## Medicines Adverse Reactions Committee

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| Meeting date | 11/09/2025 | Agenda item | 3.2.1 |
| Title | **Possible interaction between GLP-1 receptor agonists and oral contraceptives** | | |
| Submitted by | Medsafe Pharmacovigilance Team | Paper type | For advice |
| **Active ingredient** | **Product name (therapeutic area)** | **Registration status** | **Sponsor** |
| dulaglutide | Trulicity (T2DM) | Marketed | Eli Lilly |
| liraglutide | Saxenda (weight) | Marketed | Novo Nordisk |
| | Victoza (T2DM) | Marketed | Novo Nordisk |
| semaglutide | Ozempic (T2DM) | Not marketed | Novo Nordisk |
| | Wegovy (weight) | Marketed | Novo Nordisk |
| Pharmac funding | Trulicity and Victoza are funded on the community schedule under special authority | | |
| Previous MARC meetings | None | | |
| International action | UK MHRA (June 2025): Women on "skinny jabs" must use effective contraception, MHRA urges in latest guidance | | |
| *Prescriber Update* | None | | |
| Classification | Prescription medicine | | |
| Advice sought | **The Committee is asked to advise:**<br>• On the strength of the evidence and clinical relevance of the interaction between GLP-1 receptor agonists and oral contraceptives. The committee could consider this for each individual GLP-1 receptor agonist, or for the medicines as a group.<br>• If the data sheets require updating. | | |

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# 1 PURPOSE

In June 2025, the Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom reminded women using GLP-1 receptor agonists to use effective contraception. This was particularly highlighted for Mounjaro (tirzepatide) which may reduce the effectiveness of oral contraceptives in those who are overweight. Therefore, those who are overweight and use Mounjaro and an oral form of contraception were advised to also use a non-oral form of contraception. This is especially important for the first 4 weeks after starting Mounjaro and after any dose increase.

Tirzepatide is a dual glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptor agonist. There are no tirzepatide products approved for use in New Zealand [redacted]. Approved GLP-1 receptor agonists include dulaglutide, liraglutide, and semaglutide.

The purpose of this paper is to review the possible interaction between GLP-1 receptor agonists and oral contraceptives. The focus is on GLP-1 receptor agonists that are approved for use in New Zealand. However, information on other GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists are included where appropriate.

# 2 BACKGROUND

## 2.1 GLP-1 and GIP

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are incretin hormones secreted in the intestines in response to food intake. Both hormones promote glucose-dependent insulin release and decrease glucagon secretion. Additionally, GLP-1 decreases appetite, delays gastric emptying and improves satiety whereas GIP assists with nutrient and energy metabolism [1]. The actions of GLP-1 and GIP in peripheral tissues are shown in Figures 1 and 2, respectively.

**Figure 1: Actions of GLP-1 in peripheral tissues**

## 2.2 GLP-1 receptor agonists

GLP-1 receptor agonists bind to and activate the GLP-1 receptor. Those that are currently approved for use in New Zealand include dulaglutide, liraglutide, and semaglutide, which are administered subcutaneously. The approvals for exenatide and lixisenatide have lapsed in New Zealand. An oral form of semaglutide is also approved in other countries but not in New Zealand.

Tirzepatide is a dual GLP-1 and GIP receptor agonist approved in some countries. Tirzepatide's dual agonism of both GLP-1 and GIP leads to enhancements in glucose-dependent first- and second-phase insulin secretion along with a reduction in glucagon concentrations. The mechanism of action also leads to a greater effect of delayed gastric emptying than typical GLP-1 receptor agonists [1].

### 2.2.1 Indication, dose, half-life

The indications, dose recommendations, and elimination half-lives for the GLP-1 receptor agonists approved for use in New Zealand and dual GLP-1 and GIP receptor agonists are summarised in Table 1. Please refer to the data sheets for full wording.

All are administered subcutaneously and are considered long-acting.

**Table 1: Summary of indications, dose, and elimination half-lives for GLP-1 receptor agonists approved for use in New Zealand, and dual GLP-1 and GIP receptor agonists**

| Brand name (substance) | Indication | Dose | Elimination half-life |
|---|---|---|---|
| **GLP-1 receptor agonists approved for use in New Zealand** | | | |
| Trulicity (dulaglutide) | T2DM | 1.5 mg once weekly | 4.7 days |
| Victoza (liraglutide) | T2DM | Dose titration to 1.8 mg daily | 13 hours |
| Saxenda (liraglutide) | weight management | Dose titration to 3.0 mg daily | |
| Ozempic (semaglutide) | T2DM | Dose titration to 1 mg once weekly | 1 week |
| Wegovy (semaglutide) | weight management | Dose titration to 2.4 mg once weekly | |
| **Dual GLP-1 and GIP receptor agonists** | | | |
| Mounjaro (tirzepatide) | T2DM<br>weight management<br>OSA | Dose titration to 5 mg, 10 mg, or 15 mg once weekly. | 5 days |
| Zepbound (tirzepatide) | | | |

Source: NZ data sheets for Trulicity, Victoza, Saxenda, Wegovy (accessed via Medsafe website on 11 August 2025) and Ozempic (dated 15 November 2024, accessed via Medsafe product file); Australian data sheet for Mounjaro (accessed via TGA ARTG on 13 August 2025); US data sheet for Zepbound (accessed via NIH DailyMed on 13 August 2025).

T2DM, type 2 diabetes mellitus; OSA, obstructive sleep apnoea

Comments:

The maintenance doses for GLP-1 receptor agonists used for weight management are higher than doses for T2DM.

### 2.2.2 Usage

The number of people in New Zealand with initial dispensings of Pharmac-funded GLP-1 receptor agonists for type 2 diabetes mellitus (T2DM) by year is shown in Table 2.

**Table 2: Number of people with initial dispensings of a Pharmac-funded GLP-1 receptor agonist, by year**

| Medicine | 2021 | 2022 | 2023 |
|---|---|---|---|
| Trulicity (dulaglutide)[1] | 4,477 | 15,898 | 24,132 |
| Victoza (liraglutide)[2] | Not Pharmac funded | | 5,669 |
| Saxenda (liraglutide) | Not Pharmac funded | | |
| Ozempic (semaglutide) | Not marketed in New Zealand | | |
| Wegovy (semaglutide) | Not Pharmac funded, launched in New Zealand on 1 July 2025 | | |

Source: Pharmaceutical data web tool (extracted 31 July 2025)

[1] Trulicity funded since 1 September 2021, therefore data for 2021 is for 4 months only
[2] Victoza funded since 1 March 2023.

Comments:

There have been recent worldwide shortages of GLP-1 receptor agonists. This led to Pharmac limiting access to funded Trulicity (dulaglutide) and Victoza (liraglutide) on 1 May 2024 by instituting a 'no new patients' restriction. This 'no new patient' restriction was subsequently lifted for Victoza on 1 March 2025 and for Trulicity on 1 July 2025.

There have also been reports of compounded replica GLP-1 receptor agonist products (ie, unapproved products) the majority of which are used for weight loss.

## 2.3 Interaction with oral contraceptives

Combined oral contraceptives contain an estrogen and a progestogen. Those available in New Zealand include ethinylestradiol in combination with either levonorgestrel, norethisterone, desogestrel, or drospirenone. Products containing ethinylestradiol + cyproterone are not recommended solely for contraception.

Progestogen-only oral contraceptives can be an alternative to combined oral contraceptives when estrogens are contraindicated. Those approved for use in New Zealand include desogestrel, levonorgestrel, and norethisterone.

Pharmac estimates that in 2023/2024, over 300,000 people used a funded combined oral contraceptive pill and about 60,000 people used a funded progestogen-only oral contraceptive pill.

In general, drug-drug interactions (DDIs) with GLP-1 receptor agonists could occur due to delayed gastric emptying, reduced fat mass and inflammation, and increasing glomerular filtration rate (GFR) and renal plasma flow, consequently altering the pharmacokinetics of the interacting medicine (Figure 3) [3]. For DDIs with oral contraceptives and other oral medicines, it is the delayed gastric emptying caused by GLP-1 receptor agonists that is thought to be the mechanism [1].

Regulatory guidance for drug interaction studies states that when the ratio of the area under the concentration-time curve (AUC) of the victim medicine with and without the perpetrator medicine falls outside the range of 0.80 to 1.25, there is a potential risk of a clinically relevant interaction. Further evaluation is needed to quantify the effect.

