PYY, physiologically released in response to fatty meal, slows the intestinal transit when administered intravenously.²¹ Also, supra-physiological levels of GLP-2 inhibits gastrointestinal motility.²² It promotes smooth muscle relaxation and possibly inhibits cholinergic activity in the small bowel and colon.²³ Furthermore, intestinal obstruction was frequently reported (incidence 4%) in clinical trials of teduglutide, a GLP-2 analogue marketed in 2012 for the management of patients with short bowel syndrome depending on parenteral nutrition.²⁴ Hence, PYY and GLP-2 represent a hypothesis to explore the differential effects of incretin-based drugs on intestinal motility.

Strength and limitations of the study

This study is based on data extracted from VigiBase, the world's largest database of spontaneous reports of adverse drug reaction, which ensures sufficient statistical power to detect signals regarding rare effects such as drug-induced intestinal obstruction. Pharmacovigilance data reflects the conditions of actual use of diabetes treatment in a more real-life setting than data from clinical trials. However, as a study of disproportionality in pharmacovigilance databases, our study presents some

limitations. First, we cannot measure the real risk of adverse drug reaction but the differences in the rate of notifications by the calculation of reporting odds ratio. The fundamental difference with a case-control study lies in the fact that subjects in the control group (non-cases) are not healthy controls but patients with other various reported adverse drug reactions. Nevertheless, by analyzing real-life surveillance data, case non-cases studies help to highlight pharmacovigilance signals that have demonstrated in the past their usefulness for detecting drug risks.^{25,26} Second, the issue of under-reporting of adverse reactions is a major disadvantage inherent to studies using pharmacovigilance databases. Notification rate for serious effects strongly varies depending on many factors but has been estimated to range approximately between 5 to 10%.²⁷ To note, applying this rate to the 452 exposed cases included in our study, the hypothetical number of actual cases of intestinal obstruction could be 4520 to 9040. Third, the lack of enough specific information retrieved from the cases did not allow the study of the time to onset of intestinal reactions or the effects of potential confounders on our results. Fourth, the possible errors in the diagnoses of intestinal obstruction (more than 25% of cases were reported by non-healthcare professionals) can potentially lead to false positives and information bias. Finally, temporal analyses did not suggest a notoriety effect for GLP-1a with a signal present before and no increase after the safety communication on the risk of intestinal obstruction released by the Japanese medicines agency in June 2012 and then taken over by the EMA.²⁸ Contrary, the signal for DPP-4i was maximal the year the EMA reported cases of intestinal obstruction with DPP4-i. However, we observed that the disproportionality signal with DPP4-i was significantly present before 2015, therefore not possibly affected by direct notoriety bias. We cannot exclude though that the signal with DPP4 before 2015 could translate an accentuated “ripple effect” from GLP-1a to DPP-4i. A ripple effect is suspected when a safety communication for an adverse drug reaction with specific drugs (here, intestinal obstruction with GLP-1a in 2012) is associated with increased reports of the same effect with other drugs belonging to the same pharmacological or therapeutic area (here, DPP-4i).²⁸ Nevertheless, we believe that the intense signal of intestinal obstruction with DPP-4i is real and needs regulatory attention.

Conclusion

Despite the limitations of this type of study, we identified a pharmacovigilance signal that suggests a risk of potentially serious intestinal obstruction associated with incretin-based drugs, as a class and with a greater signal for DPP4-i. Vigilance must be observed and other studies, including longitudinal studies in large population samples, are needed to confirm and better understand the potential risk of intestinal obstruction associated with incretin-based drugs.

Acknowledgments

The Uppsala Monitoring Centre has provided the data but the study results and conclusions are those of the authors and not necessarily those of the Uppsala Monitoring Centre, National Centers, or WHO.

Funding source

This study did not receive any specific funding.

Conflicts of interest statement

All authors declare that they have no conflicts of interest.

Author contribution

JLF, DHB and BG participated in the study design. JLF acquired the data. BG and CL did the statistical analyses. BG wrote the initial draft, and all authors critically revised the manuscript. JLF is the guarantor.

