Medicines Adverse Reactions Committee

Meeting date	14/09/2023	Agenda item	3.2.2
Title	**GLP-1 receptor agonists and DPP-4 inhibitors and the risk of gastrointestinal obstruction**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Vildagliptin	Galvus	Novartis New Zealand Ltd
Metformin + vildagliptin	Galvumet	Novartis New Zealand Ltd
Saxagliptin	Onglyza	AstraZeneca Limited
Liraglutide	Saxenda	Novo Nordisk Pharmaceuticals Ltd
Liraglutide	Victoza	Novo Nordisk Pharmaceuticals Ltd
Dulaglutide	Trulicity	Eli Lilly and Company (NZ) Limited
Approved but not available – no data sheet		
Empagliflozin + linagliptin	Glyxambi	Boehringer Ingelheim (NZ) Ltd
Linagliptin	Trajenta	Boehringer Ingelheim (NZ) Ltd
Linagliptin + metformin	Trajentamet	Boehringer Ingelheim (NZ) Ltd
Metformin + saxagliptin	Kombiglyze XR	AstraZeneca Limited
Semaglutide	Ozempic	Novo Nordisk Pharmaceuticals Ltd
Exenatide	Byetta	AstraZeneca Limited

PHARMAC funding	Vildagliptin (Galvus), metformin + vildagliptin (Galvumet), dulaglutide (Trulicity), liraglutide (Victoza).
Previous MARC meetings	Topic of intestinal obstruction with GLP-1 RAs and DPP-4 inhibitors not previously discussed.
International action	No significant international action. [redacted]
Classification	Prescription medicine
Usage data	In 2022, vildagliptin was dispensed to 33,120 people. Metformin + vildagliptin was dispensed to 57,787 people. Dulaglutide was dispensed to 15,989 people. See section 2.5.
Advice sought	**The Committee is asked to advise:** • Whether the available evidence suggests a causal association between GLP-1 RAs and/or DPP-4 inhibitors and gastrointestinal obstruction or ileus • Whether the data sheets of GLP-1 RAs and/or DPP-4 inhibitors should be updated to reflect this risk, and if so, what the most appropriate terminology would be • Whether any further regulatory action or communication should be undertaken.

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1 PURPOSE

This report presents the available information describing a possible association between GLP-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-4) inhibitors and intestinal obstruction as class effects. [redacted]. The scope of this report also considers GLP-1 RAs due to a possible common mechanism. Medsafe has previously requested data sheet updates for GLP-1 RAs to list intestinal obstruction but this request was declined by sponsors. Since then, new information has become available necessitating further review of this topic.

2 BACKGROUND

2.1 Glucagon-like peptide-1 receptor agonists

Glucagon like peptide-1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin release, suppresses glucagon secretion, inhibits gastric emptying, and supresses appetite (Figure 1). Plasma levels of GLP-1 are low in a fasted state and increase rapidly after eating. Circulating levels of intact GLP-1 decrease quickly through dipeptidyl peptidase-4 (DPP-4) enzymatic degradation and renal clearance. GLP-1 plays a crucial role in glucose regulation and acts on GLP-1 receptors expressed in α and β pancreatic islet cells and in peripheral tissue [1].

Figure 1: Physiology of GLP-1 secretion and action on GLP-1 receptors in different organs and tissues [1]

GLP-1 based therapies (GLP1-RA and DPP-4 inhibitors) affect glucose control through several mechanisms, including enhancement of glucose-dependent insulin secretion, delayed gastric emptying and reduction of postprandial glucagon and food intake [2].

GLP-1 RAs are synthetic agents that are less resistant to degradation by DPP-4 and therefore have a space in clinical use for T2DM and obesity. In a meta-analysis of 34 randomised trials., all GLP-1RAs reduced glycated haemoglobin (HbA1c) by 0.55-1.38% in patients with T2DM in comparison with placebo. GLP-1 RAs are also associated with a reduction in weight, atherosclerotic cardiovascular events, and progression of diabetic renal

disease independent of glycaemic control. When used in T2DM they are less likely to cause hypoglycaemia compared to other classes of glucose lowering medicines [2].

For these reasons, GLP-1 RAs are a preferred second-line agent in cardiovascular and renal disease and New Zealand guidance states that they should be strongly considered in all patients with diabetic renal disease or cardiovascular disease/high cardiovascular risk [3]. When choosing an add-on therapy, GLP-1 RAs inhibitors may be preferred if cerebrovascular disease is predominant [4].

2.1.1 Dulaglutide [5]

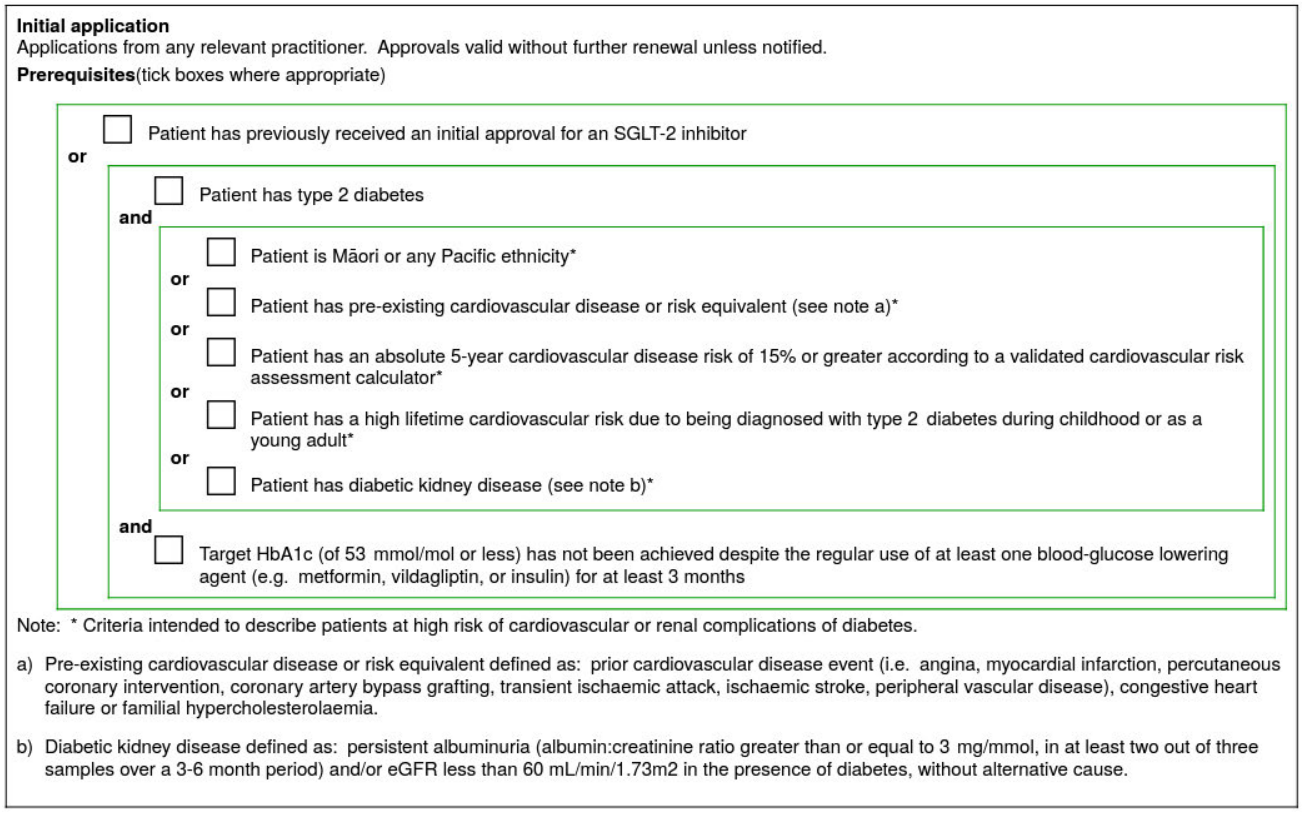
Dulaglutide (Trulicity) is a long-acting GLP-1 RA indicated for the treatment of T2DM as monotherapy or in combination with other blood glucose lowering agents. It is also indicated to reduce the risk of major cardiovascular events in those with T2DM and established cardiovascular disease or multiple risk factors. Dulaglutide has been funded in NZ for selected patients via special authority since September 2021 (Figure 2).

Dulaglutide is administered once a week as a subcutaneous injection (pre-filled pen). The recommended dose for adults (≥18 years old) is 1.5mg once a week. Safety and efficacy of dulaglutide has not been established in children or adolescents under 18 years of age. Dulaglutide should not be used in patients with type 1 diabetes, severe gastrointestinal disease, patients with symptoms of acute pancreatitis, and end stage renal disease. Patients should be warned about the signs of symptoms of acute pancreatitis, and risk of hypoglycaemia in patients receiving dulaglutide in combination with sulfonylureas or insulin. Dulaglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral mediciness. Pharmacology studies suggest dulaglutide does not affect the absorption of orally administered medicines to a clinically relevant degree.

