Medicines Adverse Reactions Committee

Meeting date	10/03/2022	Agenda item	3.2.1
Title	**Glucagon like peptide-1 receptor agonists and drug induced liver injury.**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active ingredient	**Product name**	**Sponsor**
Dulaglutide	Trulicity	Eli Lilly and Company NZ Limited
Exenatide	Bydureon	AstraZeneca Limited
	Byetta	AstraZeneca Limited
Liraglutide	Saxenda	Novo Nordisk Pharmaceuticals Limited
Semaglutide	Ozempic	Not approved/available in NZ
	Rybelsus	Not approved/available in NZ
Lixisenatide	Adlyxin	Not approved/available in NZ

PHARMAC funding	Dulaglutide is funded via special authority
Previous MARC meetings	This topic has not been discussed previously.
International action	[redacted]
Classification	Prescription medicine
Advice sought	**The Committee is asked to advise:** • Whether the current evidence supports an association between drug induced liver injury and glucagon like peptide-1 agonists? • If the association is considered valid, should the data sheets for all medicines in this class be updated to include the risk of liver injury? • This topic requires further communication other than MARC's Remarks in *Prescriber Update*?

Table of Contents

1 PURPOSE ... 3
2 BACKGROUND ... 3
2.1 Glucagon Like Peptide 1 Receptor Agonists ... 3
2.1.1 Dulaglutide [3] ... 3
2.1.2 Exenatide [4,5] ... 4
2.1.3 Liraglutide [6] ... 5
2.2 Type 2 Diabetes Mellitus ... 6
2.3 Obesity ... 6
2.4 Drug-induced liver injury (DILI) ... 7
2.5 Regulatory action ... 8
2.6 Data sheets ... 8
2.6.1 Dulaglutide ... 8
2.6.2 Exenatide ... 9
2.6.3 Liraglutide ... 9
2.6.4 Summary ... 12
2.7 Usage ... 12
3 SCIENTIFIC INFORMATION ... 12
3.1 Case reports ... 12
3.1.1 Neahusan et al (2021) ... 12
3.1.2 Maor et al (2021) ... 12
3.1.3 Parvataneni et al (2021) ... 13
3.1.4 Kern et al (2014) ... 13
3.2 Published literature ... 14
3.2.1 Armstrong et al (2012) ... 14
3.2.2 Lv et al (2020) ... 15
3.2.3 Hupa-Breier et al (2021) ... 20
[redacted]
3.4 Spontaneous ADR reporting data ... 22
3.4.1 CARM data ... 22
3.4.2 FAERS data (United States) ... 22
3.4.3 VigiLyze data ... 22
4 DISCUSSION AND CONCLUSIONS ... 23
5 ADVICE SOUGHT ... 23
6 ANNEXES ... 24
7 REFERENCES ... 24

1 PURPOSE

[redacted]

In New Zealand, dulaglutide is indicated for the management of type 2 diabetes mellitus (T2DM) and is the only funded GLP1-RA. T2DM affects many New Zealanders, therefore the expected use of this medicine is high. As DILI is potentially a serious adverse event, Medsafe is referring this safety concern to the MARC. For the purpose of this paper, only the three GLP1-RA products available in New Zealand (dulaglutide, exenatide, liraglutide) will be discussed.

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. 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 [1]. 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.

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].

GLP1-RA 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 comparison with placebo, all GLP1-RA reduced glycated haemoglobin (HbA1c) by 0.55-1.38% in patients with T2DM [2]. GLP1-RA 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].

Comments:

GLP1-RA are a relatively new drug class for T2DM: exenatide was the first GLP1-RA approved by the FDA in 2005 and by Medsafe in 2007. Use of GLP1-RA is rising due to the prevalence of T2DM and updates in T2DM management guidelines.

2.1.1 Dulaglutide [3]

Dulaglutide (Trulicity) is a long-acting GLP1-RA indicated for the treatment of T2DM as monotherapy or in combination with other blood lowering agents. It is also indicated to reduce the risk of 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 1).

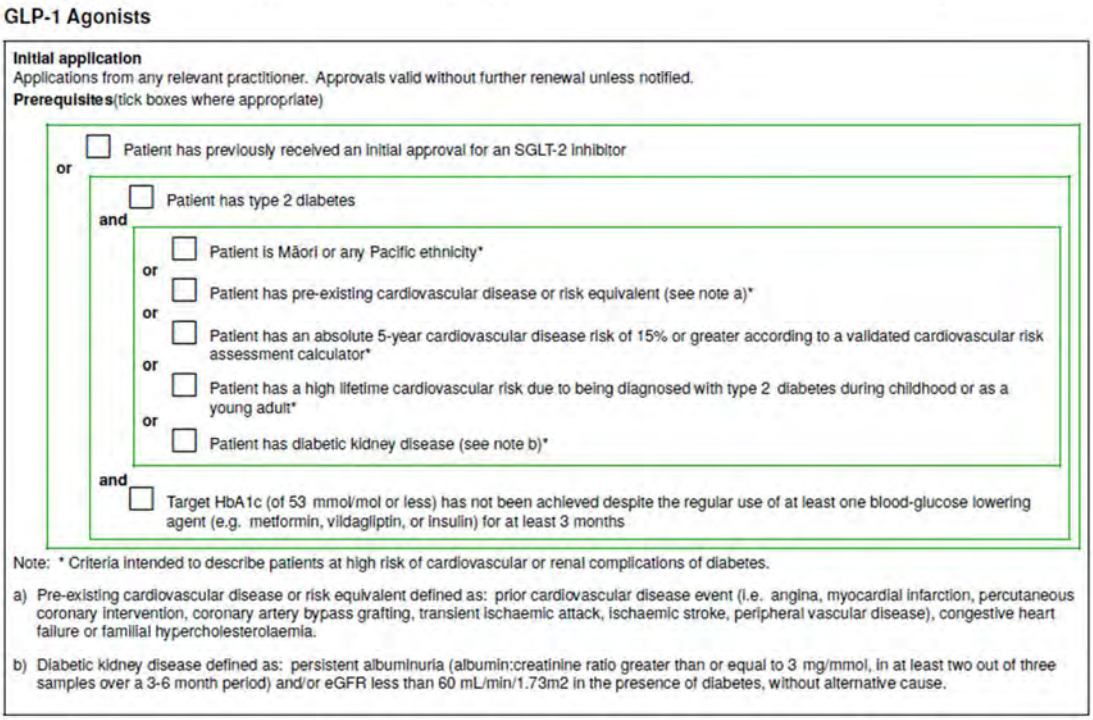
Dulaglutide is administered once a week as a subcutaneous injection. The recommended dose for adults (≥18 years old) is 1.5mg once a week, the safety and efficacy has not been established in children or adolescents under 18 years of age. Dulaglutide should not be used in patients with type 1 diabetes, 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 medications. 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, 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 1: PHARMAC Special Authority application form SA2065 for GLP-1 Agonists



GLP-1 Agonists

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: schedule.pharmac.govt.nz/2022/02/01/SA2065.pdf (accessed 21 February 2022).

