Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Semaglutide

Proprietary Product Name: Ozempic

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

October 2020

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ASA	Australia specific Annex
CMI	Consumer Medicines Information
CPD	Certified Product Details
CV	Cardiovascular
CVOT	Cardiovascular outcome trial
DLP	Data lock point
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
ER	Extended release
EU	European Union
EU-RMP	European Union risk management plan
GI	Gastrointestinal
GLP-1	Glucagon like peptide-1
GLP-1 RA	Glucagon like peptide-1 receptor agonist
GMP	Good Manufacturing Practice
GVP	Good Pharmacovigilance Practice(s)
HbA1c	Glycated haemoglobin
MACE	Major adverse coronary event(s)
PD	Pharmacodynamic(s)
PI	Product Information
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic(s)

Abbreviation	Meaning
PSUR	Periodic safety update report
RA	Receptor agonist
RMP	Risk management plan
SAE	Serious adverse event
SGLT-2	Sodium-glucose transport protein-2
SU	Sulfonylurea
T2DM	Type 2 diabetes mellitus
TGA	Therapeutic Goods Administration
TZD	Thiazolidinedione
US(A)	United States (of America)

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Product name:	Ozempic
Active ingredient:	Semaglutide (rys)
Decision:	Approved
Date of decision:	15 August 2019
Date of entry onto ARTG:	28 August 2019
ARTG numbers:	308324, 315107
, *Black Triangle Scheme:*[1]	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia.
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Pty Ltd Level 3, 21 Solent Circuit, Baulkham Hills NSW 2153
Dose form:	Solution for injection
Strength:	1.34 mg/mL
Container:	Pre-filled pen
Pack size:	Single pre-filled pen (0.25/0.5 mg); single pre-filled pen (1.0 mg)
Approved therapeutic use:	*Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:,- as monotherapy when metformin is not tolerated or contraindicated.,- in addition to other medicinal products for the treatment of type 2 diabetes.*
Route of administration:	Subcutaneous
Dosage:	Ozempic starting dose is 0.25 mg once weekly. After 4 weeks, the dose should be increased to 0.5 mg once weekly. After at least 4 weeks with a dose of 0.5 mg once weekly, the dose can be increased to 1 mg once weekly to further improve

[1] The **Black Triangle Scheme** provides a simple means for practitioners and patients to identify certain types of new prescription medicines, including those being used in new ways and to encourage the reporting of adverse events associated with their use. The Black Triangle does not denote that there are known safety problems, just that the TGA is encouraging adverse event reporting to help us build up the full picture of a medicine's safety profile.

	glycaemic control. For further information regarding dosage, refer to the Product Information.
Pregnancy category:	D Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. This must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your State or Territory.

Product background

This AusPAR describes the application by Novo Nordisk Pharmaceuticals Pty Ltd (the sponsor) to register Ozempic (semaglutide) 1.34 mg/mL solution for injection for the following proposed indication:

> *Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:*
>
> - *as monotherapy when metformin is not tolerated or contraindicated.*
> - *in addition to other medicinal products for the treatment of type 2 diabetes.*

Semaglutide is a long-acting glucagon like peptide-1 (GLP-1) receptor agonist (GLP-1 RA). Semaglutide reduces blood glucose through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both in a glucose-dependent manner. Semaglutide is a new GLP-1 RA that has been synthesised to have a longer half-life suitable for once-weekly dosing.

Type 2 diabetes mellitus (T2DM) manifests as impaired glucose homeostasis giving rise to chronic hyperglycaemia that result in micro- and macro-vascular pathology leading to significant morbidity and mortality. Complications include, but are not limited to, retinopathy and blindness, chronic kidney disease, cardiovascular (CV) disease, neuropathy and amputations; of these CV disease is the leading cause of death.

There are several classes of medicines available to treat T2DM, used alone or in combination as detailed in the following list:

- biguanides, namely metformin
- sulfonylureas (SU) such as gliclazide
- thiazolidinediones (TZD) such as pioglitazone
- meglitinides such as nateglinide
- dipeptidyl peptidase-4 (DPP-4) inhibitors such as sitagliptin
- GLP-1 RA such as dulagutide
- sodium-glucose transport protein-2 (SGLT-2) inhibitors such as empagliflozin

- amylin analogues such as pramlintide
- insulin and insulin analogues

Regulatory status

This product is considered a new biological entity for Australian regulatory purposes.

At the time the TGA considered this application, a similar application had been approved in the European Union (EU) (8 February 2018), the United States of America (USA) (5 December 2017) and Canada (4 January 2018).