Dulaglutide is relatively resistant to degradation by DDP-4, its large size slows absorption and reduces renal clearance and it has a prolonged half-life of 4.7 days making it suitable for once weekly administration. In addition, the dulaglutide molecule was engineered to prevent the Fcγ-receptor dependent immune response and to reduce its immunogenic potential. Following subcutaneous administration peak plasma concentrations are reached in 48 hours and steady state concentrations were achieved after 2 to 4 weeks of therapy. Dulaglutide is presumed to be degraded into its component amino acids by general protein catabolism pathways. No dose adjustment is needed based on age, gender, race, ethnicity, body weight, renal or hepatic impairment.

Common adverse reactions (≥5%) reported are gastrointestinal related and include nausea, vomiting, diarrhoea, abdominal pain, reduced appetite, dyspepsia, and fatigue. These reactions are mild to moderate in severity and usually subside after 6 weeks. Other adverse events identified (less common) include potentially immune-mediated injection site reactions, urticaria, angioedema, atrial fibrillation, mean increase in heart rate, and an elevation in pancreatic enzymes. In clinical studies treatment with dulaglutide at any dose was associated with a 1.6% incidence of treatment emergent dulaglutide anti-drug antibodies.

Figure 2: PHARMAC Special Authority application form SA2065 for dulaglutide



Initial application
Applications from any relevant practitioner. Approvals valid without further renewal unless notified.
Prerequisites(tick boxes where appropriate)

☐ Patient has previously received an initial approval for an SGLT-2 inhibitor

or

☐ Patient has type 2 diabetes

and

☐ Patient is Māori or any Pacific ethnicity*

or

☐ Patient has pre-existing cardiovascular disease or risk equivalent (see note a)*

or

☐ Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator*

or

☐ Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult*

or

☐ Patient has diabetic kidney disease (see note b)*

and

☐ Target HbA1c (of 53 mmol/mol or less) has not been achieved despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin, or insulin) for at least 3 months

Note: * Criteria intended to describe patients at high risk of cardiovascular or renal complications of diabetes.

a) Pre-existing cardiovascular disease or risk equivalent defined as: prior cardiovascular disease event (i.e. angina, myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, transient ischaemic attack, ischaemic stroke, peripheral vascular disease), congestive heart failure or familial hypercholesterolaemia.

b) Diabetic kidney disease defined as: persistent albuminuria (albumin:creatinine ratio greater than or equal to 3 mg/mmol, in at least two out of three samples over a 3-6 month period) and/or eGFR less than 60 mL/min/1.73m2 in the presence of diabetes, without alternative cause.

Source: PHARMAC. URL: https://schedule.pharmac.govt.nz/2023/09/01/SA2065.pdf (accessed 28 August 2023).

2.1.2 Liraglutide [6]

Liraglutide (Victoza) is indicated as an adjunctive treatment for the improvement of glycaemic control in T2DM and the prevention of major cardiovascular events in adults with T2DM at high cardiovascular risk. Liraglutide has been funded by PHARMAC since 1 March 2023, with similar funding criteria to dulaglutide (Figure 2). Liraglutide was funded due ongoing uncertainty regarding supply of dulaglutide, caused by a global increase in demand for GLP-1 RAs [7]. There is another approved product, Saxenda, which is indicated for weight management and is not funded.

Liraglutide stimulates insulin secretion in a glucose-dependent manner and improves beta-cell function. Simultaneously, liraglutide lowers inappropriately high glucagon secretion, also in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a minor delay in gastric emptying. Liraglutide reduces body weight and body fat mass through mechanisms involving reduced hunger and lowered energy intake.

Victoza is administered subcutaneously and comes as a pre-filled pen. The starting dose is 0.6 mg once daily for at least the first week, to improve gastrointestinal tolerability, and then should be increased to 1.2 mg. The dose can be increased to a maximum of 1.8 mg based on clinical response. No dosage adjustment is necessary for elderly patients, patients with hepatic impairment, or patients with mild, moderate or severe renal impairment. There is no experience with patients with end stage renal disease and use in these patients is therefore not recommended.

Liraglutide is not recommended in patients with congestive heart failure New York Heart Association (NYHA) class IV and patients with inflammatory bowel disease and diabetic gastroparesis.

The most frequently reported adverse reactions during clinical trials were gastrointestinal disorders: nausea and diarrhoea were very common whereas vomiting, constipation, abdominal pain, and dyspepsia were common. At the beginning of Victoza therapy, these gastrointestinal adverse events may occur more

frequently while they usually diminish within a few days or weeks on continued treatment. Liraglutide has been associated with acute pancreatitis, signs and symptoms of dehydration, including renal impairment and acute renal failure, thyroid disease, and hypoglycaemia when used in combination with a sulfonylurea or insulin.

The small delay of gastric emptying with liraglutide may influence absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption and therefore no dose adjustment is required.

2.1.3 Exenatide [8]

Exenatide is a subcutaneous injection indicated as an adjunctive treatment in T2DM. Exenatide is not funded by PHARMAC. Two products (Byetta and Bydureon) have been approved in NZ. Byetta is not available, however has a published NZ data sheet. The approval for Bydureon has lapsed.

2.2 Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) is an enzyme expressed on the surface of most cell types that deactivates a variety of bioactive peptides, including GLP-1 and glucose-dependent insulinotropic polypeptide (GIP). Inhibition of DPP-4 could potentially affect glucose regulation through multiple effects. However, DPP-4 inhibitors have a modest effect on GLP-1 levels and activity compared with GLP-1 receptor agonists [9].

All of the DPP-4 inhibitors appear to have similar glycaemic efficacy and result in modest improvement in HbA1c. They can be used in combination with most other diabetes medications except GLP-1 RAs due to lack of additive glucose-lowering effects [9].

New Zealand diabetes guidelines state that the DPP-4 inhibitors may be used as a second-line agent in T2DM [10]. When choosing an add-on therapy, DPP-4 inhibitors may be preferred in the absence of comorbidities of heart failure, renal disease or cerebrovascular disease [4].

2.2.1 Vildagliptin [11]

Vildagliptin is indicated for the improvement of glycaemic control in patients with T2DM. By increasing the endogenous levels of GLP-1 and GIP, vildagliptin enhances the sensitivity of beta cells to glucose resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with type 2 diabetes significantly improves markers of beta cell function. Vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance. The enhanced increase in the insulin/glucagon ratio during hyperglycaemia due to increased incretin hormone levels results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

Vildagliptin has been funded by PHARMAC since October 2018. Vildagliptin is the only fully subsidised DPP-4 inhibitor and funding is not subject to Special Authority criteria.

The recommended dose is 50 mg once or twice daily. Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5x the upper limit of normal. No dosage adjustment is required in patients with mild renal impairment. In patients with moderate or severe renal impairment or end stage renal disease, the recommended dose of is 50 mg once daily. No dosage adjustments are necessary in elderly patients.

Reported ADRs in monotherapy clinical trials were dizziness (common) and headache, constipation and peripheral oedema (all uncommon). Vildagliptin has been associated with hepatic dysfunction (including hepatitis) and liver function tests should be monitored three-monthly during the first year of treatment and periodically thereafter. Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an ACE inhibitor. Pancreatitis has also been reported.

2.2.2 Saxagliptin [12]

Saxagliptin is indicated as an adjunctive treatement for the improvement of glycaemic control in T2DM. Saxagliptin is not funded in New Zealand.

Treatment with saxagliptin 5 mg once daily produces improvements in HbA1c, fasting plasma glucose (FPG) and postprandial glucose (PPG) compared to placebo in monotherapy, in combination with metformin (initial or add-on therapy), in combination with a sulphonylurea, and in combination with a thiazolidinedione. Saxagliptin is not associated with a change in body weight.

The recommended dose of saxagliptin is 5 mg once daily. When used in combination with a sulphonylurea, a lower dose of sulphonylurea may be required to reduce the risk of hypoglycaemia. For patients with moderate or severe renal impairment or ESRD, the dose is 2.5 mg once daily. Assessment of renal function is recommended prior to initiation and periodically thereafter.

The most commonly reported adverse reactions in placebo-controlled trials are upper respiratory tract infection, urinary tract infection and headache. Saxagliptin has been associated with acute pancreatitis, hypersensitivity reactions, rash, bullous pemphigoid and arthralgia.

2.3 Role of GLP-1 and incretin-based therapies in inhibition of gastrointestinal motility

There is some evidence that GLP-1 inhibits intestinal motility. Animal studies have shown inhibition of small intestinal motility by exogenous GLP-1. Suppression of fasting small intestinal motility by exogenous GLP-1 is also evident in healthy humans and those with irritable bowel syndrome. There is some evidence from animal studies that GLP-1 slows large intestinal transit, but evidence in humans is limited to reports of GLP-1 secreting tumours and their association with severe constipation and markedly delayed colonic transit [13]

It is well-established that GLP-1 RAs delay gastric emptying as part of their mechanism, however this effect has not been established with DPP-4 inhibitors. Two small studies in healthy subjects found that sitagliptin had no effect on gastric emptying when compared to placebo [14, 15]. A 2011 review article found that there is limited evidence describing the effects of exogenous GLP-1 in humans on intestinal motility, and a lack of evidence to show an effect with GLP-1 RAs and DPP-4 inhibitors (Table 1) [13]. However, a small 2017 study on the effects of liraglutide on gastrointestinal motility found that intestinal transit time was increased in diabetic patients without neuropathy, but not those with diabetic neuropathy [16].