2.1.2 Exenatide [4,5]

Exenatide is a subcutaneous injection available in two formulations (Byetta Immediate Release and Bydureon Modified Release). It is indicated as an adjunctive treatment in T2DM. Exenatide is not funded by PHARMAC. The dose for Byetta immediate release is 5mcg twice daily (increased to a maximum of 10mcg twice daily) and for Bydureon modified release is 2mg once weekly. Safety and efficacy for use in children and adolescents <18 years of age has not been established.

Exenatide is contraindicated in patients with end stage renal disease or severe renal impairment. Exenatide should not be used in patients with type 1 diabetes, it should be used in caution in patients with renal

impairment, altered renal function, severe gastrointestinal disease, acute pancreatitis, rapid weight loss and hypoglycaemia. Exenatide improves glycaemic control through the sustained effects of lowering both postprandial and fasting glucose concentrations in patients with type 2 diabetes.

Once weekly dosing has demonstrated in patients with T2DM a restoration of first phase insulin secretion and improved second phase insulin secretion in response to an intravenous bolus of glucose. Mean exenatide concentrations exceeded the minimal efficacious concentrations in 2 weeks, and average plasma concentrations gradually increase over 6 to 7 weeks. Nonclinical studies show exenatide is predominantly eliminated by glomerular filtration with subsequent proteolytic degradation. Gender, race, and body weight have no clinically relevant influence of exenatide pharmacokinetics, exenatide is primarily cleared by the kidneys therefore hepatic dysfunction is not expected to affect blood concentrations of exenatide.

Mild to moderate nausea is the most frequently reported adverse reaction that occurred in a dose dependent fashion, in patients that continue exenatide therapy the frequency and severity of symptoms reduce over time. Other reported adverse events included injection site reactions, drug induced thrombocytopenia and pancreatitis. Exenatide, a peptide pharmaceutical may produce an immunogenicity reaction. In clinical studies approximately 45% of patients developed antibodies to exenatide at the study endpoint. Patients who developed antibodies tended to have more injection site reactions.

2.1.3 Liraglutide [6]

Liraglutide (Saxenda) binds and activates GLP-1 receptors in different regions of the brain to reduce appetite and increase satiety. Liraglutide like other pharmacological treatments for weight management, is not funded by PHARMAC. It is available as a daily subcutaneous injection and is indicated as an adjunctive treatment for weight management in individuals with a body mass index (BMI) of ≥30kg/m^2 or in people with a BMI of ≥27kg/m^2 with at least one weight related comorbidity who are on insulin or another GLP1-RA. The dose of liraglutide in adults begins at 0.6mg once daily and increased by 0.6mg per week until a maintenance dose of 3.0mg is reached. The safety and efficacy of liraglutide has not been studied in paediatric patients.

Liraglutide is not to be used in conjunction or as a substitute for insulin for patients with diabetes, it is not indicated for the treatment of T2DM or for patients with obesity secondary to endocrinological or eating disorders or to treatment with medicinal products that may cause weight gain. It is not recommended in patients with renal or hepatic insufficiency, it should be used in caution in people 65-74 years old, it is not recommended in patients 75 years or older. Conditions for which liraglutide should be used with caution include pancreatitis, cholelithiasis and cholecystitis, inflammatory bowel disease and diabetic gastroparesis, hypoglycaemia with concomitant use of anti-diabetic therapy, malignancies, thyroid disease and patients with suicidal behaviour and ideation.

No clinically significant drug interactions have been demonstrated with liraglutide however, the delay in gastric emptying caused by liraglutide may impact the absorption of concomitantly administered oral medicines. Liraglutide is an acylated human GLP-1 analogue with 97% amino acid sequence homology to endogenous human GLP-1. It is relatively stable against metabolic degradation and has a plasma half-life of 13 hours after administration. The weight loss effect of liraglutide is mediated by regulation of appetite and food intake through increasing the feeling off fullness and satiety while lowering feelings of hunger and prospective food consumption. Liraglutide also effects glucose homeostasis resulting in the lowering of fasting and post-prandial glucose. The absorption of liraglutide following administration is slow reaching a maximum concentration approximately 11 hours post dosing, it is endogenously metabolised without a specific organ as the major route of elimination. Similarly, with other protein and peptide pharmaceuticals, patients may develop anti-liraglutide antibodies following treatment. In clinical trials, 2.5% of patients developed anti-liraglutide antibodies, the formation of antibodies is not associated with reduced efficacy.

Across the clinical trial population, greater proportions of patients achieved ≥5% weight loss with Saxenda than with placebo. As with the other GLP-1 RA, common side effects of liraglutide include nausea, diarrhoea, constipation, vomiting and headache. Other adverse events include increases in heart rate, prolonged PR

interval, cardiac conduction changes, hypoglycaemia, acute pancreatitis, suicidal behaviour and ideation, abnormalities in liver enzymes, and elevated serum calcitonin.

2.2 Type 2 Diabetes Mellitus

T2DM is a common chronic metabolic condition characterised by two primary factors: defective insulin secretion by pancreatic β-cells and the inability of insulin-sensitive tissues to respond appropriately to insulin. The dysregulation of glucose homeostasis results in a chronic hyperglycaemic state [7]. T2DM is commonly associated with obesity, physical inactivity, hypertension, and hyperlipidaemia. If blood glucose levels are not adequately controlled, patients can suffer long term microvascular and macrovascular complications. These complications significantly reduce quality of life and life expectancy.

T2DM is a multifactorial condition with a high burden of disease for the individual, wider family, and the health system. It is estimated that 5% of the New Zealand population has T2DM, this is predicted to increase to 7% of the population by 2040 (equating to an estimated 430,000). Pacific, Māori, and South Asian populations are more likely to have T2DM and develop complications from the conditions compared to other ethnic groups in New Zealand [8].

Optimal management, including lifestyle approaches (healthy diet and exercise), diabetes education/support, and pharmacological treatments, are key to reducing the risk of long-term complications and help people with T2DM to live well [8]. The New Zealand Society for the Study of Diabetes and the Ministry of Health have developed national guidelines for the management of T2DM (see Annex 2 for a summary).