**Figure 3: Flowchart showing the process of pharmacokinetic DDIs mediated by GLP-1 receptor agonists and a dual GLP-1/GIP receptor agonist**

The MHRA's guidance for GLP-1 medicines states that GLP-1 receptor agonists should not be used during pregnancy or just before trying to get pregnant. This is due to insufficient data on harms to the fetus if GLP-1 receptor agonists are used during pregnancy. As a precautionary measure, the wash-out periods shown in Figure 4 are recommended.

**Figure 4: MHRA recommended wash-out periods for GLP-1 receptor agonists before pregnancy**

| | How many months should GLP-1 be stopped before pregnancy? |
|---|---|
| **Semaglutide** (Wegovy, Ozempic and Rybelsus) | At least 2 months |
| **Tirzepatide** (Mounjaro) | At least 1 month |
| **Liraglutide** (All brands) | 0 months* |

*These medicines leave your body much quicker than the other GLP-1 medicines, which means they should be stopped just before trying to become pregnant.

Source: MHRA guidance for GLP-1 medicines (accessed 11 August 2025)

For those using Mounjaro (tirzepatide) and taking an oral contraceptive, the advice is to add a non-oral barrier form of contraception (eg, condoms) for four weeks after starting the medicine, and for four weeks after any increase in dose. This is because GLP-1 receptor agonists may reduce the effectiveness of oral contraceptives in those who are overweight or obese. Alternatively, people may switch to a non-oral form of hormonal contraception (eg, IUD, implant) which are not as affected by GLP-1 receptor agonists.

Comments:

The MHRA's contraceptive advice for Mounjaro (tirzepatide) aligns with the UK data sheet (see section 2.4.4 of this report). The advice mainly applies to those who are overweight or obese.

There is some data on the possible reduced effectiveness of hormonal contraception in those who are overweight for a levonorgestrel-containing implant (Jadelle [4]) and the levonorgestrel emergency contraceptive pill [5].

## 2.4 Data sheets

In summary, the GLP-1 receptor agonist New Zealand and Australian data sheets are aligned:

- All state there is no clinically relevant interaction with oral contraceptives.
- Dulaglutide data sheet advises it should only be used in pregnant women if the benefits outweigh the risks.
- Liraglutide and semaglutide data sheets note that treatment should be discontinued in women who are pregnant or planning a pregnancy. The semaglutide data sheet also notes that treatment should be discontinued at least 2 months before a planned pregnancy due to the long half-life.

Comparing the international data sheets:

- Most of the wording for each GLP-1 receptor agonist is similar.
- The UK and EU data sheets are aligned except for Wegovy (semaglutide) and Mounjaro (tirzepatide).
- Canadian data sheets have stronger wording in the pregnancy section. For example, discontinue Trulicity (dulaglutide) 1 month before planned pregnancy, and liraglutide (Victoza, Saxenda), Wegovy (semaglutide) and tirzepatide (Mounjaro, Zepbound) are contraindicated in pregnancy.

Further detail on relevant information in New Zealand and international data sheets are shown on the following pages. Main differences when compared with the New Zealand data sheets are highlighted in orange text.

### 2.4.1 Dulaglutide

| | Section 4.5 Interactions | Section 4.6 Pregnancy |
|---|---|---|
| **Trulicity (T2DM)** | | |
| New Zealand<br>Australia | Dulaglutide causes a delay in gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology studies, dulaglutide did not affect the absorption of the orally administered medications tested to any clinically relevant degree (e.g., warfarin, metformin, lisinopril, metoprolol, digoxin, paracetamol, norelgestromin, ethinyloestradiol, sitagliptin, atorvastatin). No dosage adjustments of concomitant medications are required. | There are no adequate and well controlled studies of dulaglutide in pregnant women. Administer TRULICITY to pregnant women only if the potential benefit justifies the potential risk to the foetus. |
| United Kingdom<br>Europe | Dulaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. In the clinical pharmacology studies described below, dulaglutide doses up to 1.5 mg did not affect the absorption of the orally administered medicinal products tested to any clinically relevant degree. For the 4.5 mg dose, absence of major clinically relevant interactions was predicted by physiologically-based pharmacokinetic (PBPK) modelling simulations.<br>For patients receiving dulaglutide in combination with oral medicinal products with rapid gastrointestinal absorption or prolonged release, there is a potential for altered medicinal product exposure, particularly at the time of dulaglutide treatment initiation.<br>Oral contraceptives: Coadministration of dulaglutide (1.5 mg) with an oral contraceptive (norgestimate 0.18 mg/ethinyl estradiol 0.025 mg) did not affect the overall exposure to norelgestromin and ethinyl estradiol. Statistically significant reductions in $C_{max}$ of 26 % and 13 % and delays in $t_{max}$ of 2 and 0.30 hours were observed for norelgestromin and ethinyl estradiol, respectively. These observations are not clinically relevant. No dose adjustment for oral contraceptives is required when given together with dulaglutide. | There are no or limited amount of data from the use of dulaglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Therefore, the use of dulaglutide is not recommended during pregnancy. |
| United States | Oral medications: TRULICITY delays gastric emptying and thus has the potential to reduce the rate of absorption of concomitantly administered oral medications. The delay in gastric emptying is dose-dependent but is attenuated with the recommended dose escalation to higher doses of TRULICITY [see Dosage and Administration (2.1)]. The delay is largest after the first dose and diminishes with subsequent doses. In clinical pharmacology studies, TRULICITY 1.5 mg did not affect the absorption of the tested orally administered medications to a clinically relevant degree [see Clinical Pharmacology (12.3)]. There is limited experience with the use of concomitant medications in clinical trials with TRULICITY doses of 3 mg and 4.5 mg. | Limited data with TRULICITY in pregnant women are not sufficient to determine a drug-associated risk for major birth defects and miscarriage. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy [see Clinical Considerations]. Based on animal reproduction studies, there may be risks to the fetus from exposure to dulaglutide during pregnancy. TRULICITY should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |

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| Canada | Drug interactions overview: Dulaglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology studies, dulaglutide did not affect the absorption of the tested, orally administered medications to any clinically relevant degree as described below in Table 5.<br>Oral contraceptives [Table 5]: Dulaglutide reduced norelgestromin and ethinyl estradiol Cmax by 26% and 13%, respectively, and delayed tmax by 2 and 0.3 hours, respectively, but did not affect AUC. Changes are not considered clinically relevant; no dose adjustment required. | No clinical trials in pregnant women have been conducted. Studies in animals have shown reproductive and developmental toxicity, including teratogenicity (see 16 NON-CLINICAL TOXICOLOGY). Trulicity should not be used during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant, Trulicity should be discontinued at least 1 month before due to the long wash out period for Trulicity. |

### 2.4.2 Liraglutide

| | Section 4.5 Interactions | Section 4.6 Pregnancy |
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| **Victoza (T2DM)** | | |
| New Zealand<br>No Australian data sheet | 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.<br>Oral contraceptives: Liraglutide lowered ethinylestradiol and levonorgestrel $C_{max}$ by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. $T_{max}$ was 1.5 h later with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide. | Studies in animals have shown reproductive toxicity (see 5.3 Preclinical safety data). The potential risk for humans is unknown. Victoza must not be used during pregnancy and the use of insulin is recommended. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza should be discontinued. |
| United Kingdom<br>Europe | 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.<br>Oral contraceptives: Liraglutide lowered ethinyloestradiol and levonorgestrel $C_{max}$ by 12 and 13%, respectively, following administration of a single dose of an oral contraceptive product. $T_{max}$ was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinyloestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide. | There are no adequate data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.<br>Liraglutide should not be used during pregnancy, and the use of insulin is recommended instead. If a patient wishes to become pregnant, or pregnancy occurs, treatment with Victoza should be discontinued. |