The mechanisms by which incretin-based therapies inhibit gastrointestinal motility are not fully known but appear to be complex. Some studies have indicated involvement of the vagal nerves in mediating some of these effects of GLP-1. Inhibition of fasting small intestinal motility in rats by exogenous GLP-1 is mediated via nitric oxide, while suppression of postprandial motility is independent of NO. Studies of the rodent duodenum and colon suggest that GLP-1 can decrease excitatory cholinergic neurotransmission in the enteric nervous system via presynaptic GLP-1 receptors, which modulate NO release. Some gastrointestinal motor effects of GLP-1 appear to be centrally mediated [13].

Table 1: Summary of motor effects of GLP-1 and incretin-based therapies on the gastrointestinal tract (2011 review) [13]

ANNEX 3 for references.

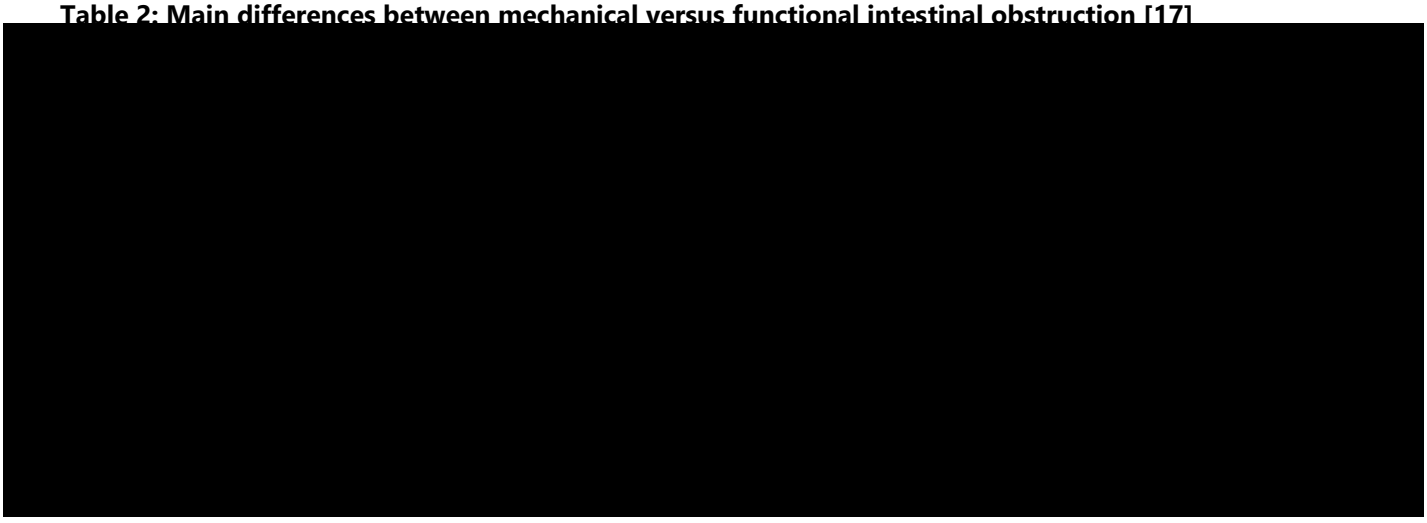
2.4 Gastrointestinal obstruction and ileus

Intestinal obstruction occurs when the normal flow of intraluminal contents is interrupted, and can be mechanical (a physical blockage) or functional (due to dysfunctional peristalsis; also known as ileus or paralytic ileus. Functional disorders include post-operative ileus (POI), acute intestinal pseudo-obstruction (AIPO) and chronic intestinal pseudo-obstruction (CIPO) (Table 2) [17].

Paralytic ileus can be caused by abdominal surgery, peritonitis, trauma, intestinal ischemia, and some medicines. The symptoms are similar to mechanical obstruction, however radiological examination shows air in the large intestine and CT shows no mechanical obstruction. Several medicines have been associated with paralytic ileus, including α-glucosidase inhibitors, antineoplastic agents, antipsychotics, dantrolene, drugs for urinary frequency and incontinence, opium alkaloids, and polystyrene sulfonate. Treatment is usually supportive, as the condition is generally self-limiting but may include management of electrolyte imbalances and nasogastric decompression [17-19].

Chronic intestinal pseudo-obstruction is characterized by symptoms of recurrent abdominal distention that may be associated with nausea, vomiting, and diarrhoea. No mechanical cause can be demonstrated [17].

Table 2: Main differences between mechanical versus functional intestinal obstruction [17]



2.5 New Zealand and international product information

The wording in the local and international product information for GLP-1 RAs that is relevant to gastrointestinal obstruction and ileus is listed in Table 3.

Intestinal obstruction and ileus are not listed in any NZ data sheet for a DPP-4 inhibitor. Internationally, ileus is listed as a post-market ADR in the US Nesina (alogliptin) prescribing information. Intestinal obstruction, ileus or related terms are not listed in any other DPP-4 product information in New Zealand, Australia, UK, Europe, US or Canada. Delayed gastric emptying is not listed in any DPP-4 inhibitor product information in New Zealand, Australia, UK, Europe, US or Canada.

Table 3: Wording in local and international product information for GLP-1 RAs that is relevant to gastrointestinal obstruction and ileus

	NZ	Australia	UK	Europe	US	Canada
Liraglutide (Victoza)	-	-	4.8 Uncommon: delayed gastric emptying Rare: intestinal obstruction	4.8 Uncommon: delayed gastric emptying Rare: intestinal obstruction	Post-market: ileus	-
Dulaglutide (Trulicity)	-	-	4.8 Rare: delayed gastric emptying Not known: non-mechanical intestinal obstruction	4.8 Rare: delayed gastric emptying Not known: non-mechanical intestinal obstruction	Post-market: ileus	-
Exenatide (Byetta)	4.8 Uncommon: delayed gastric emptying; Rare: intestinal obstruction including ileus	4.8 Uncommon: delayed gastric emptying; Rare: intestinal obstruction including ileus	4.8: Uncommon: delayed gastric emptying; Rare: intestinal obstruction	4.8: Uncommon: delayed gastric emptying; Rare: intestinal obstruction	-	-
Semaglutide (Ozempic)	No data sheet	-	4.8 Uncommon: delayed gastric emptying	4.8 Uncommon: delayed gastric emptying	-	-
Lixisenatide (Adlyxin)	Not approved	Not approved	Not approved	Not approved	-	-
Semaglutide (Rybelsus)	Not approved	No PI	-	4.8 Uncommon: delayed gastric emptying	Post-market: ileus	-

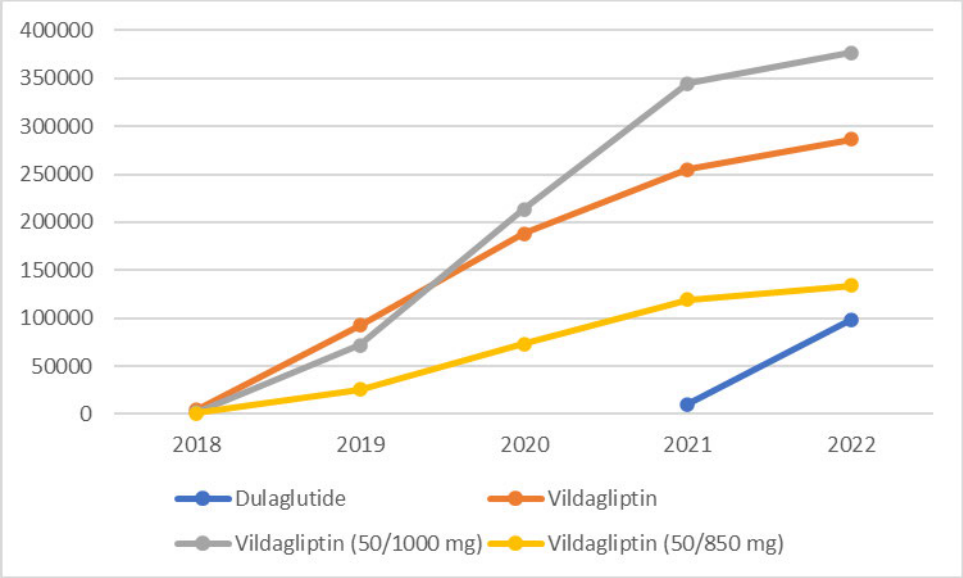
	NZ	Australia	UK	Europe	US	Canada
Exenatide extended release (Bydureon)	Approval lapsed	4.8 (post-market) Not known: ileus	4.8 Uncommon: intestinal obstruction, delayed gastric emptying	4.8 Uncommon: intestinal obstruction, delayed gastric emptying	Post-market: ileus	-

Note: All product information for GLP-1 RAs acknowledges delayed gastric emptying as part of the mechanism, without necessarily listing this as an adverse reaction

2.6 Usage

Dispensing data is available for funded products only and is shown in Figure 3. There is no information on liraglutide as it has only been funded from March 2023.

Figure 3: Number of dispensings of vildagliptin products, 2018-2022



Source: Pharmaceutical Data Web Tool. URL: https://tewhatuora.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 29 August 2023)

3 SCIENTIFIC INFORMATION

3.1 Published literature

The available literature describing a possible association between GLP-1 RAs and DPP-4 inhibitors and gastrointestinal obstruction is described below.

3.1.1 Faillie et al, 2022. Incretin-based drugs and risk of intestinal obstruction among patients with type 2 diabetes [20]

This publication is provided as **Annex 1**.