The guidelines follow a stepwise progression. Initial management consists of lifestyle changes in conjunction with metformin. During this stage, patients and their healthcare provider should discuss individualised glycaemic targets. GLP1-RA are the preferred second line pharmacological agent in the management of T2DM. The guidelines state that GLP1-RA reduce mortality from cardiovascular events and renal disease progression independent of effects on glycaemic control. Other benefits include weight loss and reduction in blood pressure. In comparison to other agents, GLP1-RA are less likely to cause hypoglycaemia (although the risk still exists). The guidelines strongly encourage the use of a GLP1RA in all patients with diabetic renal disease or known cardiovascular disease or 5-year CVD risk >15%, regardless of their glycaemic control. Alternative second line therapy options include sodium glucose co-transporter 2 inhibitors (SGLT2i) or a DPP4i. Therapy is escalated, and patients may require multiple agents including insulin therapy, until HbA1c targets are met.

In order to be dispensed a funded GLP1-RA or SGLT2i, patients require a valid special authority. The special authority criteria assist high risk patients to access treatment however, the restrictions on funding do not align with best practise recommendations to manage T2DM [9].

Comments:

The NZ guidelines for T2DM suggest that GLP1-RA and SGLT2i can be used in combination before the addition of another antidiabetic drug class. When used together they will likely lead to greater improvements in glycaemic control and offer additional cardiorenal protection. Due to funding restrictions in NZ, patients are not eligible for this recommendation and may suffer worse outcomes due to less effective therapy combinations.

2.3 Obesity

Obesity is a chronic disease with an increasing prevalence in adults, adolescents, and children. The condition is now considered to be a global epidemic and is a major contributor to poor health. Obesity is associated with a significant increase in morbidity and mortality. A number of conditions including T2DM, cardiovascular disease, sleep apnoea, and cancer are associated with excess body weight [10].

An obese individual is defined as a person having a body mass index (BMI) of 30kg/m^2 or more. Findings from the *New Zealand Health Survey 2020-2021* found [11]:

- about one in three adults (34.4%) were classified as obese (up from 31.2% in 2019/2020)

- about one in eight children aged 2-14 years (12.7%) were classified as obese (up from 9.5% in 2019/2020)
- 1.5 million New Zealanders were classified as being obese in 2020/2021
- children living in the most deprived areas were 2.5 times more likely to be obese compared to children living in the least deprived areas, after adjusting for differences in age, gender, and ethnicity
- Pacific and Māori populations have higher rates of obesity compared to other ethnic groups.

New Zealand and international guidelines for weight management focus on behavioural modifications to lifestyle and include healthy diet, exercise. Pharmacological interventions can be considered as an adjunct to lifestyle change. The Ministry of Health *Clinical Guidelines for Weight Management in New Zealand Adults* advise that pharmacological interventions should be considered if [12]:

- lifestyle changes have failed to product clinically significantly benefits after 6 months, and
- the person has a BMI ≥30kg/m^2.

Current pharmacological options available for weight management in NZ include:

- liraglutide: a GLP1-RA (see section 2.1.3)
- orlistat: an oral pancreatic lipase inhibitor
- phentermine: an oral centrally acting appetite suppressant
- bupropion+naltrexone: an oral centrally acting appetite suppressant.

Comments:

No pharmacological treatments for weight management available in NZ are funded by PHARMAC, therefore the use of these medicines is likely to be low.

The benefits of orlistat and phentermine are not well supported by published scientific literature. The role of phentermine and weight management has been discussed at a prior MARC meeting (September 2021).

2.4 Drug-induced liver injury (DILI)

DILI (also known as drug-induced hepatotoxicity) is a well-recognised problem that occurs when prescription medicines, over-the-counter medicines, herbal and dietary supplements can symptomatically mimic acute or chronic liver disease. The annual estimated incidence of DILI worldwide is between 1.3 and 19.1 per 100,000 persons exposed [13]. The clinical presentation of DILI varies between individuals, and the diagnosis of DILI is typically made by establishing a temporal relationship between drug exposure and development of signs and symptoms of liver disease.

Risk factors associated with the development of DILI include adult age, female gender, genetic polymorphisms in the cytochrome isoenzymes, concomitant drug administration and drug interactions [14]. Hepatoxicity may arise through a variety of mechanisms and can be intrinsic or idiosyncratic. DILI is characterised by the type of hepatic injury: hepatocellular injury (hepatitis), cholestatic injury (cholestasis) or a mixed picture which includes features of both hepatocellular and cholestatic injury [13].

Acute presentation of DILI will vary and many patients with DILI are asymptomatic with cases detected via routine laboratory tests. Patients may also have elevations in liver enzymes and clinical features of hepatitis, pruritis and cholestasis, acute illness with jaundice, or non-specific symptoms acute liver failure. Chronic DILI can resemble other causes of chronic liver disease including autoimmune hepatitis, primary biliary cholangitis, sclerosing cholangitis or alcohol-associated liver disease. The majority of DILI cases resolve after discontinuation of the causative agent however, in some patient's chronic liver injury secondary to DILI can progress to cirrhosis [13].

Comments:

The LiverTox database concludes that GLP1-RAs have little or no hepatic metabolism and they have not been convincingly implicated in causing clinically apparent liver injury. Liraglutide and dulaglutide are degraded through general protein catabolism pathways and exenatide through glomerular filtration.

2.5 Regulatory action

[redacted]

2.6 Data sheets

The following tables summarise relevant sections of the dulaglutide, exenatide and liraglutide product information/data sheets from NZ, Australia, the United States, the United Kingdom and Ireland (as a proxy for the European Union). The summaries include information about hepatic/hepatobiliary adverse events, and patient counselling points.

2.6.1 Dulaglutide

Country **Product name** **Revision date**	**Statement**
New Zealand Trulicity 12 Aug 2021	4.8 Undesirable effects No hepatic reactions listed
Australia Trulicity 14 Jul 2020	4.8 Undesirable effects No hepatic reactions listed
United States Trulicity Sep 2021	6.1 Adverse Reactions Cholelithiasis and cholecystitis In a cardiovascular outcomes trial with a median follow up of 5.4 years, cholelithiasis occurred at a rate of 0.62/100 patient-years in TRULICITY-treated patients and 0.56/100 patient-years in placebo-treated patients after adjusting for prior cholecystectomy. Serious events of acute cholecystitis were reported in 0.5% and 0.3% of patients on TRULICITY and placebo respectively
United Kingdom Trulicity 19 Oct 2021	4.8 Undesirable effects Hepatobiliary disorders Uncommon: cholelithiasis, cholecystitis
Ireland Trulicity 5 Jul 2021	4.8 Undesirable effects Hepatobiliary disorders Uncommon: cholelithiasis, cholecystitis

Comments:

The NZ data sheet for Dulaglutide does not contain information on hepatic injury, hepatobiliary disorders, hyperbilirubinemia, hepatitis, or elevations of liver enzymes.