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| United States | VICTOZA causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, VICTOZA did not affect the absorption of the tested orally administered medications to any clinically relevant degree [see Clinical Pharmacology (12.3)]. Nonetheless, caution should be exercised when oral medications are concomitantly administered with VICTOZA. | Based on animal reproduction studies, there may be risks to the fetus from exposure to VICTOZA during pregnancy. VICTOZA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| Canada | Drug-drug interaction has been investigated using acetaminophen, digoxin, lisinopril, griseofulvin and atorvastatin representing various degrees of solubility and permeability properties. In addition, the effect of liraglutide on the absorption of ethinylestradiol and levonorgestrel administered in an oral combination contraceptive drug has been investigated.<br>The delay of gastric emptying caused by liraglutide did not affect the absorption of orally administered medicinal products to any clinically relevant degree.<br>Oral contraceptives: liraglutide lowered ethinylestradiol and levonorgestrel $C_{max}$ by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. $T_{max}$ was 1.5 h later with Victoza for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with Victoza. | There have been no studies conducted in pregnant women with Victoza. Studies in animals have shown reproductive and developmental toxicity, including teratogenicity, at or above 0.8 times the clinical exposure (see 16 NON-CLINICAL TOXICOLOGY).<br>Victoza should not be used during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant, or pregnancy occurs, treatment with liraglutide should be discontinued. |
| **Saxenda (weight management)** | | |
| New Zealand<br>Australia | Oral medications: The delay of gastric emptying caused by liraglutide may impact absorption of concomitantly administered oral medicinal products. Interaction studies did not show any clinically relevant delay of absorption of the compounds that were studied, however clinically relevant interactions with other compounds where the effect is dependent on $C_{max}$ and $t_{max}$, drugs with narrow therapeutic index, or medications associated with local gastrointestinal irritation (e.g. bisphosphonates, potassium chloride) cannot be excluded.<br>Oral contraceptives: A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel $C_{max}$ by 12% and 13%, respectively. $T_{max}$ was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the | There are limited data from the use of SAXENDA in pregnant women. SAXENDA should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, treatment with SAXENDA should be discontinued. |

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| | levonorgestrel AUC0-∞ by 18%. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide. | |
| United Kingdom<br>Europe | 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.<br>Oral contraceptives: Liraglutide lowered ethinylestradiol and levonorgestrel $C_{max}$ by 12% and 13%, respectively, following administration of a single dose of an oral contraceptive product. $t_{max}$ was delayed by 1.5 h with liraglutide for both compounds. There was no clinically relevant effect on the overall exposure of either ethinylestradiol or levonorgestrel. The contraceptive effect is therefore anticipated to be unaffected when co-administered with liraglutide. | There are limited data from the use of liraglutide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown.<br>Liraglutide should not be used during pregnancy. If a patient wishes to become pregnant or pregnancy occurs, treatment with liraglutide should be discontinued. |
| United States | SAXENDA causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, liraglutide did not affect the absorption of the tested orally administered medications to any clinically relevant degree. Nonetheless, monitor for potential consequences of delayed absorption of oral medications concomitantly administered with SAXENDA. | Based on animal reproduction studies, there may be risks to the fetus from exposure to SAXENDA during pregnancy. SAXENDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Additionally, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus, and discontinue SAXENDA (see Clinical Considerations). |
| Canada | Oral medications: Liraglutide causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications and caution should be exercised when oral medications are concomitantly administered with Saxenda.<br>The drugs listed in this table [not shown here, please refer to the Canadian data sheet] are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).<br>Oral contraceptives: A single dose of an oral contraceptive combination product containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel was administered under fed conditions and 7 hours after the dose of liraglutide at steady state. Liraglutide lowered ethinylestradiol and levonorgestrel $C_{max}$ by 12% and 13%, respectively. There was no effect of liraglutide on the overall exposure (AUC) of ethinylestradiol. Liraglutide increased the levonorgestrel AUC0-∞ by 18%. Liraglutide delayed $t_{max}$ for both | Saxenda is contraindicated during pregnancy. Weight loss offers no benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who are already overweight or have obesity, due to the necessary weight gain that occurs in maternal tissues during pregnancy.<br>Saxenda should not be used during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant or pregnancy occurs, treatment with Saxenda® should be discontinued. |

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| | ethinylestradiol and levonorgestrel by 1.5 h. The contraceptive effect is therefore anticipated to be unaffected when co-administered with Saxenda | |

### 2.4.3 Semaglutide

| | Section 4.5 Interactions | Section 4.6 Pregnancy |
|---|---|---|
| **Ozempic (T2DM)** | | |
| New Zealand (not published)<br>Australia | The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products, therefore semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. The potential effect of semaglutide on the absorption of co-administered oral medications was studied in trials at semaglutide 1 mg steady state exposure.<br>No clinically relevant drug-drug interaction with semaglutide (Figure 1) was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.<br>Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. Cmax was not affected for any of the compounds. | Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.1 Pharmacodynamic Properties). |
| United Kingdom<br>Europe | Semaglutide delays gastric emptying and has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.<br>Oral contraceptives: Semaglutide is not anticipated to decrease the effect of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. $C_{max}$ was not affected for any of the compounds. | Women of childbearing potential are recommended to use contraception when treated with semaglutide.<br>Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2). |

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| United States | Oral medications: OZEMPIC causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials, semaglutide did not affect the absorption of orally administered medications to any clinically relevant degree [see Clinical Pharmacology (12.3)]. Nonetheless, caution should be exercised when oral medications are concomitantly administered with OZEMPIC. | There are limited data with semaglutide use in pregnant women to inform a drug-associated risk for adverse developmental outcomes. There are clinical considerations regarding the risks of poorly controlled diabetes in pregnancy (see Clinical Considerations). Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. OZEMPIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| Canada | The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products. In clinical pharmacology trials assessing the effect of semaglutide 1 mg on the absorption of co-administered oral medications at steady state no clinically relevant drug-drug interactions with semaglutide was observed based on the evaluated medications.<br>Oral contraceptives: Semaglutide did not change AUC or $C_{max}$. No dose adjustment is required for these oral medications when co-administered with semaglutide. | Studies in animals have shown reproductive toxicity (see PART II, Toxicology). No clinical trials in pregnant women have been conducted. Therefore, semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life. See 10 CLINICAL PHARMACOLOGY, Pharmacokinetics. |
| **Wegovy (weight management)** | | |
| New Zealand<br>Australia | The delay of gastric emptying with semaglutide may influence the absorption of concomitantly administered oral medicinal products; therefore, semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg.<br>In clinical pharmacology trials assessing the effect of semaglutide 1.0 mg on the absorption of coadministered oral medications at steady state no clinically relevant drug-drug interactions with semaglutide (Figure 1) was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.<br>Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an | Semaglutide should not be used during pregnancy. Women of childbearing potential are recommended to use contraception when treated with semaglutide. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2 Pharmacokinetic Properties). |

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| | increase of 20% was observed for levonorgestrel exposure at steady state. $C_{max}$ was not affected for any of the compounds. | |
| United Kingdom | As with other GLP-1 receptor agonists, semaglutide may delay gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg. In clinical pharmacology trials assessing the effect of semaglutide 1.0 mg on the absorption of co-administered oral medications at steady state, no clinically relevant drug-drug interactions with semaglutide was observed based on the evaluated medications. Therefore, no dose adjustment is required when co-administered with semaglutide.<br>Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives as semaglutide did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. $C_{max}$ was not affected for any of the compounds. | Women of childbearing potential are recommended to use contraception when treated with semaglutide.<br>Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2). |
| Europe | Semaglutide delays gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. No clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg, probably due to a tolerance effect. Semaglutide should be used with caution in patients receiving oral medicinal products that require rapid gastrointestinal absorption.<br>Oral contraceptives: Semaglutide is not anticipated to decrease the effectiveness of oral contraceptives. It did not change the overall exposure of ethinylestradiol and levonorgestrel to a clinically relevant degree, when an oral contraceptive combination medicinal product (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) was co-administered with semaglutide. Exposure of ethinylestradiol was not affected; an increase of 20% was observed for levonorgestrel exposure at steady state. $C_{max}$ was not affected for any of the compounds. | Women of childbearing potential are recommended to use contraception when treated with semaglutide (see section 4.5).<br>Studies in animals have shown reproductive toxicity (see section 5.3). There are limited data from the use of semaglutide in pregnant women. Therefore, semaglutide should not be used during pregnancy. If a patient wishes to become pregnant, or pregnancy occurs, semaglutide should be discontinued. Semaglutide should be discontinued at least 2 months before a planned pregnancy due to the long half-life (see section 5.2). |