Aim

The objective of this population-based cohort study was to determine whether GLP-1 RAs and DPP-4 inhibitors are associated with an increased risk of intestinal obstruction compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

Methods

Data sources: The United Kingdom (UK) Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases (patients deduplicated) were linked with the Hospital Episode Statistics (HES) repository and the Office for National Statistics database (ONS).

Study population: This was a new-user, active comparator study design where initiators of GLP-1 RAs and DPP-4 inhibitors were compared with initiators of SGLT-2 inhibitors between January 1, 2013 (the year the first SGLT-2 inhibitor entered the UK market) and December 31, 2019. SGLT2 inhibitors were chosen as the comparator group because they are used at the same disease stage as GLP-1 RAs and DPP-4 inhibitors and have not been associated with intestinal obstruction.

Two cohorts were created:

1. New users of GLP-1 RAs (dulaglutide, exenatide, liraglutide except the weight loss formulation), lixisenatide, semaglutide) and SGLT-2 inhibitors
2. New users of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin) and SGLT-2 inhibitors.

Cohort entry was defined as the date of first prescription of a DPP-4 inhibitor, GLP-1 RA or SGLT-2 inhibitor. Inclusion criteria were age >18 years and >1 year medical history in the CPRD. Exclusion criteria were prescription of a GLP-1 RA or DPP-4 inhibitor prior to the study period, concomitant GLP-1 RA or DPP-4 inhibitor and SGLT-2 inhibitor at cohort entry, previous diagnosis of end-stage renal disease or undergoing dialysis (contraindications to receiving SGLT-2 inhibitors).

Follow-up period: Patients were followed from cohort entry until occurrence of hospitalisation with primary or secondary diagnosis of intestinal obstruction, treatment discontinuation, crossover to one of the study drug classes, death from any cause, end of registration with the general practice, or end of the study period (March 31, 2020).

Potential confounders: There were 57 potential confounders measured at or before cohort entry. These included the year of cohort entry, age, sex, body mass index, alcohol-related disorders, and smoking status. Variables related to diabetes severity, including HbA1C, duration of diabetes, antidiabetic drugs used in the year before cohort entry, and presence of microvascular and macrovascular complications were also considered. Prescription drugs previously associated with reduced intestinal motility or constipation were considered. The authors adjusted for abdominal surgeries ever before cohort entry (a known risk factor for mechanical intestinal obstruction), other surgeries in the 30 days before cohort entry (as postoperative paralytic ileus is a common cause of intestinal obstruction), gastroparesis, abdominal cancers, and other cancers ever before cohort entry. Finally, they adjusted for a number of conditions known to be associated with constipation or bowel obstruction ever before cohort entry.

Statistical analysis: Propensity score fine stratification was used to control for confounding. For each cohort, the authors estimated the predicted probability of receiving an incretin-based drug (GLP-1 RA or DPP-4 inhibitor) versus an SGLT-2 inhibitor using multivariable logistic regression models conditional on the potential confounders listed above. Patients in the non-overlapping regions of the propensity score distributions were trimmed, and 50 strata were created based on the propensity score distribution of the incretin-based drug users. Within each stratum, patients who received an incretin-based drug received a weight of 1, while patients who received an SGLT-2 inhibitor were reweighted proportional to the number of exposed individuals in the stratum.

Descriptive statistics were used to summarize the characteristics of the exposure groups before and after propensity score weighting. Covariate balance between the exposure groups was examined using standardized differences, with standardized differences less than 0.10 indicative of good balance. Weighted incidence rates of intestinal obstruction were calculated for each exposure group, with confidence intervals (CIs) based on the Poisson distribution, as well as weighted Kaplan-Meier curves were constructed for each exposure group. Weighted Cox proportional hazards models were fit to estimate hazard ratios (HRs) with 95% CIs using robust variance estimators of intestinal obstruction, comparing incretin-based drug users with SGLT-

2 inhibitor users. The authors calculated the number needed to harm after one year of use using the Kaplan-Meier approach.

There were four sets of secondary analyses. The first examined whether the association varied according to duration of use. The second examined the association with individual GLP-1 RAs and DPP-4 inhibitors. The third repeated the analyses restricting the outcome to diagnoses more closely related to decreased motility (ICD-10 codes: K56.0, K56.7, and K59.2). The fourth assessed whether there was effect measure modification by age (≥70 vs. <70 years), sex, severity of diabetes, the use of drugs associated with decreased intestinal motility, history of abdominal surgery, and use of incretin-based drugs before cohort entry.

There were four sensitivity analyses to assess the robustness of the results. The first varied the grace periods between non-overlapping prescriptions to 30 and 90 days to assess possible exposure misclassification. The second assessed the validity of the outcome definition by restricting the hospitalised events to those recorded in the primary position. The third analysis excluded patients who underwent surgery in the 30 days before cohort entry and censored on new surgeries during the follow-up period to exclude events potentially attributable to surgeries. Finally, the potential impact of informative censoring was assessed by reweighing the cohorts using inverse probability of censoring weighting to account for treatment termination and switching, death from any cause, and administrative censoring.

Results

The first cohort included 25,617 new GLP-1 RA users and 67,261 new SGLT-2 inhibitor users. Before propensity score weighting, the exposure groups were similar on most baseline characteristics, with the exception that GLP-1 RA users were more likely to be obese, were more likely to have uncontrolled diabetes, had a higher prevalence of micro- and macrovascular complications of diabetes, and were more likely to have used certain prescription medicine. The GLP-1 RA and SGLT-2 inhibitor users were followed for a median (Q1, Q3) of 0.9 (0.4, 2.1) and 0.5 (0.2, 1.5) years, respectively.

The second cohort included131,927 new DPP-4 inhibitor users and 40,615 new SGLT-2 inhibitor users . Before propensity score weighting, DPP-4 inhibitor users had a higher prevalence of micro- and macrovascular complications of diabetes. SGLT-2 inhibitor users were more likely to be obese and have uncontrolled diabetes. The DPP-4 inhibitor and SGLT-2 inhibitor users were followed for a median (Q1, Q3) of 1.1 (0.5, 2.5) and 0.8 (0.3, 1.8) years, respectively.

Primary analyses: The use of GLP-1 RAs and DPP-4 inhibitors were both associated with an increased risk of intestinal obstruction when compared with the use of SGLT-2 inhibitors.

The weighted incidence rates of intestinal obstruction were 1.9 and 1.1 per 1,000 person-years for GLP-1 RAs and SGLT-2 inhibitors, respectively, and the weighted HR was 1.69 (95% CI: 1.04-2.74) (Table 4). The cumulative incidence curves diverged after 8 months of use (Figure 4). The risk gradually increased with duration of use, with the greatest HR observed around 1.6 years of use.

The weighted incidence rates of intestinal obstruction were 2.7 and 1.0 per 1,000 person-years for DPP-4 inhibitors and SGLT-2 inhibitors, respectively, and the weighted HR for intestinal obstruction was 2.59 (95% CI: 1.52-4.42) (Table 4). The cumulative incidence diverged after 4 months of use (Figure 5). The highest HR was observed around 1.8 years of use. Overall, the number needed to harm after 1 year of use was 1,223 for GLP-1 RAs and 603 for DPP-4 inhibitors.

Table 4: Hazard ratios for intestinal obstruction comparing GLP-1 RAs and DPP-4 inhibitors with SGLT-2 inhibitors

[redacted]

Figure 4: Weighted cumulative incidence curves of intestinal obstruction for GLP-1 RAs vs SGLT-2 inhibitors

Figure 5: Weighted cumulative incidence curves of intestinal obstruction for DPP-4 inhibitors vs SGLT-2 inhibitors

Secondary analyses: All GLP-1 RAs had elevated HRs for intestinal obstruction with wide confidence intervals, except semaglutide which did not have any events. For DPP-4 inhibitors, linagliptin had the highest HR (3.65, 95% CI: 1.93-6.90). When outcomes were restricted to diagnostic codes most related to intestinal obstruction, the association with GLP-1 RAs was lost while DPP-4 inhibitors had a higher HR. The HRs for both GLP-1 RAs and DPP-4 inhibitors were higher for those aged ≥70 years compared with those aged ≤70 years, but the confidence intervals overlapped. Sex and diabetes severity did not significantly modify the associations. The risk was increased in those taking medicines known to alter gastric motility. There was no affect modification with history of abdominal surgery or use of other incretin-based medicines prior to cohort entry.

Sensitivity analyses: The results of the sensitivity analyses were similar to the primary analyses (Figure 6). Restricting outcomes to hospitalisations with primary position decreased the HRs.

Figure 6: Forest plot summarising the primary and sensitivity analyses for the risk of intestinal obstruction associated with the use of GLP-1 RAs and DPP-4 inhibitors vs SGLT-2 inhibitors

Discussion

This study found an increased risk of intestinal obstruction in new users of both GLP-1 RAs and DPP-4 inhibitors when compared to new users of SGLT-2 inhibitors. The cumulative incidence curves diverged after 4 to 8 months of treatment and the highest associations were seen at 1.6 to 1.8 years of use. The findings generally remained consistent in sensitivity analyses. Differences when restricting the outcome to hospitalised events in the primary position or excluding and censoring on any surgery likely result from decreased number of events and loss of statistical power.