2.6.2 Exenatide

Country Product name Revision date	Statement
New Zealand Bydureon 19 Nov 2019	4.8 Undesirable effects No hepatic reactions listed
New Zealand Byetta 14 Apr 2021	4.8 Undesirable effects No hepatic reactions listed
Australia Bydureon 3 Nov 2020	4.8 Undesirable effects No hepatic reactions listed
Australia Byetta 3 May 2021	4.8 Undesirable effects No hepatic reactions listed
United States Bydureon 3 Nov 2020	6.1 Undesirable effects No hepatic reactions listed
United States Byetta 3 May 2020	6.1 Undesirable effects No hepatic reactions listed
United Kingdom Bydureon 1 Jan 2021	4.8 Undesirable effects No hepatic reactions listed
United Kingdom Byetta 23 Mar 2021	4.8 Undesirable effects No hepatic reactions listed
Ireland Bydureon 1 Mar 2021	4.8 Undesirable effects No hepatic reactions listed
Ireland Byetta 24 Sep 2021	4.8 Undesirable effects No hepatic reactions listed

2.6.3 Liraglutide

Country Product name Revision date	Statement
New Zealand Saxenda 27 Apr 2021	4.4 Special warnings and precautions for use Cholelithiasis and cholecystitis In the SAXENDA clinical trials, cholelithiasis or cholecystitis was reported more commonly in SAXENDA-treated patients than in placebo-treated patients. The majority of SAXENDA-treated patients with cholelithiasis or cholecystitis required cholecystectomy. Substantial or rapid weight loss can increase the risk of acute gallbladder disease; however the incidence was greater in SAXENDA-treated patients versus placebo-treated patients even after accounting for weight loss. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis. 4.8 Undesirable effects

	Hepatobiliary disorders: uncommon- cholecystitis Laboratory abnormalities Liver enzymes Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) SAXENDA-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo treated patient during the SAXENDA clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to SAXENDA is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).
Australia Saxenda 2 Jul 2021	4.4 Special warnings and precautions for use Cholelithiasis and cholecystitis In the SAXENDA clinical trials, cholelithiasis or cholecystitis was reported more commonly in SAXENDA-treated patients than in placebo-treated patients [see Section 4.8]. The majority of SAXENDA-treated patients with cholelithiasis or cholecystitis required cholecystectomy. Substantial or rapid weight loss can increase the risk of acute gallbladder disease; however the incidence was greater in SAXENDA-treated patients versus placebo-treated patients even after accounting for weight loss. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis. 4.8 Undesirable effects Hepatobiliary disorders: Uncommon: cholecystitis Laboratory abnormalities Liver enzymes Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) SAXENDA-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo treated patient during the SAXENDA clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to SAXENDA is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones).
Australia Victoza 26 May 2020	4.8 Adverse effects (undesirable effects) Hepatobiliary disorders Uncommon: cholelithiasis, cholecystitis
United States Saxenda 2 Jul 2020	6.1 Adverse reactions Laboratory abnormalities Liver enzymes Increases in alanine aminotransferase (ALT) greater than or equal to 10 times the upper limit of normal were observed in 5 (0.15%) SAXENDA-treated patients (two of whom had ALT greater than 20 and 40 times the upper limit of normal) compared with 1 (0.05%) placebo-treated patient during the SAXENDA clinical trials. Because clinical evaluation to exclude alternative causes of ALT and aspartate aminotransferase (AST) increases was not done in most cases, the relationship to SAXENDA is uncertain. Some increases in ALT and AST were associated with other confounding factors (such as gallstones). 6.2 Post-marketing experience Hepatobiliary disorders: hyperbilirubinemia, cholestasis, and hepatitis 17 Patient counselling information Jaundice and hepatitis: inform patients that jaundice, and hepatitis have been reported during post marketing use of liraglutide. Instruct the patients to contact their healthcare provider if they develop jaundice

United States Victoza 12 Apr 2020	6.1 Adverse reactions Cholelithiasis and cholecystitis In glycemic control trials of VICTOZA, the incidence of cholelithiasis was 0.3% in both VICTOZA-treated and placebo-treated patients. The incidence of cholecystitis was 0.2% in both VICTOZA-treated and placebo-treated patients. In the LEADER trial, the incidence of cholelithiasis was 1.5% (3.9 cases per 1000 patient years of observation) in VICTOZA-treated and 1.1% (2.8 cases per 1000 patient years of observation) in placebo-treated patients, both on a background of standard of care. The incidence of acute cholecystitis was 1.1% (2.9 cases per 1000 patient years of observation) in VICTOZA-treated and 0.7% (1.9 cases per 1000 patient years of observation) in placebo-treated patients. 6.2 Post-marketing experience Hepatobiliary disorders: elevations of liver enzymes, hepatitis 17 Patient counselling information Jaundice and hepatitis: inform patients that jaundice, and hepatitis have been reported during post marketing use of liraglutide. Instruct the patients to contact their healthcare provider if they develop jaundice
United Kingdom Saxenda 12 Oct 2021	4.4 Special warnings and precautions for use Cholelithiasis and cholecystitis In clinical trials for weight management, a higher rate of cholelithiasis and cholecystitis was observed in patients treated with liraglutide than in patients on placebo. The fact that substantial weight loss can increase the risk of cholelithiasis and thereby cholecystitis only partially explained the higher rate with liraglutide. Cholelithiasis and cholecystitis may lead to hospitalisation and cholecystectomy. Patients should be informed of the characteristic symptoms of cholelithiasis and cholecystitis. 4.8 Undesirable effects Hepatobiliary disorders Common: cholelithiasis Uncommon: cholecystitis
United Kingdom Victoza 12 Oct 2020	4.8 Adverse effects (undesirable effects) Hepatobiliary disorders Uncommon: cholelithiasis, cholecystitis
Ireland Saxenda 10 Jan 2022	4.8 Undesirable effects Hepatobiliary disorders Common: cholelithiasis Uncommon: cholecystitis
Ireland Victoza 11 Feb 2022	4.8 Adverse effects (undesirable effects) Hepatobiliary disorders Uncommon: cholelithiasis, cholecystitis

2.6.4 Summary

Table 1 below is a summary of the product information sheets listed above on whether they contain information on hepatobiliary events following use of a GLP1-RA,