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| United States | Oral medications: WEGOVY causes a delay of gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. In clinical pharmacology trials with semaglutide 1 mg, semaglutide did not affect the absorption of orally administered medications [see Clinical Pharmacology (12.3)]. Nonetheless, monitor the effects of oral medications concomitantly administered with WEGOVY. | Based on animal reproduction studies, there may be potential risks to the fetus from exposure to semaglutide during pregnancy. Additionally, weight loss offers no benefit to a pregnant patient and may cause fetal harm. When a pregnancy is recognized, advise the pregnant patient of the risk to a fetus, and discontinue WEGOVY (see Clinical Considerations). Available pharmacovigilance data and data from clinical trials with WEGOVY use in pregnant patients are insufficient to establish a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. |
| Canada | As with other GLP-1 receptor agonists, semaglutide may delay gastric emptying and could potentially influence the absorption of concomitantly administered oral medicinal products. In a pharmacodynamic study, no clinically relevant effect on the rate of gastric emptying was observed with semaglutide 2.4 mg. In clinical pharmacology trials assessing the effect of semaglutide 1 mg on the absorption of co-administered oral medications at steady state no clinically relevant drug-drug interactions with semaglutide was observed based on the evaluated medications.<br>Oral contraceptives: No clinically relevant change in AUC or $C_{max}$. No dose adjustment is required for these oral medications when co-administered with semaglutide. | WEGOVY® is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). Weight loss offers no benefit to a pregnant woman and may result in fetal harm. A minimum weight gain, and no weight loss, is recommended for all pregnant women, including those who are already overweight or have obesity, due to the necessary weight gain that occurs in maternal tissues during pregnancy. There have been no studies conducted in pregnant women with WEGOVY®. If a patient wishes to become pregnant, or pregnancy occurs, discontinue semaglutide treatment. Discontinue semaglutide at least 2 months before a planned pregnancy due to its long half-life (see 10 CLINICAL PHARMACOLOGY). |

### 2.4.4 Tirzepatide

There are no tirzepatide-containing products approved in New Zealand. However, relevant information from overseas data sheets is shown below. Information that may be of interest is shown in green text.

| | Section 4.5 Interactions | Section 4.6 Pregnancy |
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| **Mounjaro** | | |
| Australia<br>(T2DM & weight) | Tirzepatide delays gastric emptying and has the potential to affect the rate of absorption of concomitantly administered oral medications. This effect, resulting in decreased $C_{max}$ and a delayed $t_{max}$, is most pronounced at the time of tirzepatide treatment initiation.<br>Oral contraceptives: Administration of a combination oral contraceptive (0.035 mg ethinylestradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive $C_{max}$ by 55 to 66%, with a 16 to 23% reduction in area under the curve (AUC) and a delay in $t_{max}$ of 2.5 to 4.5 hours. This reduction in exposure after a single 5 mg dose of tirzepatide is not considered clinically relevant. Doses other than a single 5 mg dose of tirzepatide were not investigated in this interaction study.<br>The reduction in exposure described above may be significant in a setting with concomitant administration of medicines also affecting those exposures. Appropriate contraception methods (including non-oral contraceptives) should be discussed with the patient based on the patient's individual circumstances prior to commencing tirzepatide. | There are no adequate and well-controlled studies of tirzepatide in pregnant women. Tirzepatide should not be used during pregnancy. Women of childbearing potential are advised to use contraception during treatment with tirzepatide (see section 4.5 Interactions with other medicines and other forms of interactions). If a patient wishes to become pregnant or becomes pregnant, treatment with tirzepatide should be discontinued. |
| United Kingdom<br>(T2DM & weight) | Tirzepatide delays gastric emptying and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This effect, resulting in decreased $C_{max}$ and a delayed $t_{max}$, is most pronounced at the time of tirzepatide treatment initiation.<br>Oral contraceptives: Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate, a prodrug of norelgestromin) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive $C_{max}$ and area under the curve (AUC). Ethinyl estradiol $C_{max}$ was reduced by 59 % and AUC by 20 % with a delay in $t_{max}$ of 4 hours. Norelgestromin $C_{max}$ was reduced by 55 % and AUC by 23 % with a delay in $t_{max}$ of 4.5 hours. Norgestimate $C_{max}$ was reduced by 66 %, and AUC by 20 % with a delay in $t_{max}$ of 2.5 hours. This reduction in exposure after a single dose of tirzepatide is not considered clinically relevant. No dose adjustment of oral contraceptives is required in women with normal BMI.<br>There is limited information about the effect of tirzepatide on the pharmacokinetics and efficacy of oral contraceptives in women with obesity or overweight. Since reduced efficacy of oral contraceptives cannot be excluded, it is advised switching to a non-oral contraceptive method, or | There are no or a limited amount of data from the use of tirzepatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, tirzepatide should be discontinued at least 1 month before a planned pregnancy due to the long half-life of tirzepatide. Tirzepatide should not be used during pregnancy. |

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| | add a barrier method of contraception upon initiating tirzepatide therapy (for 4 weeks), or after each dose escalation (for 4 weeks). | |
| Europe<br>(T2DM & weight) | Tirzepatide delays gastric emptying and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This effect, resulting in decreased $C_{max}$ and a delayed $t_{max}$, is most pronounced at the time of tirzepatide treatment initiation.<br>Oral contraceptives: Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate, a prodrug of norelgestromin) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive $C_{max}$ and area under the curve (AUC). Ethinyl estradiol $C_{max}$ was reduced by 59 % and AUC by 20 % with a delay in $t_{max}$ of 4 hours. Norelgestromin $C_{max}$ was reduced by 55 % and AUC by 23 % with a delay in $t_{max}$ of 4.5 hours. Norgestimate $C_{max}$ was reduced by 66 %, and AUC by 20 % with a delay in $t_{max}$ of 2.5 hours. This reduction in exposure after a single dose of tirzepatide is not considered clinically relevant. No dose adjustment of oral contraceptives is required. | Women of childbearing potential are recommended to use contraception when treated with tirzepatide.<br>There are no or a limited amount of data from the use of tirzepatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, or pregnancy occurs, tirzepatide should be discontinued. Tirzepatide should be discontinued at least 1 month before a planned pregnancy due to the long half-life (see section 5.2). |
| United States<br>(T2DM) | Oral medications: MOUNJARO delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with MOUNJARO.<br>Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with MOUNJARO.<br>Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO. Hormonal contraceptives that are not administered orally should not be affected [see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]. | Available data with MOUNJARO use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy (see Clinical Considerations). Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. MOUNJARO should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. |
| Canada (T2DM) | MOUNJARO delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses. Dose adjustments with concomitant use of insulin secretagogues (e.g., sulfonylurea) or insulin may be necessary (see 7 WARNINGS AND PRECAUTIONS and 8.2 Clinical Trial Adverse Reactions).<br>Oral contraceptives: Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive $C_{max}$ by 55 to 66%, with a 16 to 23% reduction in AUC and a delay | MOUNJARO is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant, MOUNJARO should be discontinued at least 1 month before a planned pregnancy due to the long half-life of MOUNJARO. |

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| | in $t_{max}$ of 2.5 to 4.5 hours. These effects may be due to the impact of MOUNJARO on gastric emptying.<br>Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with MOUNJARO. | |
| **Zepbound** | | |
| United States (weight) | Oral medications: ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with ZEPBOUND.<br>Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with ZEPBOUND.<br>Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected [see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]. | Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue ZEPBOUND when a pregnancy is recognized (see Clinical Considerations). Available data with tirzepatide in pregnant patients are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. |
| Canada (weight) | ZEPBOUND KwikPen delays gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.<br>Oral contraceptives: Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive $C_{max}$ by 55 to 66%, with a 16 to 23% reduction in AUC and a delay in $t_{max}$ of 2.5 to 4.5 hours. These effects may be due to the impact of ZEPBOUND KwikPen on gastric emptying.<br>Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or to add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation with ZEPBOUND KwikPen. | ZEPBOUND KwikPen is contraindicated during pregnancy (see 2 CONTRAINDICATIONS). If a patient wishes to become pregnant, ZEPBOUND KwikPen should be discontinued at least 1 month before a planned pregnancy due to the long half-life of tirzepatide. |

# 3 SCIENTIFIC INFORMATION

## 3.1 Published literature – Reviews

Search of PubMed on 4 August 2025:

- ((exenatide) OR (dulaglutide) OR (liraglutide) OR (semaglutide) OR (tirzepatide)) AND (contracept*) 22 results
- (glucagon) AND (contracept*) 68 results

Review articles are presented first, followed by the individual DDI studies.

### 3.1.1 Skelley et al 2024 (Annex 1) [1]

Title

The impact of tirzepatide and glucagon-like peptide 1 receptor agonists on oral hormonal contraception.

Objectives

To assess trial data on the impact of tirzepatide and GLP-1 receptor agonists (eg, semaglutide, dulaglutide) on hormonal contraceptives and provide a summarised analysis of differences in safety data between oral contraceptives and incretin-based agents.

To discuss implications and impact of this interaction and the crucial need to emphasise appropriate counselling and education to patients and providers.

Methods

This literature review analyses results and background information from various clinical trials and crossover studies. An initial literature search was performed and package inserts were reviewed. Databases such as PubMed, Google Scholar, and ClinicalTrials.gov were used.