References

1. Drucker DJ. The biology of incretin hormones. *Cell Metab* 2006;3:153–65.
2. European Medicine Agency. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the meeting – 7-10 January 2013. Available at: https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-7-10-january-2013_.pdf
3. Kanasaki K, Konishi K, Hayashi R, et al. Three ileus cases associated with the use of dipeptidyl peptidase-4 inhibitors in diabetic patients. *J Diabetes Investig* 2013;4:673–5.
4. Yoshida S et al. II-P-191: Study on six cases of intestinal obstruction during therapy with DPP-4 inhibitors. *Journal of the Japan Diabetes Society*. 2014; 57(S1): 311. The 57th Annual Meeting of the Japan Diabetes Society.
5. European Medicine Agency. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the meeting – 7-10 April 2015. Available at: <https://www.ema.europa.eu/en/events/pharmacovigilance-risk-assessment-committee-prac-7-10-april-2015>
6. Uppsala Monitoring Centre. VigiBase. Available at: <https://www.who-umc.org/vigibase/vigibase/>
7. Guideline on good pharmacovigilance practices (GVP). Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products. 2017. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/08/WC500232767.pdf
8. WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. 2019. Available at: https://www.whocc.no/filearchive/publications/2019_guidelines_web.pdf. 2019.
9. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999;20(2):109–17.
10. Faillie J-L. Case-non-case studies: Principle, methods, bias and interpretation. *Therapie* 2019;74:225–32.
11. Moore N, Kreft-Jais C, Haramburu F, et al. Reports of hypoglycaemia associated with the use of ACE inhibitors and other drugs: a case/non-case study in the French pharmacovigilance system database. *Br J Clin Pharmacol* 1997;44:513–8.
12. Januskiene J. European Medicine Agency. Signal management: Sitagliptin – JANUVIA, JANUMET, EFFICIB, RISTABEN, RISTFOR, TESAVEL, VELMETIA and XELEVIA (DPP-4 inhibitor). Gastrointestinal stenosis and obstruction HLG.T. EPITT Reference: 18251. February 23 2015.

13. European Medicine Agency. Pharmacovigilance Risk Assessment Committee (PRAC). Minutes of the meeting – 5-8 October 2015. Available at: https://www.ema.europa.eu/en/documents/minutes/minutes-prac-meeting-5-8-october-2015_en.pdf.
14. Bennett D, Davé S, Sakaguchi M, Chang C, Dolin P. Association between therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors and risk of ileus: a cohort study. *Diabetol Int* 2016;7:375–83.
15. Hellström PM, Näslund E, Edholm T, et al. GLP-1 suppresses gastrointestinal motility and inhibits the migrating motor complex in healthy subjects and patients with irritable bowel syndrome. *Neurogastroenterol Motil Off J Eur Gastrointest Motil Soc* 2008;20:649–59.
16. Schirra J, Nicolaus M, Roggel R, et al. Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut* 2006;55:243–51.
17. Brubaker PL, Drucker DJ, Asa SL, Swallow C, Redston M, Greenberg GR. Prolonged gastrointestinal transit in a patient with a glucagon-like peptide (GLP)-1- and -2-producing neuroendocrine tumor. *J Clin Endocrinol Metab* 2002;87:3078–83.
18. Byrne MM, McGregor GP, Barth P, Rothmund M, Göke B, Arnold R. Intestinal proliferation and delayed intestinal transit in a patient with a GLP-1-, GLP-2- and PYY-producing neuroendocrine carcinoma. *Digestion* 2001;63:61–8.
19. Nakatani Y, Maeda M, Matsumura M, et al. Effect of GLP-1 receptor agonist on gastrointestinal tract motility and residue rates as evaluated by capsule endoscopy. *Diabetes Metab* 2017;43:430–7.
20. Estall JL, Drucker DJ. Glucagon-like Peptide-2. *Annu Rev Nutr* 2006;26:391–411.
21. Savage AP, Adrian TE, Carolan G, Chatterjee VK, Bloom SR. Effects of peptide YY (PYY) on mouth to caecum intestinal transit time and on the rate of gastric emptying in healthy volunteers. *Gut* 1987;28:166–70.
22. Drucker DJ, Yusta B. Physiology and pharmacology of the enteroendocrine hormone glucagon-like peptide-2. *Annu Rev Physiol* 2014;76:561–83.
23. Amato A, Rotondo A, Cinci L, Baldassano S, Vannucchi MG, Mulè F. Role of cholinergic neurons in the motor effects of glucagon-like peptide-2 in mouse colon. *Am J Physiol Gastrointest Liver Physiol* 2010;299:G1038-1044.
24. Product Information : GATTEX(R) subcutaneous injection, teduglutide subcutaneous injection. Shire-NPS Pharmaceuticals Inc (per manufacturer), Lexington, MA, 2019.
25. Maciá-Martínez M-A, de Abajo FJ, Roberts G, Slattery J, Thakrar B, Wisniewski AFZ. An Empirical Approach to Explore the Relationship Between

Measures of Disproportionate Reporting and Relative Risks from Analytical Studies. *Drug Saf* 2016;39:29–43.

26. Montastruc J-L, Sommet A, Bagheri H, Lapeyre-Mestre M. Benefits and strengths of the disproportionality analysis for identification of adverse drug reactions in a pharmacovigilance database. *Br J Clin Pharmacol* 2011;72:905–8.
27. Bégaud B, Martin K, Haramburu F, Moore N. Rates of spontaneous reporting of adverse drug reactions in France. *JAMA* 2002;288:1588.
28. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. *Drug Saf* 2007;30:891–8.