The authors consider that the association has biological plausibility. GLP-1 has been shown to inhibit small intestinal motility in human and animal studies, and colonic transit in rats. In human studies, gastrointestinal transit time was reduced by exendine, an inverse agonist of GLP-1 and increased by liraglutide. GLP-1 supresses intestinal contractions via a mechanism that is not fully understood. However, it may involve i) the central nervous system via vagal cholinergic pathways or direct action on central GLP-1 receptors, and/or ii) the enteric nervous system by inhibiting neurotransmission through presynaptic GLP-1 receptors modulating nitric oxide release.

In this study, DPP-4 inhibitors were associated with an increased risk of intestinal obstruction compared with GLP-1 inhibitors. This result contrasts with short-term clinical data showing slower gastric emptying with GLP-1 RAs compared with DPP-4 inhibitors. The authors hypothesise that the higher risk with DPP-4 inhibitors could imply the action of DPP-4 in the metabolism of other peptides, such as peptide YY and GLP-2. Peptide YY is released by entero-endocrine L cells in response to meal ingestions and appears to decrease intestinal transit. GLP-2 inhibits gastrointestinal motility at supra-physiological levels by promoting smooth muscle relaxation and possibly inhibiting intestinal cholinergic activity.

The analysis for interaction with medicines known to inhibit intestinal motility was close to statistical significance. The authors suggest that indicates that the risk of intestinal obstruction could be reduced by avoiding concomitant treatment with these medicines.

The strengths of the study were i) use of a high quality, representative database to achieve large cohorts, ii) use of a new user, active design to reduce prevalent user bias, and iii) use of SGLT-2 inhibitors as the comparator as these are used at a similar disease stage.

Limitations of the study were i) possible misclassification due to use of records of written prescriptions, ii) CPRD records do not include specialist prescriptions (although diabetes is usually managed in primary care) iii)

outcome misclassification is possible and the outcome definition has not been formally validated, iv) residual confounding is possible despite use of an appropriate comparator and adjustment for potential confounders, v) the secondary analyses had wide confidence intervals and should be interpreted with caution.

Comments

Given the proposed mechanism, it is surprising that direct agonists of GLP-1 receptors showed a lower risk of intestinal obstruction than DPP-4 inhibitors, which reduce degradation of GLP-1.

There were some differences in baseline characteristics between the groups which were adjusted for by propensity score weighting, however there may be residual or unmeasured confounding.

Exposure misclassification may arise from the use of prescribing records and a long grace period to define exposure status. There may be outcome misclassification due to the use of an unvalidated outcome definition. The time to event analysis based on hospitalisation may not accurately represent the onset of gastrointestinal obstruction. Use of hospitalisation data may not capture mild intestinal obstruction.

The study does not account for events occurring during follow-up that may impact the risk of intestinal obstruction.

The relatively small number of events makes analysis of risk with individual DPP-4 inhibitors difficult.

3.1.2 Bennett et al, 2016. Association between therapy with dipeptidyl peptidase-4 (DPP-4) inhibitors and risk of ileus: a cohort study [21]

This publication is provided as **Annex 2.**

Aim

To estimate and compare incidence rates of ileus among alogliptin users and users of other DPP-4 inhibitors, GLP-1 RAs and voglibose.

Methods

This was a retrospective cohort study using the Japanese Medical Data Vision (MDV) database. The MDV contains medical records from mostly tertiary hospitals covering eight million patients. The authors state that the database population is approximately representative of the Japanese population. The study period was 1 April 2010 to 30 September 2014. Patients with type 2 diabetes who received a first-time prescription for alogliptin, other DPP-4 inhibitors, GLP-1 RAs, or voglibose (an alpha-glucosidase inhibitor not approved in New Zealand) during the study period were eligible for inclusion.

Exposure cohorts: There were four exposure cohorts:

1. New users of alogliptin
2. New users of other DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, linagliptin, teneligliptin, or anagliptin)
3. New users of GLP-1 RAs (exenatide, lixisenatide, exenatide-LAR, or liraglutide)
4. New users of voglibose.

The inclusion criteria were first-time use of a study medicine of interest, diagnosis of T2DM, age ≥40 years, at least 12 months of medical history in MDV prior to cohort entry, and at least 1 day of follow-up after cohort entry. Patients were excluded if they had previous prescriptions for a DPP-4 inhibitor, GLP-1 RA or voglibose, started use of more than one of the study medicines on the same day, or had a diagnosis of ileus in the year prior to cohort entry to avoid misclassification of prevalent ileus cases as incident cases.

Cohort entry was defined as the date of the first prescription of the medicine of interest. Follow up ended with incident diagnosis of ileus, end of study period, or end of index treatment episode. The latter was captured as the earliest of either the ending date of supply of the last prescription for that medicine or the day before the

start date of a new study medicine. The study allowed for up to 30 days between prescription supply periods as continuous therapy.

Outcomes: ICD-10 codes K56.7 for 'ileus, unspecified' and K56.0 for 'paralytic ileus'.

Confounders: The study considered medical history such as chronic kidney disease, myocardial infarction, peripheral vascular disease, congestive heart failure, coronary artery disease, diabetic retinopathy, diabetic nephropathy, peripheral neuropathy, urinary infection, and other potential confounders believed to affect the risk of ileus including abdominal surgery, laparoscopy, appendectomy, cholecystectomy, gastrectomy, herniorrhaphy (hernia repair), intra-abdominal infections/inflammation including peritonitis, appendicitis, and diverticulitis; serious infection such as pneumonia; metabolic derangements including diabetic ketoacidosis or diabetic hyperosmolar coma; colorectal cancer, bowel disorders including irritable bowel syndrome (IBS), Crohn's disease, and coeliac disease; medication history including calcium channel blockers, antihistamines, and psychotropics including phenothiazines, tricyclic antidepressants, and opiates.

Statistical analysis: Descriptive statistics were used to examine patient baseline characteristics. Incidence rates of ileus per 1000 person-years with 95 % confidence intervals (CIs) for each exposure cohort were calculated. Risk windows of within 30 days, 31-90 days, within 90 days and ≥91 days after cohort entry were examined. Kaplan–Meier survival curves were used to estimate ileus events over time in each cohort. Poisson regression models with adjustment for potential confounding factors assessed at baseline were used to estimate incidence rate ratios for ileus and 95% CIs by comparing the alogliptin cohort with each of the other exposure cohorts. This was carried out for the 90 day risk window. To assess potential confounding, a bivariate analysis identified covariates associated with both exposure and outcome at the 10% alpha level and those significantly associated with both were then tested in the models. Only those covariates significant at the 5 % alpha level were included in the final models.

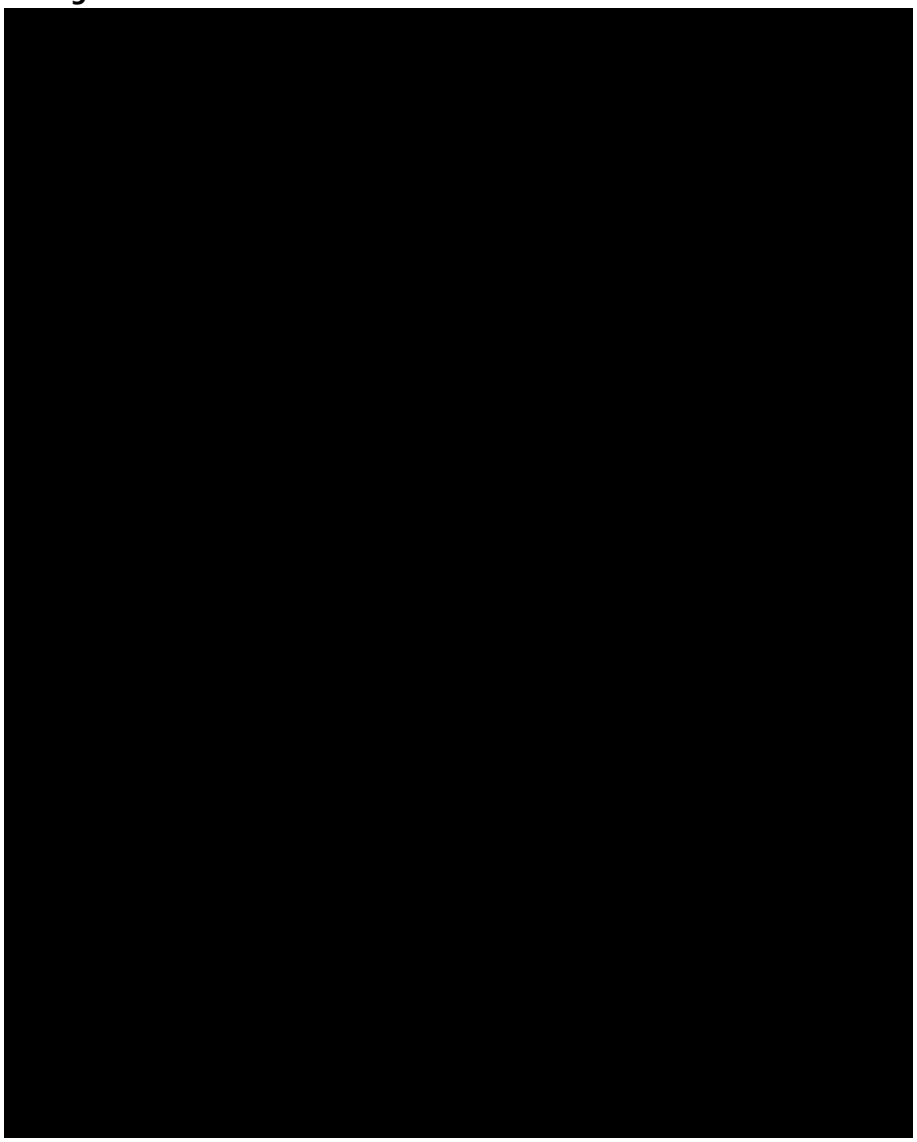
Results

Between 1 April 2010 and 30 April 2014, there were 82,386 eligible patients with type 2 diabetes identified in the MDV database, of whom 9,663 (11.7 %), 55,919 (67.9 %), 1,904 (2.3 %), and 14,900 (18.1 %) were new users of alogliptin, other DPP-4 inhibitors, a GLP-1 receptor agonists, and voglibose, respectively.