Table 1: Summary of international product information sheets for GLP1-RA and hepatobiliary events

	New Zealand	Australia	United States	United Kingdom	Ireland
Dulaglutide (Trulicity)	-	-	∴	∴	∴
Exenatide (Bydureon)	-	-	-	-	-
Exenatide (Byetta)	-	-	-	-	-
Liraglutide (Saxenda)	*∴	*∴	* ∴	∴	∴
Liraglutide (Victoza)	N/A	∴	* ∴	∴	∴

- No information included

* Includes information on elevation of liver enzymes and/or hepatitis and/or jaundice

∴ Includes information on cholelithiasis and/or cholecystitis

Sources (accessed 3 February 2022):

New Zealand Data Sheet: https://www.medsafe.govt.nz/Medicines/infoSearch.asp

TGA Product Information: https://www.ebs.tga.gov.au/

FDA Product Label: https://labels.fda.gov/

MHRA Summary of product characteristics: https://www.medicines.org.uk/emc/

HPRA Summary of product characteristics: https://www.hpra.ie/

2.7 Usage

Usage data is not available for any of the GLP-1 RA medicines. Dulaglutide was funded in New Zealand in September 2021 and Medsafe does not have access to usage data. Exenatide and liraglutide are not funded and usage is therefore expected to be low. Dispensing information on non-funded medicines is not stored in the Ministry of Health Pharmaceutical Collections database.

3 SCIENTIFIC INFORMATION

3.1 Case reports

3.1.1 Neahusan et al (2021)

Autoimmune hepatitis-like drug injury of the liver associated with the glucagon-like peptide 1 agonist Dulaglutide [15]

Neahusan et al describe a case report of a 53-year-old female patient with a history of diabetes who was initiated on dulaglutide 0.75mg per week 15 days prior to presentation. The patient presented with two weeks of diffuse pruritis, yellowing of the eyes, pale stools, dark urine, and fatigue. Laboratory results found elevated AST, ALT, ALP, lipase, total and direct bilirubin indicating liver injury of a hepatocellular pattern. IgG antibody levels had risen whilst viral and autoantibody panels were negative. A core liver biopsy found necroinflammatory activity with mixed infiltrates. Dulaglutide was stopped and symptoms resolved. During a follow up, laboratory results normalised, and symptoms have not recurred. The authors conclude that dulaglutide was the likely cause of autoimmune hepatitis-like drug injury.

3.1.2 Maor et al (2021)

Liraglutide-induced hepatotoxicity [16]

Maor et al describe a case of idiosyncratic acute liver injury from liraglutide. A 52-year-old woman was treated with subcutaneous liraglutide as part of her weight reduction program. Over a period of three months, the patient lost 10kg of weight and her BMI had reduced to 27.5kg/m^2 from 31.2kg/m^2. Elevated liver enzymes showed a mixed cholestatic-hepatocellular pattern of liver injury. In addition to raised ALT, AST, ALP, γGT and total bilirubin, eosinophilia and elevated ESR were present. Viral analyses were negative for hepatitis, Epstein-Barr, cytomegalovirus, and herpes simplex. Genetic liver diseases were excluded and there is no history of smoking or alcohol and substance misuse.

An abdominal ultrasound identified fatty liver and lymphocyte toxicity assay detected elevated levels of pro-inflammatory cytokines and chemokines. The authors proposed that DILI may result from an imbalance between pro- and anti-inflammatory markers, resulting in hepatocellular inflammation and cell necrosis. The patient was diagnosed with non-alcoholic fatty liver disease (NAFLD) and following discontinuation of liraglutide, clinical improvement and normalisation of liver enzymes occurred over a three-month period.

3.1.3 Parvataneni et al (2021)

An exceedingly rare case of liraglutide-induced liver injury [17]

The authors describe a case of hepatocellular injury in a 64-year-old woman who presented to hospital after experiencing four days of diffuse abdominal pain. Medical history included hypertension, diabetes mellitus, hyperlipidaemia, and previous history of cholecystectomy. Medicines on admission included liraglutide, lisinopril and metformin. Laboratory tests found elevations in ALT, AST, ALP, and total bilirubin suggesting hepatocellular injury. Viral and autoantibody panels were negative. Abdominal ultrasound found fatty changes in the liver without evidence of biliary obstruction. The patient was started on liraglutide six months prior to admission and normal baseline liver function test values during this time. Liraglutide was stopped following concern of possible DILI. After three days the patient's symptoms resolved and two months following discharge her laboratory values returned to normal. Based on the temporal relationship between the initiation of liraglutide and development of liver injury, the authors consider this to be a case of liraglutide-induced liver injury.

3.1.4 Kern et al (2014)

Liraglutide-induced autoimmune hepatitis (AIH) [18]

The authors describe a case of a Hispanic woman with a history of T2DM and vitiligo who presented to hospital with acute hepatitis, nausea and emesis. Her current drug regimen during admission included oral metformin, topical tacrolimus and subcutaneous liraglutide. Exenatide was replaced with liraglutide four months prior to admission.

Mild scleral icterus was noted upon admission, laboratory results showed elevations in ALT, AST, and total/direct bilirubin. Results for viral analyses and metabolic studies were within reference limits and autoimmune studies were not significantly elevated. Liver biopsy noted interface hepatitis with a mixed inflammatory infiltrate. The patient was given antiemetic therapy and intravenous fluid, liraglutide was stopped and the patient was given insulin and metformin on discharge.

Nine days following discharge the patient noted worsening jaundice and fatigue, symptoms continued to persist and one month after initial discharge the patient was readmitted to hospital, her liver enzymes remained elevated. A second liver biopsy found hepatic necrosis and extensive eosinophilic infiltrate. The patient was started on a tapering dose of prednisone for presumed liraglutide-induced marker negative autoimmune hepatitis, six months later the patient continues to receive prednisone without a complete return of enzyme levels to the reference rate.

The authors suspect the diagnosis to likely be marker-negative autoimmune hepatitis secondary to liraglutide. Immune-mediated liver injury may arise from the formation of anti-liraglutide antibodies, approximately 8% of patients will form anti-liraglutide antibodies that may cross react with native GLP-1 and stimulate GLP-1 receptors found on hepatocytes. It is hypothesised that this reaction may form a neoantigen and create an

inflammatory immune system response. The authors state that the reported case strongly implicates liraglutide in the aetiology of liver injury, although a causal relationship cannot be firmly established. Anti-liraglutide antibodies levels were not measured in the patient.