The PubMed search was performed using combinations of the generic names of GLP-1 receptor agonists, hormonal contraceptives, and free-text searches. Filters were applied to narrow the results.

Articles identified for inclusion include an open label clinical trial of dulaglutide and oral contraceptives, a double-blind crossover study of liraglutide and oral contraceptives, an open label crossover study of semaglutide and oral contraceptives, an open label crossover study of exenatide and oral contraceptives, and a crossover study of oral semaglutide and oral contraceptives.

Results

A total of 1055 records were identified by searching the published literature. After removing duplicates, excluding studies that did not meet the criteria and evaluating studies for eligibility, 6 studies remained and were included in the review.

All 6 studies evaluated area under the plasma drug concentration-time curve (AUC), maximum concentration ($C_{max}$), and $T_{max}$ of an incretin agent coadministered with an oral contraceptive. Each study used blood sampling to collect AUC, $C_{max}$, and $T_{max}$ levels of hormonal contraceptives after administration of the incretin agent. A summary of the 6 studies is shown in Table 3, and a summary of the results is shown in Table 4.

The authors state the results of this literature review revealed coadministration of an incretin-based therapy and an oral contraceptive can be associated with differing AUC, $C_{max}$, and $T_{max}$ values depending on the incretin agent used. Long-acting incretin agents have a larger effect on gastric emptying than short-acting incretin agents. The once weekly and high doses of tirzepatide caused a larger delay in gastric emptying and therefore a larger impact on absorption of oral medicines. Results from clinical studies demonstrated that the use of tirzepatide and an oral hormonal contraceptive had the most clinically significant effect on the AUC, $C_{max}$, and $T_{max}$ of the oral hormonal contraceptives.

**Table 3: Summary of the six studies included in the review**

[redacted]

**Table 4: Summary of results**

[redacted]

Comments:

The only interaction with oral contraceptives that was clinically relevant was with tirzepatide (reduced AUC by 20% for ethinylestradiol, 21% for norgestimate; reduced $C_{max}$ of ethinylestradiol by 59%, norgestimate by 66%; delayed $T_{max}$ of 2.5 to 4.5 hours).

All the studies listed in Table 4 are shown in sections 3.2 and 3.3 of this report.

### 3.1.2 Min et al 2025 (Annex 2) [3]

Title

A comprehensive review on the pharmacokinetics and drug-drug interactions of approved GLP-1 receptor agonists and a dual GLP-1/GIP receptor agonist.

Objective

The main objective was to examine the pharmacokinetics of exenatide, liraglutide, dulaglutide, semaglutide, and tirzepatide. The pharmacokinetic DDIs of the medicines were also examined.

Pharmacokinetic DDIs of peptide medicines

Peptide medicines are mainly eliminated by protease enzymes, while liver uptake is minimal. This allows them to bypass metabolism by hepatic enzymes such as CYPs or UDP-glucuronosyltransferases (UGTs). In addition, many peptide medicines are not known to be substrates or inhibitors of transporters, indicating that transporter-mediated biliary or renal excretion may not be a major pathway for their elimination.

However, there is increasing evidence of the involvement of peptide medicines in the occurrence of CYP or transporter-mediated DDIs. For example, this has been seen with coadministration of warfarin and octreotide leading to high INR levels in humans which may be attributed to the increased warfarin exposure caused by octreotide's inhibitory effect on CYP3A4. Another example is cyclosporin which has been identified as a substrate for CYP3A4, P-gp and organic anion transporting polypeptides (OATPs), while also acting as a potent inhibitor of CYP3A4, multidrug resistance-associated protein 2 (MRP2), OATPs, P-gp, and breast cancer resistance protein (BCRP).

There are limited data on clinically significant metabolic enzyme- or transporter-mediated DDIs involving GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists. In vitro DDI studies detailed in clinical pharmacology and biopharmaceutic reviews were not included in the review for exenatide and dulaglutide, but were included for liraglutide, semaglutide, and tirzepatide. All the investigated GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists exhibited minimal inhibition or induction of CYP enzymes.

DDIs with oral contraceptives

Some GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists altered the exposure of oral contraceptives, implying the potential for clinically significant DDIs (Table 5). The $C_{max}$ and AUC values of ethinylestradiol and levonorgestrel were not affected by the administration of 14 mg oral or 1 mg subcutaneous semaglutide, indicating that it is not clinically relevant (Table 5). Notable changes in the $C_{max}$ ratios of oral contraceptives after the administration of 10 µg exenatide twice daily seem to be caused by their administration 30 min after exenatide when the delayed gastric emptying effect was at its peak. Therefore, it was concluded that clinically significant pharmacokinetic changes are unlikely to occur. Similarly, alterations in the pharmacokinetics after 1.8 mg liraglutide and 1.5 mg dulaglutide administration have also been shown to have minimal clinical significance.

The most significant pharmacokinetic alterations were reported following the administration of a single 5 mg dose of tirzepatide, with the $C_{max}$ and AUC values of ethinylestradiol decreasing by 59% and 21%, respectively, and those of norelgestromin by 55% and 22%, respectively (Table 5). However, the pharmacokinetic/pharmacodynamic relationship of oral contraceptives is not yet fully defined; therefore, additional studies are required to explore how changes in exposure influence their effectiveness. In addition, this implies that tirzepatide more strongly affects the absorption of oral contraceptives and that this increased

impact may be driven by rapid dose escalation. Unlike other pharmacodynamic effects, such as lowering blood glucose or reducing appetite, the delay in gastric emptying shows tachyphylaxis with the effect gradually decreasing over time. Therefore, investigators have suggested switching to a non-oral contraceptive option or adding a barrier method of contraception for 4 weeks after tirzepatide treatment is initiated or if the dose is substantially increased.

**Table 5: Changes in oral contraceptive pharmacokinetics without and with treatment with GLP-1 receptor agonists or a dual GLP-1/GIP receptor agonist**

Comments:

This was a thorough review, including the mechanisms involved in drug interactions with GLP-1 receptor agonists and dual GLP-1/GIP receptor agonists. A number of DDIs were discussed, but only information on oral contraceptives is included here. All the studies on oral contraceptives listed in Table 6 were included in Skelley et al's review and shown in section 3.2 of this report.

The authors note that most of the GLP-1 receptor agonists and tirzepatide did not show clinically significant DDIs related to delayed gastric emptying. However, coadministration of oral contraceptives and tirzepatide showed notable changes in AUC of the oral contraceptive, implying there is a potential risk of a clinically significant DDI. This could indicate that close monitoring is needed when these medicines are coadministered, especially when starting treatment or increasing the dose.

### 3.1.3 Calvarysky et al 2024 [6]

Title

Drug-drug interactions between glucagon-like peptide 1 receptor agonists and oral medications: A systematic review.

Purpose

To summarise data on DDIs between GLP-1 receptor agonists and oral medicines.

Methods

PubMed and EMBASE were searched up to 1 November 2023. Reference lists of all publications were queried to find studies not identified during the initial search. GLP-1 data sheets were screened for information about DDIs not published elsewhere. Only injectable GLP-1 receptor agonists were considered eligible (exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, semaglutide).

The primary pharmacokinetic outcomes were the rate ($C_{max}$, $t_{max}$) and the extent (AUC) of drug absorption when an oral drug of interest was given concomitantly with vs. without a GLP-1 receptor agonist. Other outcomes were pharmacodynamic parameters, including gonadotropins or progesterone levels for combined oral contraceptive (COC) studies.

Overall results

The initial search yielded 5221 potentially relevant references of which 40 records were retrieved for full-text review. 22 reports were included in the study cohort, including 15 pharmacokinetic (PK) studies, 1 pharmacodynamic (PD) study, 1 review with detailed PK data not elsewhere published, 3 conference abstracts, 1 case report, and 1 case series.

Drug interactions of exenatide were described in 8 manuscripts, liraglutide in 5, semaglutide in 3, lixisenatide, dulaglutide and albiglutide in 2 each and synthetic GLP-1 in 1. 3 studies enrolled participants with diabetes mellitus, and all others enrolled healthy subjects. 2 studies on a DDI with COCs enrolled post-menopausal women and 3 studies enrolled pre-menopausal women.

Most studies showed good reporting quality implying an overall low risk of bias.