Patient characteristics: The mean age at cohort entry was 68.7 years and 60.8% of participants were men. Of the patients with diabetes, 57.5% had not used any diabetes medicines in the year prior to cohort entry. Among patients who used antidiabetic medicines, sulfonylureas (6–22%), insulins (10–35%), and biguanides (3–18 %) were the most common. Insulin therapy among alogliptin users in the year prior to cohort entry was relatively low compared with users of other DPP-4 inhibitors (12 vs 21%). The most common baseline medical conditions were congestive heart failure, diabetic nephropathy, chronic kidney disease and diabetic retinopathy.

Incidence of ileus: The crude overall incidence of ileus was 9.05 per 1,000 person-years (95% CI 7.36-11.13) for alogliptin, 10.26 per 1000 person-years (95% CI 9.50–11.08) for other DPP-4 inhibitors, 32.16 per 1000 person-years (95% CI 14.45–71.59) for GLP-1 RAs, and 12.24 per 1000 person-years (95 % CI 10.64–14.08) for voglibose (Table 5).

Table 5: Incidence of ileus among new users of alogliptin, other DPP-4 inhibitors, GLP-1 RAs, and voglibose



At 3 months after cohort entry, 1.11 % of users of GLP-1 receptor agonists had developed ileus, compared with only 0.31, 0.29, and 0.51 % of alogliptin, other DPP-4 inhibitors and voglibose users, respectively. At 6 months, 1.93, 0.48, 0.59, and 0.85 % of users of GLP-1 agonists, alogliptin, other DPP-4 inhibitor, and voglibose had experienced ileus, respectively. At 1 year after cohort entry, the percentage of GLP-1 receptor agonist users who developed ileus remained at 1.93 %; however, 1.03, 1.09, and 1.38 % of users of alogliptin, other DPP-4 inhibitors, and voglibose, respectively, had developed ileus at that time (Figure 7).

Figure 7: Kaplan–Meier survival curves for incidence of ileus after first use of alogliptin, other DPP-4 inhibitors, GLP-1 RAs and voglibose

Multivariate analysis: For the risk window of ≤90 days, there was no difference in risk of ileus among patients exposed to alogliptin compared with either of the other DPP-4 inhibitor-exposed patients [incident rate ratio (IRR) 1.15, 95% CI 0.75–1.75] or patients exposed to GLP-1 receptor agonists (IRR 0.42, 95 % CI 0.14–1.20). The risk of significantly lower for patients exposed to alogliptin compared with patients exposed to voglibose (IRR 0.55, 95 % CI 0.35–0.88) (Table 6: Multivariate analysis of incidence of ileus among patients exposed to alogliptin compared with other DPP-4 inhibitors: ≤90-day exposure-risk window (N=65,582)Table 7: Multivariate analysis of incidence of ileus among patients exposed to alogliptin compared with GLP-1 receptor agonists: ≤90-day exposure-risk window (N=11,567) (Table 6, Table 7 and Table 8).

Table 6: Multivariate analysis of incidence of ileus among patients exposed to alogliptin compared with other DPP-4 inhibitors: ≤90-day exposure-risk window (N=65,582)

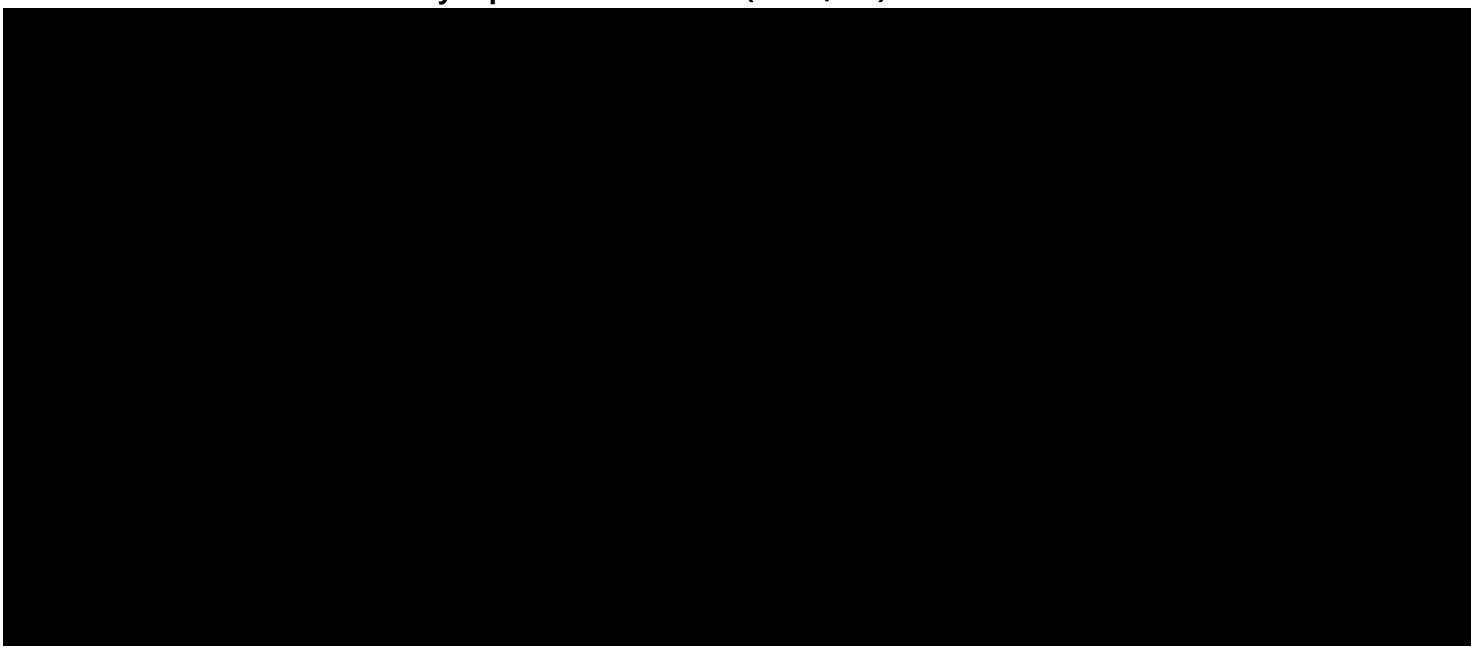


Table 7: Multivariate analysis of incidence of ileus among patients exposed to alogliptin compared with GLP-1 receptor agonists: ≤90-day exposure-risk window (N=11,567)

Table 8: Multivariate analysis of incidence of ileus among patients exposed to alogliptin compared with voglibose: ≤90-day exposure-risk window (N = 24,563)

Discussion

The authors state that the results of this study show that the unadjusted incidence of ileus among users of alogliptin was similar to rates among users of other DPP-4 inhibitors, while the rate for users of GLP-1 receptor agonists was higher. The adjusted analysis did not indicate a difference in risk between alogliptin and other DPP-4 inhibitors or GLP-1 RAs. However, the number of events with GLP-1 RAs was small and the confidence intervals were wide. The authors noted the higher proportion of patients with diabetic complications in the GLP-1 RA group.

The risk was lower in patients taking alogliptin compared to voglibose. The authors were not surprised by this finding, given the published case reports of incident ileus among patients taking a-glucosidase inhibitors, which have documented gastrointestinal side effects.

The post hoc power calculations based on an observed annual incidence of ileus among users of other DPP-4 inhibitors of 1.184 % at 11,908 patient-years exposure showed the study had 96 % power to detect a doubling of the risk of ileus.

The limitations of the study that were noted by the authors were the possibility of residual confounding, lack of generalisability to other populations and healthcare settings, risk of information bias if patients received medicines in healthcare institutions that did not contract with MDV, and lack of information of disease duration.

Conflicts of interest: All authors declare that they have no conflict of interest except that they are all employees of Takeda Pharmaceutical Company Limited (MAH for alogliptin products).

Comments

The database that was used consisted of mostly tertiary hospitals and it is uncertain whether this would reflect overall patterns of prescribing and incidents of ileus. Type 2 diabetes is usually managed in a primary care setting. The study was conducted in a Japanese population and may not be generalisable to other populations.

There were differences between the cohorts in terms of medical history (including indicators of diabetes severity) and prior use of antidiabetic medicines, and there is likely to be residual confounding.