Tables

Table 1. Characteristics of intestinal obstruction cases exposed to incretin-based drugs.

| Characteristics | Exposed cases (n=452) |
|------------------------------|----------------------------------|
| Age, n (%) | |
| 0-17 | 1 (0.4%) |
| 18-44 | 12 (4.7%) |
| 45-64 | 98 (38%) |
| 65-74 | 69 (26.7%) |
| >74 | 78 (30.2%) |
| Unknown | 194 |
| Gender, n (%) | |
| Male | 234 (54.3%) |
| Female | 197 (45.7%) |
| Unknown | 21 |
| Reporter type, n (%) | |
| Healthcare professionals | 309 (71.9%) |
| Physician | 264 (61.4%) |
| Pharmacist | 17 (4%) |
| Other | 28 (6.5%) |
| Non-healthcare professionals | 121 (28.1%) |
| Unknown | 22 |
| Country, n (%) | |
| USA | 244 (54%) |
| Japan | 159 (35.2%) |
| Germany | 8 (1.8%) |
| Great-Britain | 4 (0.9%) |
| France | 3 (0.7%) |
| Other EU | 8 (1.8%) |
| Other | 26 (5.8%) |
| Outcome, n (%) | |
| Fatal | 11 (4.3%) |
| Not recovered | 15 (5.9%) |
| Recovered with sequelae | 3 (1.2%) |
| Recovering | 51 (20.2%) |
| Recovered | 173 (68.4%) |
| Unknown | 199 |
| Reporting year, n (%) | |

| | |
|---------|-------------|
| 2017 | 69 (15.5%) |
| 2016 | 69 (15.5%) |
| 2015 | 103 (23.1%) |
| 2014 | 76 (17.1%) |
| 2013 | 43 (9.7%) |
| 2012 | 12 (2.7%) |
| 2011 | 11 (2.5%) |
| 2010 | 7 (1.6%) |
| 2009 | 13 (2.9%) |
| 2008 | 29 (6.5%) |
| 2007 | 0 (0%) |
| Unknown | 7 |

Incretin-based drugs, n (%)

| | |
|------------------|-------------|
| GLP-1 analogues | 185 (40.7%) |
| Exenatide | 115 (25.4%) |
| Liraglutide | 66 (14.6%) |
| Dulaglutide | 34 (7.5%) |
| Lixisenatide | 2 (0.4%) |
| Albiglutide | 1 (0.2%) |
| Semaglutide | 1 (0.2%) |
| DPP-4 inhibitors | 291 (64.1%) |
| Sitagliptin | 151 (33.4%) |
| Vildagliptin | 40 (8.8%) |
| Alogliptin | 23 (5.1%) |
| Linagliptin | 19 (4.2%) |
| Teneligliptin | 10 (2.2%) |
| Saxagliptin | 8 (1.8%) |
| Anagliptin | 6 (1.3%) |

Type of intestinal obstruction (MedDRA Preferred Terms), n (%)

| | |
|------------------------------|-------------|
| Intestinal obstruction | 176 (38.9%) |
| Ileus | 131 (29%) |
| Small intestinal obstruction | 63 (13.9%) |
| Gastric obstruction | 23 (5.1%) |
| Duodenal obstruction | 11 (2.4%) |
| Large intestinal obstruction | 9 (2%) |
| Mechanical ileus | 9 (2%) |
| Oesophageal stenosis | 9 (2%) |
| Sub-ileus | 8 (1.8%) |
| Volvulus | 6 (1.3%) |
| Other | 7 (1.5%) |

Table 2. Disproportionality analysis of intestinal obstruction associated with incretin-based drugs compared to other diabetes drugs.

| Drug | Cases | Non cases | ROR (95% CI) |
|----------------------|--------------|------------------|---------------------|
| Incretin-based drugs | 452 | 144 686 | 4.52 (3.87–5.28) |
| GLP-1 analogues | 216 | 102 565 | 3.05 (2.54–3.66) |
| DPP-4 inhibitors | 258 | 43 096 | 8.66 (7.27–10.32) |
| Other diabetes drugs | 246 | 355 860 | 1 [Reference] |

Table 3. Disproportionality analysis of intestinal obstruction considered serious associated with incretin-based drugs compared to other diabetes drugs

| Drug | Cases | Non cases | ROR (CI 95%) |
|----------------------|--------------|------------------|---------------------|
| Incretin-based drugs | 125 | 12 834 | 10,65 (7.68–14.75) |
| GLP-1 analogues | 37 | 5418 | 7,40 (4.84–11.31) |
| DPP-4 inhibitors | 92 | 7872 | 12,67 (8.99–17.65) |
| Other diabetes drugs | 51 | 55 745 | 1 [Reference] |

Serious adverse drugs reactions reported in patient over 40 years old from January 2013 to March 2016

Figure 1. Evolution of disproportionality estimates of intestinal obstructions associated with GLP-1 analogues and DPP-4 inhibitors