3.2 Published literature

3.2.1 Armstrong et al (2012)

Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program [19]

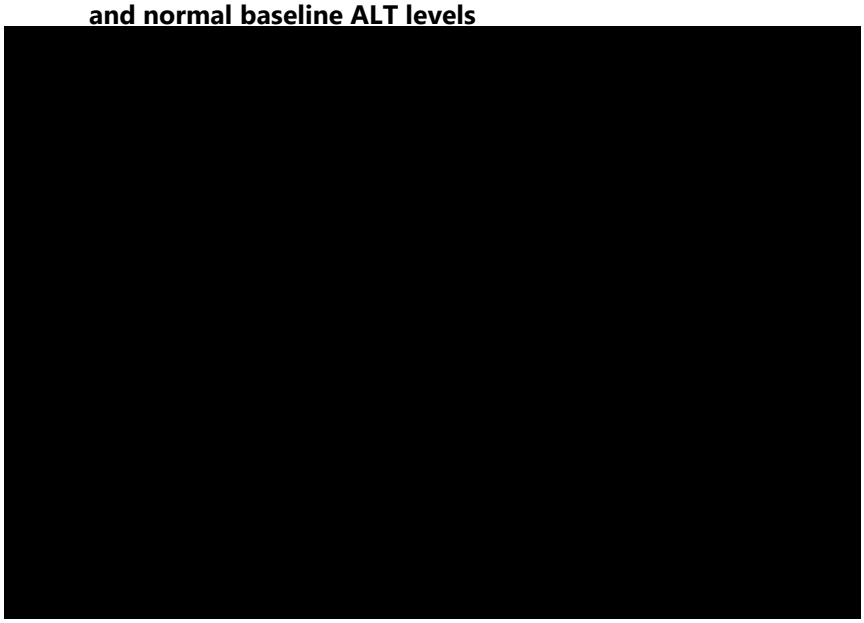
Armstrong et al conducted a meta-analysis on the safety and efficacy on liraglutide in patients with T2DM. Patient level data was collected from six 26-week phase III randomised control trials that comprised of the 'Liraglutide Effect and Action in Diabetes' (LEAD) program. The meta-analysis was performed to assess the safety and efficacy of liraglutide on liver parameters (ALT levels) and the effects of liraglutide on hepatic steatosis.

A total of 4442 patients were included in the meta-analysis and 2241 participants had an abnormal ALT at baseline. Individuals were given either liraglutide (n= 2734), active placebo (n= 524) or another antidiabetic medicine (n= 1184).

Patients with abnormal baseline ALT treated with 1.8mg of liraglutide had significantly reduced ALT compared with active placebo (-8.20 vs -5.01 IU/L) (Figure 2). No significant differences in ALT were seen between placebo and lower doses of liraglutide (1.2mg and 0.6mg). The LEAD 2 sub-study used CT imaging to identify the presence of hepatic steatosis in 96 participants at baseline, of which 56 participants had at least 30% hepatic steatosis. At 26 weeks of liraglutide 1.8mg there was a trend towards a reduction in hepatic steatosis compared with active placebo, this effect was not significant with lower doses of liraglutide.

Overall, the analysis of the LEAD program found that 26 weeks of liraglutide is well tolerated and results in significant improvements of liver enzymes in T2DM patients. The main limitations of the study is that six of the randomised control trials used were powered on glycaemic control and not changes in liver parameters, across the six trials patient populations had different eligibility therefore introducing a degree of heterogeneity into the study, lastly liver biopsy results were not performed and therefore the accuracy in describing hepatic injury pre and post drug exposure is limited to ALT levels.

Figure 2: Changes in ALT with 26 weeks treatment of liraglutide vs placebo in patients with abnormal and normal baseline ALT levels



3.2.2 Lv et al (2020)

Glucagon-like peptide-1 receptor agonists for the management of non-alcoholic fatty liver disease: a systematic review [20]

Non-alcoholic fatty liver disease (NAFLD) refers to the presence of hepatic steatosis when no other causes for secondary hepatic fat accumulation are present. It can develop into non-alcoholic steatohepatitis (NASH), which is associated with hepatocellular injury with or without fibrosis. There are no licensed drugs for NAFLD and patients with T2DM are particularly susceptible to NAFLD. Therefore, the authors sought to evaluate the efficacy of GLP1-RA in the management of NAFLD by conducting a systematic review.

A total of 24 clinical trial articles were selected and met the proposed inclusion criteria. The outcomes of the trials included histological improvement in NAFLD, presence of steatosis, hepatocyte ballooning, inflammation, changes in hepatic enzyme levels, non-invasive biomarkers, insulin resistance and anthropometric measures.

Of the 21 clinical trials reporting the change in hepatic enzymes as their end point, 18 studies supported the efficacy of GLP1-RA on the improvement of hepatic enzymes (ALT, AST, γGT). Of the 8 clinical trials reporting the change in hepatic steatosis as their end point, 6 studies demonstrated a significant reduction in liver fat content following GLP1-RA therapy. If left untreated, NAFLD may lead to hepatic fibrosis and cirrhosis. Four clinical trials reported improvements in the non-invasive assessment of liver fibrosis. Of these, 3 studies found an improvement on the magnitude of liver fibrosis following GLP1-RA therapy. A summary of these findings are included in Table 2 below.

The authors acknowledge that hepatic enzymes are not the ideal markers of inflammation or liver damage and changes in hepatic enzymes and non-invasive biomarkers may not correlate with histological improvements. However, the systematic review of published and ongoing trials suggest that GLP1-RA may be effective in reducing hepatic steatosis and inflammation.

Table 2: Summary of study characteristics and findings from clinical trials for GLP1-RA therapy and NAFLD.