It is unclear whether the comparator groups were suitable for detecting an increased risk of ileus with DPP-4 inhibitors. GLP-1 RAs carry a possible risk of ileus due to their direct agonism of GLP-1. The authors state that voglibose may be associated with ileus.

The authors had competing interests in that they were employed by a sponsor of alogliptin products. There are no alogliptin products approved in New Zealand.

3.1.3 Kanasaki et al, 2013. Three ileus cases associated with the use of dipeptidyl peptidase-4 inhibitors in diabetic patients [22]

This case series presents three cases of ileus in diabetic patients that were considered to be closely related to the use of DPP-4 inhibitors.

Case 1

The first patient was a 70-year-old Japanese man with a history of diabetes without diabetic nephropathy or retinopathy. He had undergone surgery for appendicitis. In addition, the patient had been treated for Parkinson's disease with levodopa–carbidopa tablets for 2 years, and his condition was stable with mild rigidity. The patient presented at the hospital complaining of persistent nausea, vomiting, and diarrhoea for 2 days. The patient had been prescribed alogliptin 25 mg daily to replace mitiglinide 11 days prior to his presentation at hospital. Abdominal X-ray and computed tomography (CT) revealed air–fluid levels in his intestines. After admission, the condition resolved without intervention. Alogliptin was discontinued.

Case 2

The second patient was a 61-year-old Japanese woman with myeloperoxidase ANCA-positive rapidly progressive glomerulonephritis being treated with prednisolone. The patient was in a stable condition (eGFR 29 mL/min per 1.73 m^2). The patient had undergone surgery for early gastric cancer 25 years previously.

The patient had undergone a number of changes to her diabetes medicines, and was treated with vildagliptin, mitiglinide and miglitol for four months. Vildagliptin was then changed to alogliptin. Thirty-eight days later, she developed intermittent abdominal pain and vomiting. She had experienced difficulty in emptying her bowel for the past month. She was identified with air–fluid levels in her colon and was admitted to the surgical unit for further assessment. X-Ray and CT imaging indicated that her ileus was becoming worse. Gastrointestinal decompression was performed via a nasoenteric tube but was not effective. Surgical decompression and reconstructive surgery were performed for a collapsed small intestine, which revealed an internal hernia.

Case 3

The third patient was a 78-year-old Japanese man with a history of type 2 diabetes. The patient had chronic kidney disease (eGFR 46 mL/min per 1.73 m2). The patient had undergone total gastrectomy with partial pancreatosplenectomy and left adrenalectomy 12 years ago for advanced gastric cancer. He had an ileus that was resolved with conservative treatment 5 years ago. One day prior to admission, the patient experienced intermittent lower left abdominal pain with nausea and vomiting. X-Ray and CT scans revealed air–fluid levels in his intestines. The patient was admitted to hospital for ileus. Gastrointestinal decompression via a

nasoenteric tube was successful and the patient was discharged 3 weeks after admission. His diabetes had been treated with glargine, metformin, miglitol, repaglinide, and sitagliptin. The patient was also taking amlodipine, aliskiren, calcium polystyrene sulfonate, camostat mesilate, liver hydrolysate, and mosapride citrate hydrate. His diabetes was relatively stable, with an HbA1c of 8.0% (NGSP4), but random sampling revealed blood sugar levels >300 mg/dL. Thirty-three days prior to his admission for the ileus, the vildagliptin was prescribed to replace sitagliptin.

Discussion

The authors acknowledge that concomitant medicines, history of major abdominal surgery, history of ileus, and comorbidities such as ANCA-associated vasculitis and Parkinson's disease may have affected gastrointestinal motility in these patients. However, the authors also note that in all three cases, medication changes resulting in increased inhibition of DPP-4 were made within 40 days of onset of ileus. The authors suggest that incretin-associated drug effects on bowel motility may interact with underlying conditions, such as a history of abdominal surgery, microangiopathy in the gastrointestinal system, or autonomic defects.

3.1.4 Gudin et al, 2020. Incretin-based drugs and intestinal obstruction: A pharmacovigilance study [23]

Aim

To investigate the risk of serious intestinal obstruction associated with incretin-based drugs and explore the potential for a class effect by performing a disproportionality analysis in a global pharmacovigilance database.

Methods

VigiBase is a global database of spontaneous reports of ADR managed by the World Health Organisation which contains more than 20 million spontaneous ADR reports from more than 130 countries. The data that as extracted was age, gender, country, reporter type, exposure dates, description of adverse event, seriousness, onset and outcome.

The authors extracted all reports of adverse reactions of patients exposed to at least one diabetes medicine (ATC class A10) between January 2007 (the first year of marketing of an incretin-based drug) and January 2018. The reporting odds ratio (ROR) was calculated, comparing exposure to incretin-based medicines between cases and non-cases. Cases were defined as reports with a reaction under the MedDRA High Level Group Term (HLGT) 'Gastrointestinal stenosis and obstruction'. Temporal analyses examined the potential effect of safety communications. A restricted analysis was conducted in serious cases in patients aged over 40 years between January 2013 and March 2016. The intention of this was to limit the sample size and allow the extraction of individual data necessary to interpret information on seriousness.

Results

Between January 2007 and January 2018, 501,244 adverse reactions reported with diabetes medicines were recorded in VigiBase. There were 698 cases of intestinal obstruction identified, of which 452 cases involved an incretin-based medicine: 258 (57.1%) reported a DPP-4 inhibitor, 216 (47.8%) a GLP-1 analogue, and 11 (2.5%) both classes of medicines. The most frequently reported incretin-based medicines were sitagliptin (33.4%), exenatide (25.4%), liraglutide (14.6%), vildagliptin (8.8%), and dulaglutide (7.5%).

Intestinal obstruction was 4.5 times more frequently reported with incretin-based medicines than with other diabetes medicines (ROR 4.52, 95%CI: 3.87–5.28). The disproportionate reporting was statistically significant for each incretin-based medicine (except for albiglutide, lixisenatide and semaglutide for which the ROR was not computable because of too few exposed cases). There was a greater signal for DPP-4 inhibitors (ROR 8.66, 95%CI: 7.27–10.32) compared to GLP-1 RAs (ROR 3.05, 95%CI: 2.54–3.66).

The RORs did not increase after the issuing of a safety communication by the Japanese regulatory authority. The ROR peaked in 2015, which was the same year that the EMA reported several cases of intestinal obstruction associated with sitagliptin and vildagliptin, and decreased afterwards.

The secondary analysis that was restricted to serious adverse reactions only, based on 125 exposed cases, showed a higher ROR for incretin-based drugs with a greater signal for DPP-4 inhibitors (ROR 12.67, 95%CI: 8.99–17.65).

Conclusion

The authors state that this 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-4 inhibitors compared to GLP-1 RAs.

Comments

Disproportionality analysis is a crude method of signal detection and due to its limitations, it cannot provide information on causality.

3.2 Company signal review

The following signal evaluation notifications have been received from sponsors. The full notifications are included as **Annex 4**.

[redacted]

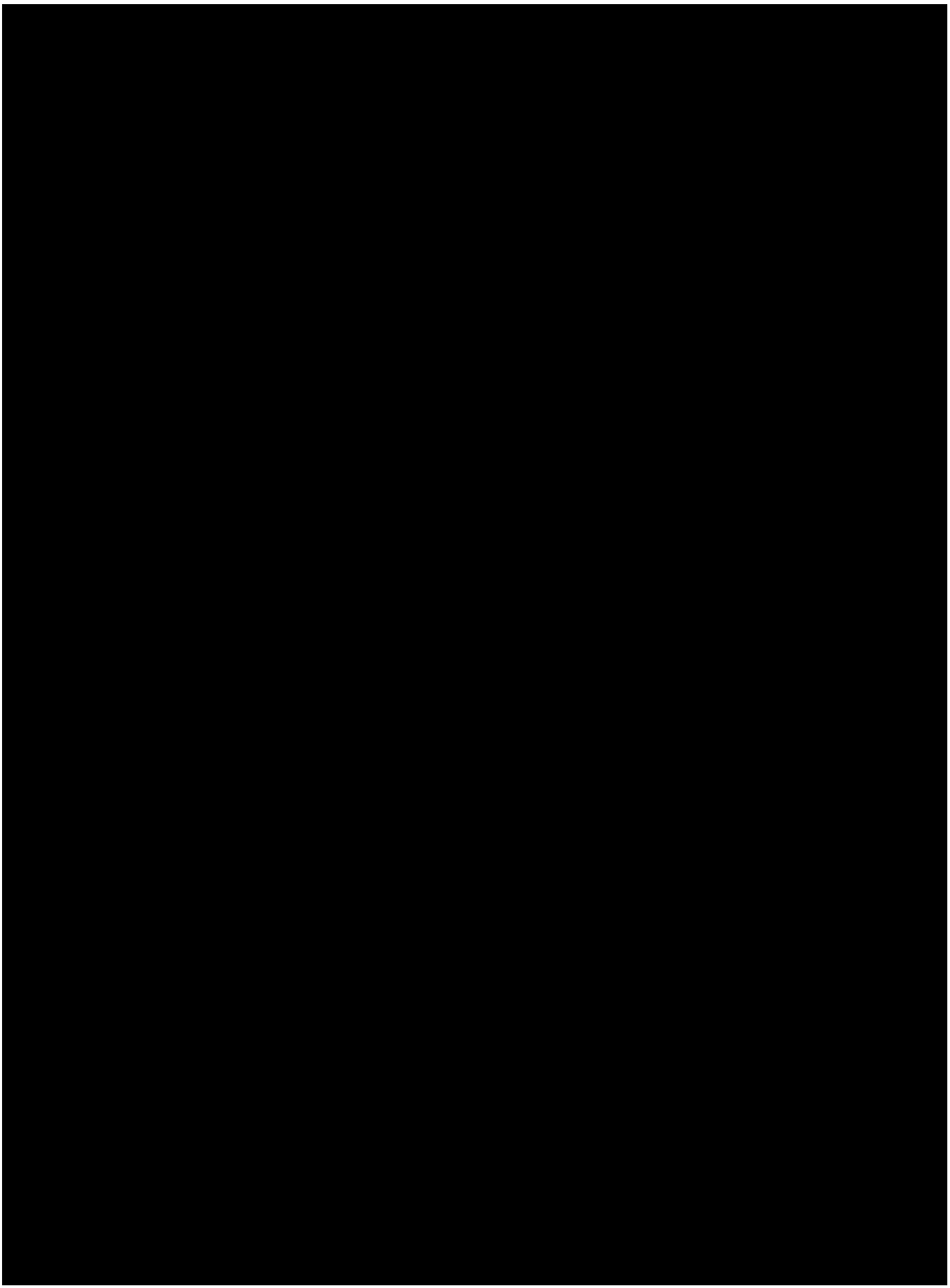
3.2.1 AstraZeneca (Onglyza, Kombiglyze)