Combined oral contraceptives (COCs)

Pharmacokinetic studies of GLP-1 receptor agonists given concomitantly with COCs are shown in Table 6. Overall, administration of GLP-1 receptor agonists resulted in reduced $C_{max}$ and delayed $T_{max}$ of the estrogen and progesterone elements, consistent with a right shift of the concentration-time curve of drug absorption resulting from the expected prolonged gastric transit time. However, the bioequivalence criterion for the AUC was met for ethinylestradiol in all cases, and the AUC for the progestin component was either unaffected or showed approximately 20% higher mean exposure, which is not considered to affect the safety or efficacy of the COCs. This attests to an overall unchanged bioavailability of the COCs when given with a GLP-1 analogue.

**Table 6: Pharmacological studies with GLP-1 receptor agonists and COCs**

In addition, given the right shift of the concentration-time curve with a similar AUC, it is expected that the minimum concentration of the COCs will not be lower. Direct measurement of the minimum concentration of ethinylestradiol and norethindrone was similar with or without coadministration of albiglutide. This is

especially important with the use of low-dose contraceptives that are dependent on threshold blood levels for birth control. Pharmacodynamic studies were conducted only for albiglutide, which found coadministration did not affect the plasma levels of gonadotropins or progesterone.

A clinically significant DDI between GLP-1 receptor agonists and COCs is probably not expected and there is no recommendation in any GLP-1 receptor agonist data sheet for dose adjustment of COCs in this context.

Comments:

This review didn't include tirzepatide. There was one study (Bush et al, 2012 [7]) involving albiglutide that wasn't included in the Skelley et al and Min et al reviews.

The review findings are consistent with those reported by Skelley et al and Min et al.

## 3.2 Published literature – Drug-drug interaction studies

### 3.2.1 de la Peña et al 2017 – Dulaglutide [8]

Title

No dose adjustment is recommended for digoxin, warfarin, atorvastatin or a combined oral contraceptive when coadministered with dulaglutide.

Purpose

This article reports the results from four different studies in healthy subjects in which the effects of dulaglutide on the pharmacokinetics of digoxin, warfarin, atorvastatin and Ortho-Cyclen (oral contraceptive containing norgestimate and ethinylestradiol) were evaluated.

Methods

The timing of PK analyses for the concomitant medicines was designed to coincide with the approximate time of peak dulaglutide concentration. Three of the study designs, including the with Ortho-Cyclen, used a sequential design while the warfarin study used a crossover design (Table 7).

**Table 7: Summary of study designs**

[redacted]

For Ortho-Cyclen, subjects received a full cycle of once daily oral doses of Ortho-Cyclen treatment during the 28-day lead-in phase and each of the two successive treatment periods. A sample size of 14 completers was chosen to provide at least 90% power to demonstrate that the 90% CI of the ratio of ethinylestradiol and norelgestromin (test/reference) is within 0.80-1.25 for AUC and 0.70-1.43 for $C_{max}$. This estimate assumes that the true ratios for AUC and $C_{max}$ are equal to 1.05 and that the intrasubject coefficients of variation for ethinylestradiol are 13.8% and 25.3% for AUC and $C_{max}$, respectively (based on a previous study), and those for norelgestromin are 8.07% and 13.71% for AUC and $C_{max}$, respectively (inferred from Kearney and Mathias, [9]).

Each treatment period lasted 28 days and was comprised of 21 days of active tablets containing norgestimate 0.25 mg and ethinylestradiol 0.035 mg, as well as 7 days of non-active tablets.

Results – Ortho-Cyclen study

A total of 22 subjects were enrolled. Seven subjects did not complete the study: one withdrew due to an AE of rash (not considered related) prior to dulaglutide dosing, four voluntarily withdrew before receiving dulaglutide, one voluntarily withdrew after experiencing gastrointestinal AEs following dulaglutide administration, and one was lost to follow-up.

Figure 5 shows the mean concentration versus time profiles of the analytes for Ortho-Cyclen administered alone and coadministered with subcutaneous dulaglutide 1.5 mg. There was a general trend for the exposure of the concomitant medicines (AUC and $C_{max}$) to be lower following administration with dulaglutide, and for their $t_{max}$ to be delayed.

**Figure 5: Arithmetic mean (one-sided SD) steady-state serum concentration-time profiles for Ortho-Cyclen**

Coadministration of dulaglutide had no effect on AUC of norelgestromin and ethinylestradiol with the 90% CI of the ratios of the geometric LS means falling within 0.80-1.25 (Table 8). However, the mean $C_{max}$ for norelgestromin and ethinylestradiol were reduced by 26% and 13%, respectively. A delay in $t_{max}$ was seen for all coadministered medicines with the smallest increases (up to 1 hour) observed for digoxin, ethinylestradiol, and norelgestromin (Table 9).

**Table 8: Statistical analysis of pharmacokinetic parameters**

Comments:

There are no oral contraceptives containing norelgestromin (norgestimate) approved for use in NZ.

Delayed gastric emptying with dulaglutide is largest after the first dose and decreases with subsequent doses. For this reason, the Ortho-Cyclen study used a single dulaglutide dose, rather than dosing to steady state.

Coadministration of Ortho-Cyclen with dulaglutide had no effect on the overall exposure (AUC∞) to norelgestromin and ethinylestradiol. There was a decrease in $C_{max}$ and an increase in $t_{max}$. The authors considered that these observations are not clinically relevant for a long-term treatment given that overall norelgestromin and ethinylestradiol exposures were unchanged.

The authors also note large inter-subject variability of the concentration data is characteristic of oral contraceptives and ethinylestradiol AUCs can vary by almost a factor of 4. In food-effect studies with oral contraceptives, reductions in $C_{max}$ of up to 40% are common without changes in AUC. Despite this, oral contraceptives can be taken with or without food.

### 3.2.2 Jacobsen et al 2011 – Liraglutide [10]

Title

Treatment with liraglutide – a once-daily GLP-1 analog – does not reduce the bioavailability of ethinyl estradiol/levonorgestrel taken as an oral combination contraceptive drug.

Objective

To investigate the effect of liraglutide (if any) on the pharmacokinetics of the components of an oral contraceptive containing ethinylestradiol 0.03 mg and levonorgestrel 0.15 mg.

Methods

A single-centre, randomised, double-blind, placebo-controlled, 2-period crossover study comparing the influence of liraglutide and placebo on the pharmacokinetics of ethinylestradiol and levonorgestrel given as an oral combination contraceptive (brand name: Neovletta).

A total of 21 postmenopausal women participated and completed the study. Postmenopausal women who had undergone oophorectomy or had at least 1 year of amenorrhea were selected with the aim of eliminating any hormonal fluctuations that might influence the interpretation of the pharmacokinetics of ethinylestradiol or levonorgestrel.

Each subject received either liraglutide or placebo once daily for 3 weeks, in random order, before switching to the alternate treatment (placebo or liraglutide) for 3 weeks. In each crossover period, subjects took liraglutide 0.6 mg (or corresponding injection volume of placebo) for week 1, followed by liraglutide 1.2 mg (or corresponding placebo) during week 2, and finally liraglutide 1.8 mg (or corresponding placebo) during week 3.

In each crossover period, subjects attended the study site for the DDI investigation after 5 days of daily dosing with liraglutide 1.8 mg or corresponding placebo. On the DDI investigation day, a single oral tablet of the contraceptive was administered 7 hours after the administration of liraglutide/placebo, whereby the maximum concentration of ethinylestradiol and levonorgestrel was planned to coincide with the time of $C_{max}$ of liraglutide.

The primary endpoint was the AUC for ethinylestradiol and levonorgestrel, and exposures during liraglutide and placebo were declared equivalent if the 90% CI for the ratios of AUC was contained within the limits 0.80 to 1.25.

Results

Figure 7 shows the mean serum concentration-time profile and Table 10 the mean pharmacokinetic endpoints.

**Figure 6: Mean concentration-time profiles**

**Table 10: Mean pharmacokinetic end points**

[redacted]

AUC for ethinylestradiol was equivalent during liraglutide/placebo as the 90% CI for the estimated ratio was within the prespecified limits for equivalence (0.80 to 1.25). Equivalence was shown for $AUC_{0\text{-}48h}$ and Vz/F but was not demonstrated for $C_{max}$ and $t_{1/2}$ (Table 11). $C_{max}$ and $t_{1/2}$ were estimated to be 12% and 2% lower, respectively, during liraglutide steady-state conditions than during placebo. In addition, the $t_{max}$ for ethinylestradiol occurred 1.5 hours later with liraglutide treatment than with placebo.