Author	Study design	Dose and participant	Duration (week)	Response (liver enzymes, liver fat, histology)	Drop out	Author comments
John et al. 2007 USA	RCT + open-label extension	Phase 1 (RCT) 1446 Exe + PLA Phase 2 (open label) 974 open label	96	Individuals with elevated ALT at baseline had a significant mean reduction in ALT	Phase 1: 22.2% Phase 2: 45.7%	No liver fat imaging or histology measured. High dropout rates.
Klonoff et al. 2008 USA	RCT + open-label extension	217 patients completed 3 years of exenatide exposure	>144	Individuals with elevated ALT had a significant reduction in ALT and 41% achieved normal ATL	NA	No liver fat imaging or histology measured. Exenatide significantly improved several cardiovascular risk factors.
Jendle et al. 2009 USA	RCT	20 PLA, 37 Glim, 35 Lira (0.6mg), 31 Lira (1.2mg), 37 Lira (1.8mg)	26	No significant improvement in liver enzymes with Lira than placebo. Fat % with Lira was significantly reduced.	3.7%	Liver to spleen attenuation ratio used as an index of liver fat
Kenny et al. 2010 USA	Case series	8 Exe (5-10mcg bd)	28	Mean ALT was significantly improved. No significant improvement in histology.	No dropout	Liver histology improved in 3 of 8 patients
Sathyanarayana et al. 2011 USA	RCT	10 Pio (45mg), 11 Pio (45mg) + Exe (10mcg)	50	Both groups had reduced ALT and AST, there was a significant reduction in ALT with the Pio+Exe group. Reduced LFC with both groups.	No dropout	Both groups had significantly reduced TG.
Ohki et al. 2012 Japan	Retrospective studies	26 Lira (0.9mg), 20 Pio (15mg), 36 Sita (100mg)	48	Lira decreased AST, Sita decreased ALT	No dropout	Lira significantly reduced APRI index
Cuthbertson et al. 2012 Italy	Observational studies	19 Exe (10mcg bd), 6 Lira (1.2mg qd)	25	Mean ALT and GGT improved, mean LFC reduced	19.4%	Relative reduction in LFC correlated with HbA1c

Suzuki et al. 2013 Japan	Single-arm study	59 Lira (0.9mg)- 8 of the 59 patients treated with Pio pre treatment	25	NA for liver enzymes. The liver/kidney CT ratio was improved.	23.7%	Lira alone significantly decreased the subcutaneous but not visceral fat areas
Fan H et al. 2013 China	RCT	49 Exe (10mcg bd), 68 Met (0.5g bd)	12	Both group showed significant reduced ALT (the Exe group had a significantly greater reduction). The proportion of patients with improvements in fatty liver was comparable.	18.7%	Exe is superior to Met in reducing body weight
Shao et al. 2014 China	RCT	30 Exe (10mcg bd) + insulin glargine, 30 insulin aspartate + glargine	12	ALT, AST and γ-GGT were significantly decreased in two groups, and Exe was associated with a lower level of hepatic enzymes. Reversal rate of fatty liver in Exe group > insulin group.	No dropout	FBG, PBG, HbA1c, TC, TG and TBIL were significantly decreased in both groups.
BlaslovK et al. 2014 Croatia	Open label parallel group uncontrolled study	87 Exe (10mcg) + Met or/and SU, 38 OHA + Met or/and SU	25	ALT was improved in both Exe and OHA groups	No dropout	ΔFLI improved in Exe and OHA
Yan et al. 2014 China	RCT	11 Exe (10mcg bd), 11 Pio (45mg), 11 Ins	26	NA for liver enzymes. LFC was significantly reduced in all groups.	No dropout	ΔLFC is related to ΔHbA1c and Δweight. Early metabolic control plays a vital role in slowing progression of fatty liver in T2DM.
Eguchi et al. 2015 Japan	Single arm	10 Lira (0.9mg qd)	96	ALT and AST improved, liver/spleen ration improved, histological inflammation improved in 6/10 patients.	14.8%	Lira has a good safety profile

Tang et al. 2015 Canada	RCT	18 Lira (1.8mg qd), 17 insulin glargine	12	No improvements in liver enzymes. Ins associated with significant decrease in liver fat,	4 of Lira group (due to AE)	Weight improvement in Lira group
Armstrong et al. 2016 UK	RCT	26 Lira (1.8mg qd), 26 PLA	48	Serum γ-GGT level significantly differed between liraglutide and placebo groups. No significant difference was detected in the change in serum ALT and AST. Liver histology in Lira group showed increased odds of NASH resolution	13.46%	AE were mild to moderate in severity, transient and similar between groups/
Smits et al. 2016 Netherlands	RCT	17 Lira (1.8mg qd), 18 Sita (100mg), 17 PLA	12	No significant improvement in liver enzymes. No significant improvement in hepatic steatosis	1.9%	Neither liraglutide nor sitagliptin affected NFS, FIB-4 or APRI compared with the placebo.
Dutour et al. 2016 France	RCT	22 Exe (10mcg bd), 22 PLA	24	NA for liver enzymes. Exe significantly reduced LFC	13.6%	Longer exposure time to exenatide might be needed to reveal significant improvement in myocardial triglyceride content
Yuya Seko et al. 2017 Japan	Single arm study	15 Dula (0.75mg once weekly)	12	ALT and AST improved. Liver steatosis was not improved.	13.3%	Liver stiffness significantly improved.
Khoo et al. 2017 Singapore	RCT	12 Lira (3mg qd), 12 DE	26	Reductions in both ALT and AST. Both groups had significant but similar reductions in LFC,	No dropout	Both groups had significant reductions in liver stiffness

Petit et al. 2017 France	Non-RCT	68 Lira (3mg qd), 16 Ins	26	Reduction in ALT and GGT, Lira associated with a reduction in LFC	15%	The effects of Lira in reducing LFC mainly driven by bodyweight reduction.
Feng et al. 2017 China	RCT	29 Gli (120mg qd), 29 Lira (1.8mg qd), 29 Met (1g bd)	24	ALT improved in all arms, AST improved in Lira and Met groups, LFC significantly reduced in all groups	6.4%	Changes in LFC were positively linked to reductions in hepatic enzymes and triglyceride levels.
Tian et al. 2018 China	RCT	52 Lira (1.2mg qd), 57 Met (1-1.5g bd)	12	ALT improved in both groups. Both groups associated with a lower presence of NAFLD	1.5%	Nine patients in the Lira group experienced mild/moderate GI events
K.Cusi et al. 2018 Multicentre	Post hoc analysis	971 Dula (1.mg once weekly), 528 PLA	24	Dula significantly reduced ALT, AST, GGT levels	6.7-29.9%	In population with ALT >ULN more pronounced reductions from baseline ALT seen in dula vs PLA
Newsome et al. 2018 Multicentre	Post hoc analysis (data from 2 RCT)	718 Sema (0.05-0.4mg/day), 103 Lira (3mg), 136 PLA	52	Dose dependent decrease in ALT	19.85%	The maximal decline in ALT occurring by approx. week 28

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CT, computed tomography; De, diet exercise; Dula, dulaglutide; Exe, exenatide; FBG, fasting blood glucose; FIB-4, fibrosis 4 score; FLI, fatty liver index; GGT, gamma-glutamyl transpeptidase; Gli, gliclazide; Glim, glimepiride; HAb1c, glycosylated haemoglobin; Ins, insulin; LFC, liver fat content; Lira, liraglutide; Met, metformin; MRS, magnetic resonance spectroscopy; NA, not assessed; OHA, oral hypoglycaemic agents; PBG, postprandial blood glucose; PDFF, proton density fat content; Pio, pioglitazone; PLA, placebo; Sema, semaglutide; Sita, sitagliptin; SU, sulphonylureas; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; ULN, upper limit of normal.