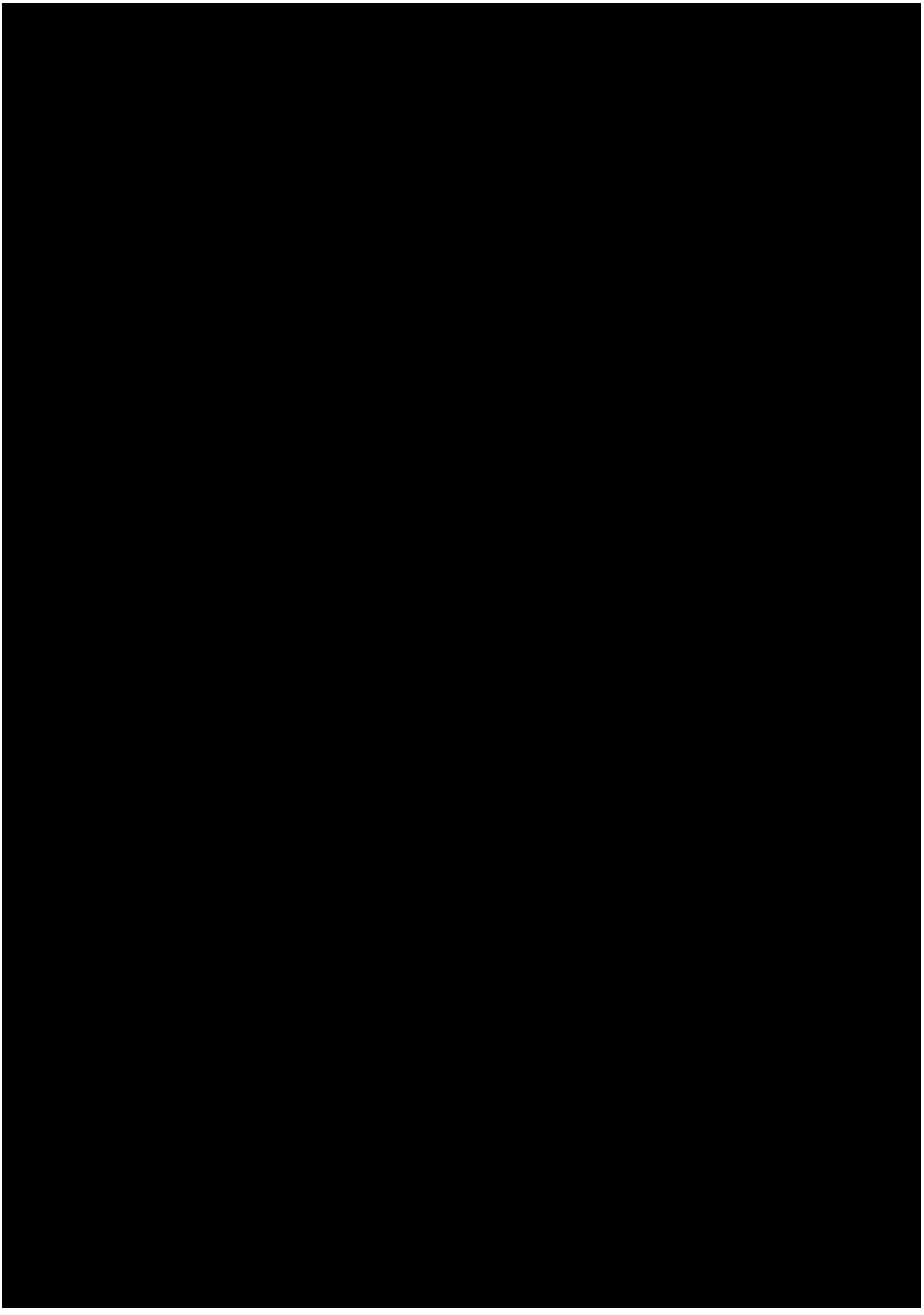
[redacted]

[redacted]

3.2.2 Novo Nordisk (Ozempic, Saxenda, Victoza)

[redacted]





[redacted]

3.3 Spontaneous reporting data

3.3.1 CARM data

There have been no relevant reports to CARM of any terms in the Standardised MedDRA Query 'Intestinal obstruction' in relation to DPP-4 inhibitors or GLP-1 RAs.

3.3.2 Vigilyze

[redacted]

Figure 8: Number of VigiLyze case reports of under the SMQ Gastrointestinal obstruction (narrow) associated with each GLP-1 RA, as of 29 August 2023

3.3.2.2 DPP-4 inhibitors

Figure 9: Number of VigiLyze case reports of under the SMQ Gastrointestinal obstruction (narrow) associated with each DPP-4 inhibitor, as of 29 August 2023

4 DISCUSSION AND CONCLUSIONS

This report presents the available information describing a possible association between the classes of GLP-1 RAs and DPP-4 inhibitors and intestinal obstruction.

This review was triggered [redacted] The scope of this report has been expanded to also consider GLP-1 RAs due to a possible common mechanism. Medsafe has previously requested data sheet updates for GLP-1 RAs to list intestinal obstruction but this request was declined by sponsors. Since then, new information has become available necessitating further review of this topic. Usage of these medicines has rapidly increased in New Zealand over the last five years. However, no local reports of gastrointestinal obstruction or ileus have been received to date in relation to these medicines. No international reports of regulatory action have been published.

An association between GLP-1 RAs and/or DPP-4 inhibitors and gastrointestinal obstruction or ileus is thought to have biological plausibility based on a theoretical effect of GLP-1 in reducing gastrointestinal motility.

Intestinal obstruction is listed as an ADR for GLP-1 RAs (excluding semaglutide) in the UK and Europe. In the US, ileus is listed as a post-market ADR for some GLP-1 RAs. In New Zealand and Australia, only exenatide lists intestinal obstruction. These terms are not listed for DPP-4 inhibitors in New Zealand, Australia, UK, Europe, US or Canada.

Spontaneous reporting data shows disproportional reporting for many reaction terms associated with gastrointestinal obstruction and ileus. However, this information is hypothesis generating only and does not provide information on causality.

There is limited scientific literature describing this association. The most recent cohort study by Faillie et al examined whether GLP-1 RAs and DPP-4 inhibitors are associated with an increased risk of intestinal obstruction compared with sodium-glucose cotransporter-2 (SGLT-2) inhibitors. The study found that both GLP-1 RAs and DPP-4 inhibitors were associated with an increased risk of gastrointestinal obstruction. The risk with DPP-4 inhibitors was higher than with GLP-1 RAs, which is surprising given the proposed mechanism. The study had limitations such as potential misclassification of exposure and residual confounding which may have affected the results.

Another cohort study by Bennett et al found similar rates of ileus between alogliptin and other DPP-4 inhibitors and a much higher rate with GLP-1 RAs. The comparators in this study are also suspected to be associated with ileus. The study is likely to be affected by residual confounding due to differences in baseline characteristics between the cohorts.

There is limited evidence of an increased risk of gastrointestinal obstruction with GLP-1 RAs and DPP-4 inhibitors and there may be confounding by indication. There have been no case reports in New Zealand to date.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the available evidence suggests a causal association between GLP-1 RAs and/or DPP-4 inhibitors and gastrointestinal obstruction or ileus
- Whether the data sheets of GLP-1 RAs and/or DPP-4 inhibitors should be updated to reflect this risk, and if so, what the most appropriate terminology would be
- Whether any further regulatory action or communication should be undertaken.

6 ANNEXES

Annex 1 – Faillie et al.

Annex 2 – Bennett et al.

Annex 3 – List of references describing effects of GLP-1 and incretin-based therapies on gastrointestinal motility in Table 1.

Annex 4 – Company signal notifications.

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8 ANNEX 3

List of references describing effects of GLP-1 and incretin-based therapies on gastrointestinal motility in Table 1.

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