For levonorgestrel AUC, equivalence was not demonstrated being 18% larger with liraglutide compared with placebo (Table 11). However, for a number of subjects AUC was not calculated. Prior to unblinding the treatment code it was evaluated that these profiles had too flat an elimination phase for the AUC to be extrapolated to infinity. This happened equally frequently for liraglutide and placebo administration (9 profiles in each group). Although similar ratios for AUC and $AUC_{0\text{-}t}$ ($AUC_{0\text{-}74h}$) were found, equivalence was shown for $AUC_{0\text{-}t}$. As with ethinylestradiol, $C_{max}$ and $t_{1/2}$ did not meet the equivalence criterion and were lower (13% and 4%, respectively) during liraglutide treatment than during placebo, and $t_{max}$ occurred 1.5 hours later during liraglutide treatment.

[redacted]

Comments:

The authors conclude that there is no clinically relevant decrease in overall bioavailability when liraglutide is coadministered with ethinylestradiol and levonorgestrel.

### 3.2.3 Kapitza et al 2015 – Semaglutide [11]

Title

Semaglutide, a once-weekly human GLP-I analog, does not reduce the bioavailability of the combined oral contraceptive, ethinylestradiol/levonorgestrel.

Objective

To investigate if semaglutide altered the pharmacokinetics of ethinylestradiol and levonorgestrel in postmenopausal women with T2D.

Methods

A single-centre, open-label, one-sequence crossover study. Postmenopausal women who had undergone bilateral oophorectomy or had at least 1 year of spontaneous amenorrhoea, with serum follicle stimulating hormone >40 mIU/mL and estrogen deficiency (estradiol levels <30 pg/mL or a negative gestagen test), were selected for the study.

Figure 7 shows the study design. Semaglutide was administered once weekly by subcutaneous injection on the same day each week. Semaglutide steady-state was reached using a dose-escalation regimen. The Microgyn oral contraceptive (1 tablet per day; 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel) was prescribed for 8 days before (semaglutide-free) and during the last week of dosing with semaglutide 1.0 mg (steady-state); the last dose of oral contraceptive was administered 24 hours after the last dose of semaglutide.

The primary endpoint was area under the curve ($AUC_{0-24h}$) for ethinylestradiol and levonorgestrel at steady-state.

Ethinylestradiol and levonorgestrel exposure at semaglutide-free and semaglutide steady-state were established as bioequivalent if the 90% CI for the ratio of the $AUC_{0-24h}$ was within the prespecified 0.80-1.25 limits (both inclusive; the power was calculated using 2 one-sided t-tests of equivalence in means on a 5% significance level).

**Figure 7: Study design**

Results

A total of 43 postmenopausal women were enrolled and 39 completed the study. Figure 8 shows the mean plasma concentration-time profile and Table 12 shows the pharmacokinetic results.

**Figure 8: Mean concentration-time profile**

**Table 12: Pharmacokinetic endpoints**

For ethinylestradiol, the bioequivalence criterion was met for both $AUC_{0\text{-}24h}$ (semaglutide steady-state/semaglutide-free 1.11, 90% CI 1.06-1.15) and $C_{max}$ (1.04, 90% CI 0.98-1.10). There were no apparent differences in any of the other pharmacokinetic parameters between the 2 treatment periods.

For levonorgestrel, the estimated mean $AUC_{0\text{-}24h}$ for levonorgestrel was 20% higher during the semaglutide steady-state than the semaglutide-free period (1.20, 90% CI 1.15-1.26). The bioequivalence criterion was met for $C_{max}$ for levonorgestrel (1.05, 90% CI 0.99-1.12). The median $t_{max}$ was 1 hour for both treatment periods. However, during the semaglutide steady-state period, individual $t_{max}$ values were right-shifted indicating a slight delay of $t_{max}$.

The authors conclude that semaglutide did not reduce the bioavailability of ethinylestradiol and levonorgestrel.

### 3.2.4 Jordy et al 2021 – Semaglutide oral [12]

Title

Effect of oral semaglutide on the pharmacokinetics of levonorgestrel and ethinylestradiol in healthy postmenopausal women and furosemide and rosuvastatin in healthy subjects.

Objective

To investigate the effects of oral semaglutide on the pharmacokinetics of a combined oral contraceptive (OC) containing ethinylestradiol and levonorgestrel (Trial 1), and furosemide and rosuvastatin (Trial 2).

Methods

An open-label, one-sequence, crossover trial design. As semaglutide has a half-life of about 1 week, dosing with once-daily oral semaglutide 14 mg for 4 weeks prior to assessment of the interaction was considered adequate.

25 healthy postmenopausal women (aged ≥45 years with ≥12 consecutive months since last spontaneous menstrual bleeding) received once-daily combined ethinylestradiol and levonorgestrel (Trial 1). Subjects received Microgynon containing 0.03 mg ethinylestradiol and 0.15 mg levonorgestrel in three 8-day periods: the first period as monotherapy, the second together with SNAC (an absorption enhancer) and the third period together with semaglutide (Figure 9).

Lack of a DDI was concluded if 90% CIs for the ratio of area under the plasma concentration-time curve (AUC) or maximum concentration ($C_{max}$) with/without oral semaglutide were within a pre-specified interval (0.80-1.25).

**Figure 9: Trial design for Trial 1 (combined OC)**

Results

Mean concentration-time profiles for ethinylestradiol and levonorgestrel for the three treatment periods (OC, OC + SNAC, OC + oral semaglutide) are shown in Figure 10. The estimated treatment ratio of $AUC_{0-24,SS}$ for ethinylestradiol was 1.06 (90% CI 1.01-1.10) and for levonorgestrel was 1.06 (90% CI 0.97-1.17) which were within the pre-specified 'no effect' interval. Similarly, the 90% CIs for the estimated ratios of $C_{max}$ for ethinylestradiol and levonorgestrel were within the pre-specified interval indicating that coadministration of oral semaglutide had no effect on the exposure of ethinylestradiol or levonorgestrel.

The authors conclude coadministration with oral semaglutide did not affect the pharmacokinetics of ethinylestradiol or levonorgestrel.

**Figure 10: Mean concentration-time profiles for the primary endpoints**

Comments:

This study was with oral semaglutide which is not an approved formulation in New Zealand. It has been included in this paper for completeness.

### 3.2.5 Kothare et al 2012 – Exenatide [13]

Title

Effect of exenatide on the pharmacokinetics of a combination oral contraceptive in healthy women: an open-label, randomised, crossover trial.

Objective

The primary objective was to evaluate the effect of exenatide on the multiple-dose PK of a combination oral contraceptive (OC; ethinylestradiol (EE) and levonorgestrel (LV)) administered 1 hour before and 30 minutes after the exenatide dose.