3.2.3 Hupa-Breier et al (2021)

Dulaglutide alone and in combination with empagliflozin attenuate inflammatory pathways and microbiome dysbiosis in a non-diabetic mouse model of NASH [21].

The authors investigated the effects of dulaglutide and empagliflozin on body weight, adipose tissue composition, glycaemic control, changes in hepatic enzymes, histological findings for NASH, innate an adaptive immune system response, inflammatory pathway response, and microbiome diversity in a non-diabetic mouse model.

After 16 weeks of a high-fat high-fructose diet and surplus cholesterol, mice were treated with dulaglutide (10nmol/kg), empagliflozin (10mg/kg), a combination of both, or placebo. The relevant findings after a 4-week treatment period with dulaglutide include significant weight loss, reduction in adipose tissue, diminished AST-elevation (Figure 3), reduction in pro-inflammatory and pro-fibrotic molecular markers (CCL2, CD11c, TNF, IL-1, TIMP-1) (Figure 4), and enhanced microbiome diversity.

A limitation of this study is that the outcomes seen in the mouse model may not be generalizable to humans. The authors acknowledge that the results of the study should be open to interpretation and that further studies are required to evaluate the effects of both medicines on NASH and hepatic fibrosis.

However, this study suggests dulaglutide alone or in conjunction with empagliflozin demonstrates anti-inflammatory effects through modulation of pro-inflammatory immune response and microbiome dysbiosis and therefore maybe an option for the treatment of NASH.

Figure 3: Change in AST and ALT levels in mice models over a 4-week treatment period

Figure 4: Change in the level of inflammatory markers in mice models over a 4-week treatment period

Comments:

Published literature on the role of GLP1-RA and their effects on the liver seem to focus on non-alcoholic fatty liver disease. The currently available information suggests that GLP1-RA can reduce hepatic liver enzymes and possibly hepatic inflammation. Reports of GLP1-RA and DILI is not well supported by published literature and is limited to case reports.

3.4 Spontaneous ADR reporting data

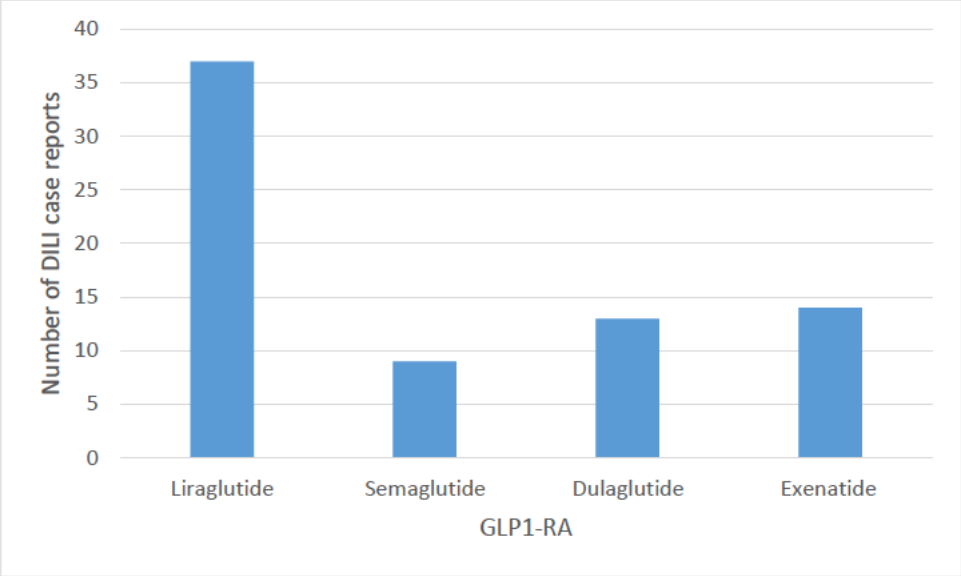
3.4.1 CARM data

[redacted]

3.4.2 FAERS data (United States)

The FDA's Adverse Events Reporting System (FAERS) has received 73 reported cases of DILI associated with a GLP1-RA from 1 January 2012 to 8 February 2022. Of these, 72 reports describe a serious reaction, and 9 cases were fatal. The majority of these reports were associated with liraglutide (37), as depicted in Figure 5 below.

Figure 5: Number of FAERS case reports of DILI associated with each GLP1-RA, 1 January 2012 to 8 February 2022



Source: Food and Drug Administration, Qlik App. FAERS public dashboard (accessed 8 February 2022).

3.4.3 VigiLyze data

[redacted]

[redacted]

4 DISCUSSION AND CONCLUSIONS

Drug-induced liver injury is a well-recognised event that is often found during the post-marketing phase of medicine use but can also occur with herbal products and supplements. GLP1-RA are a relatively new class of medicines indicated for the treatment of T2DM and weight management. The NZ specific guidelines for the management of T2DM suggest GLP1-RA as the preferred second line option when escalating pharmacological therapy, due to their beneficial effects on HbA1c and weight reduction. Dulaglutide is the only funded GLP1-RA available in NZ but its prescribing and use is limited by the special authority criteria set by PHARMAC.

Adverse reactions associated with GLP1-RA include nausea, vomiting, gastrointestinal pain and changes in bowel motions. The NZ data sheets for dulaglutide and exenatide do not list any hepatobiliary adverse events; the data sheet for liraglutide mentions hepatobiliary adverse events and changes in liver enzymes.

The US product information for liraglutide was updated [redacted]. To date, there are limited published case reports of DILI and GLP1-RA, and the majority of these cases are reported with liraglutide. Proposed mechanisms suggested by the case report authors include cross reactivity of anti-GLP1-RA antibodies resulting in the formation of neoantigens, and an imbalance of pro and anti-inflammatory markers resulting in hepatocyte injury and necrosis. Additional evaluation is required to confirm the hypotheses.

Other published information is conflicting and suggests GLP1-RA may have a beneficial effect on the liver through the reduction of liver enzyme abnormalities and pro-inflammatory pathways. Novo Nordisk and AstraZeneca have conducted investigations into their marketed products and do not consider the signal of DILI and GLP1-RA products to be valid and have refuted the signal.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the current evidence supports an association between drug induced liver injury and glucagon like peptide-1 agonists?
- If the association is considered valid, should the data sheets for all medicines in this class be updated to include the risk of liver injury?
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*?

6 ANNEXES

1. NZSSD Management Guidance for T2DM

[redacted]

[redacted]

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