Methods

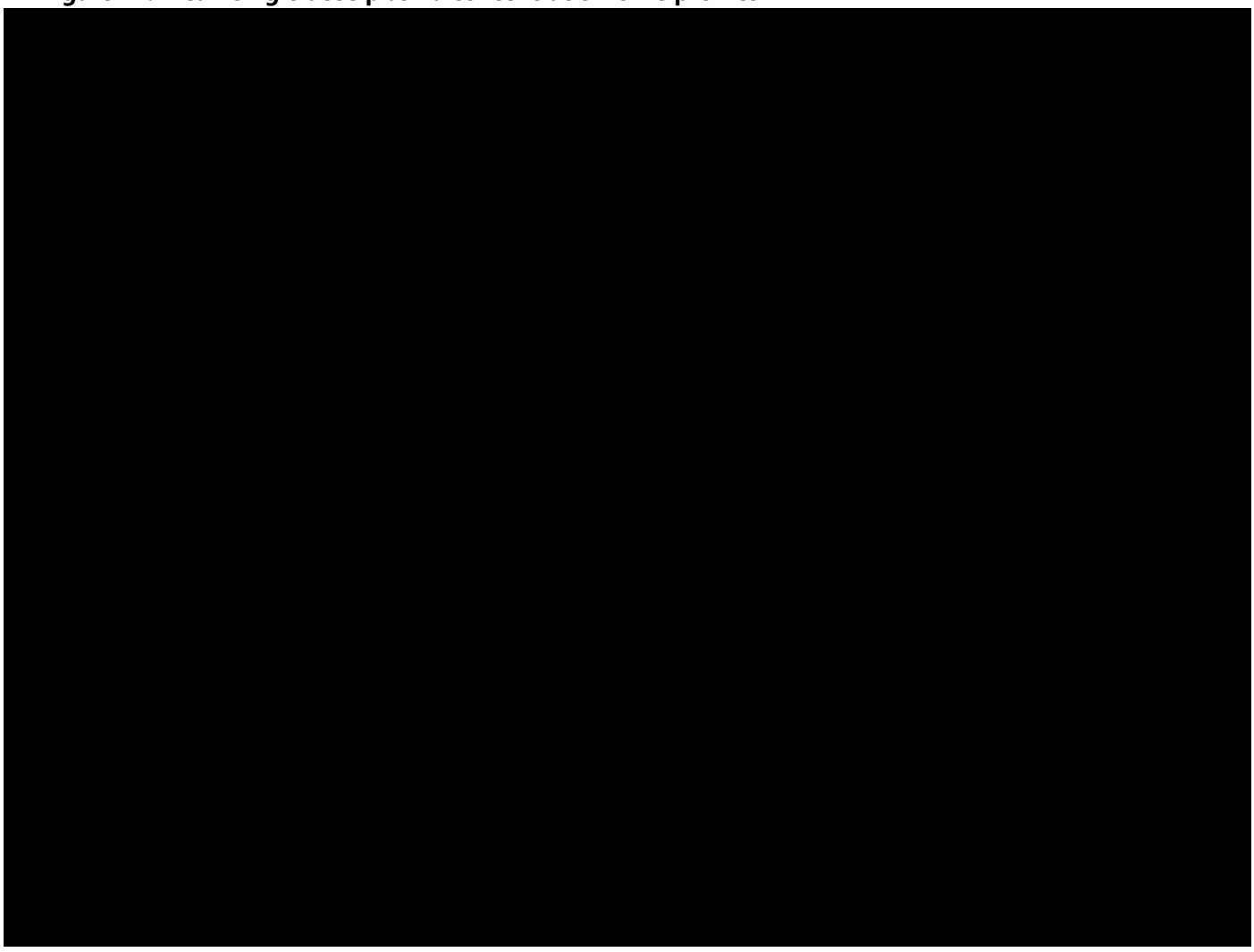
32 healthy female subjects participated in an open-label, randomised, crossover trial with 3 treatment periods (each of 28 days) (OC alone, OC 1 hour before exenatide, OC 30 minutes after exenatide). Subjects were required to be taking an OC prior to study entry and be healthy pre-menopausal females 18 to 45 years old.

Subjects received a single dose of oral contraceptive (Microgynon 30 containing ethinylestradiol 30 mcg, levonorgestrel 150 mcg) on day 8 of each period and once-daily doses on days 10 to 28. During treatment periods of concomitant usage, exenatide was administered subcutaneously prior to morning and evening meals at 5 mcg twice daily from days 1 through 4 and at 10 mcg twice daily from days 5 through 22.

Results

Mean plasma concentration time profiles following single-dose administration EE and LV are shown in Figure 11. Mean plasma concentration time profiles associated with OC given 1 hour before exenatide were similar to those observed with OC alone. Mean plasma EE and plasma LV concentration time profiles following OC administration 30 minutes after exenatide were characterised by a reduced $C_{max}$ and delayed $T_{max}$.

**Figure 11: Mean-single dose plasma concentration-time profiles**



Exenatide did not alter the bioavailability nor decrease daily trough concentrations for either oral contraceptive component. Single-dose oral contraceptive administration 30 minutes after exenatide resulted in mean (90% CI) $C_{max}$ reductions of 46% (42-51%) and 41% (35-47%) for EE and LV, respectively. Repeated daily oral contraceptive administration 30 minutes after exenatide resulted in $C_{max}$ reductions of 45% (40-50%) and 27% (21-33%) for EE and LV, respectively. Peak oral contraceptive concentrations were delayed approximately 3 to 4 hours.

The authors conclude the observed reduction in $C_{max}$ is likely of limited importance given the unaltered oral contraceptive bioavailability and trough concentrations. However, for oral medicines that are dependent on threshold concentrations for efficacy, such as contraceptives and antibiotics, patients should be advised to take those medicines at least 1 hour before exenatide injection.

Comments:

The New Zealand approval for exenatide has lapsed but this paper was included for completeness.

Exenatide is rapidly absorbed following subcutaneous injection with a $T_{max}$ of about 2 hours and a terminal half-life of 2.4 hours. The administration of an oral contraceptive 30 minutes after exenatide would almost coincide with the peak concentration of exenatide which could explain the reductions in $C_{max}$ of ethinylestradiol and levonorgestrel.

## 3.3 Other drug-drug interaction studies

### 3.3.1 National library of medicine – Tirzepatide

This clinical study sponsored by Eli Lilly is complete with results published on the NIH ClinicalTrials.gov website.

Official title

Effect of tirzepatide on oral contraceptive pharmacokinetics in healthy female subjects.

Purpose

To look at how the body processes the commonly prescribed birth control pill, ethinylestradiol + norgestimate (EE/NGM) in healthy female participants and the effect of tirzepatide on how EE/NGM is processed by the body.

Methods

An open-label, non-randomised study conducted in healthy adult females aged 18 to 45 years with BMI ≥18.5 kg/m$^2$ at screening. The oral contraceptive used contained 0.035 mg EE and 0.25 NGM (21 active tablets, 7 days of non-active tablets). The study consisted of 2 periods:

- Period 1: EE/NGM alone. Participants received a packet of oral contraceptive to self-administer for 28 days at about the same time each day.
- Period 2: EE/NGM + tirzepatide. Participants received a packet of oral contraceptive to self-administer for 28 days at about the same time each day and a single dose of 5 mg tirzepatide administered subcutaneously.

For each participant, the study lasted about 20 weeks, including screening. The study was completed in February 2021.

Results

40 participants were enrolled in the study and 38 completed the study. Table 13 provides a summary of the findings.

**Table 13: Geometric means of AUC and $C_{max}$ for ethinylestradiol (EE) and norgestimate (NGM) when administered alone or with tirzepatide**

| | EE/NGM alone | EE/NGM + tirzepatide |
|---|---|---|
| **AUC EE** | 966 | 811 |
| **AUC NGM** | 19,900 | 14,600 |
| **$C_{max}$ of EE** | 119 | 49.6 |
| **$C_{max}$ NGM** | 2070 | 892 |

Comments:

Details of this study have not been published in the literature and there were no conclusions included in the information that's publicly available on the ClinicalTrials.gov website.

## 3.4 Spontaneous case reports

### 3.4.1 New Zealand

There are no New Zealand case reports reporting an interaction between a GLP-1 receptor agonist and an oral contraceptive, and no reports of unintended pregnancy.

### 3.4.2 International

[redacted]

[redacted]

Comments:

Reports of an unintended pregnancy following an interaction resulting in contraceptive failure are difficult to retrieve. It is possible that there are relevant reports that haven't been retrieved due to the search criteria used.

# 4 DISCUSSION AND CONCLUSIONS

GLP-1 receptor agonists (eg, dulaglutide, liraglutide, semaglutide) bind to the GLP-1 receptor and one of the resulting actions is delayed gastric emptying. Tirzepatide is a dual GLP-1/GIP receptor agonist and it is thought to have a greater effect on delayed gastric emptying compared to typical GLP-1 receptor agonists.

Delayed gastric emptying by GLP-1 receptor agonists could lead to DDIs with oral medicines, including oral contraceptives. Drug interaction studies mostly used an oral contraceptive containing ethinylestradiol and levonorgestrel, and two studies used ethinylestradiol and norgestimate. Overall, based on study measures such as changes in AUC, $C_{max}$ and $T_{max}$ of the oral contraceptive components, a clinically relevant DDI is not expected when a GLP-1 receptor agonist is coadministered with an oral contraceptive. However, the potential risk of a clinically relevant DDI was observed for tirzepatide.

Information on this interaction in each of the GLP-1 receptor agonist (dulaglutide, liraglutide, semaglutide) New Zealand data sheets align with Australia. This includes that there is no clinically relevant interaction with oral contraceptives. Overall, the intent of the wording in the New Zealand, Australian, United Kingdom, United States, and Canadian data sheets are the same, though it is noted that some advice in the Canadian data sheets is stronger.

There are no tirzepatide products approved for use in New Zealand. The United Kingdom and United States data sheets both advise patients to switch to a non-oral contraceptive method or add a barrier method for 4 weeks after initiation and for 4 weeks after each dose escalation.

[redacted]

# 5 ADVICE SOUGHT

The Committee is asked to advise:

- On the strength of the evidence and clinical relevance of the interaction between GLP-1 receptor agonists and oral contraceptives. The committee could consider this for each individual GLP-1 receptor agonist, or for the medicines as a group.
- If the data sheets require updating.

# 6 ANNEXES

1. Skelley et al 2024
2. Min et al 2025

# 7 REFERENCES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