Table 1: International regulatory status of Ozempic as of August 2019

Region	Submission date	Status	Approved indications
EU	5 December 2016	Approved on 8 February 2018	*Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise:* • *as monotherapy when metformin is considered inappropriate due to intolerance or contraindications* • *in addition to other medicinal products for the treatment of diabetes.*
USA	5 December 2016	Approved on 5 December 2017	*Ozempic is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus*

Region	Submission date	Status	Approved indications
Canada	18 January 2017	Approved on 4 January 2018	*Ozempic is indicated for the once-weekly treatment of adult patients with type 2 diabetes mellitus to improve glycemic control, in combination with:* • *diet and exercise in patients for whom metformin is inappropriate due to contraindication or intolerance.* • *metformin, when diet and exercise plus maximal tolerated dose of metformin do not achieve adequate glycemic control.* • *metformin and a sulfonylurea, when diet and exercise plus dual therapy with metformin and a sulfonylurea do not achieve adequate glycemic control.* • *basal insulin with metformin, when diet and exercise plus basal insulin with metformin do not achieve adequate glycemic control*

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 2: Timeline for Submission PM-2018-02748-1-5

Description	Date
Submission dossier accepted and first round evaluation commenced	3 October 2018
First round evaluation completed	7 March 2019
Sponsor provides responses on questions raised in first round evaluation	7 May 2019
Second round evaluation completed	14 June 2019
Delegate's Overall benefit-risk assessment	2 August 2019

Description	Date
Sponsor's pre-Advisory Committee response	Not applicable
Advisory Committee meeting	Not applicable
Registration decision (Outcome)	15 August 2019
Completion of administrative activities and registration on the ARTG	28 August 2019
Number of working days from submission dossier acceptance to registration decision*	177 days

*Statutory timeframe for standard applications is 255 working days

III. Submission overview and risk/benefit assessment

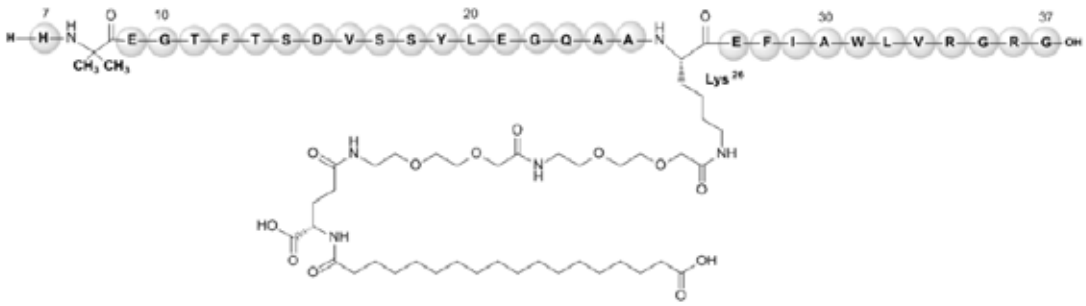
The submission was summarised in the following Delegate's overview and recommendations.

Quality

Semaglutide is a recombinant long acting analogue of human GLP-1. Semaglutide acts as a GLP-1 RA that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. Compared to native GLP-1, semaglutide has a prolonged half-life of around 1 week making it suitable for once-weekly *subcutaneous* administration.

Semaglutide is produced using recombinant deoxyribonucleic acid (DNA) technology in yeast (*Saccharomyces cerevisiae*) and chemical modification. The molecular formula of semaglutide is $C_{187}H_{291}N_{45}O_{59}$, structure shown below.

Figure 1: The structural formula of semaglutide



All manufacturing steps are validated and there are no outstanding Good Manufacturing Practice (GMP) issues. There are outstanding microbiology evaluation issues as discussed below.

From an infectious disease safety assessment viewpoint, the evaluator has concluded that sufficient evidence has been provided to demonstrate that the risks related to the presence of adventitious agents (prions, viruses and mycoplasmas) in the manufacturing of Ozempic (semaglutide) have been controlled to an acceptable level.

From an evaluation of the endotoxin aspects of safety, there are no outstanding issues and the evaluator has recommended in the report that, 'based on the evaluation conducted;

there are no further concerns with regard to endotoxin testing that need delay registration'.

Outstanding microbiology recommendation

There is still an outstanding issue;[2] regarding the open shelf life of Ozempic pen.

In a response dated 27 June 2019, the sponsor concludes that the available evidence, both clinical, post marketing and stability testing data demonstrate that there is no increased risk of microbial contamination for Ozempic administered once weekly.

The sponsor does not agree with the evaluator's conclusions with respect to the proposed open shelf life of 42 days and provides the following arguments.

- The evaluator states that an open shelf life of greater than 28 days has never been approved due to microbial concerns in Australia. The sponsor states that it has provided substantial data demonstrating no increased risk of microbial contamination over the proposed 42 day in use period for Ozempic. Further, there is available clinical and post marketing experience demonstrating no increased risk for microbial contamination.
- When compared to once daily dosing of insulin and other daily dosed GLP-1 drugs, the number of times Ozempic will be accessed over the in use period is less than one quarter of the times these comparative products are accessed, as the product is administered once weekly. It follows that the reduced number of access points by the patient over the in use period also reduces the opportunity for contamination to be introduced into the product, and therefore allays the concerns expressed by the evaluator.

In response to the evaluator's concerns that the data is based on simulated testing and the assertion that patients may administer the product incorrectly the sponsor states that during development of Ozempic, validation of patient's ability to administer doses correctly and to use the device as intended has been successfully undertaken. Furthermore, the PDS290 device in which Ozempic will be supplied;[3] is an established device platform and is used for many different Novo Nordisk products.

- The sponsor draws attention to the post marketing experience with Ozempic in overseas markets with an approved in use shelf life of either 6 or 8 weeks and note that no reports of microbial contamination have been received, nor have there been any safety issues identified with respect to injection site reactions (which might be indicative of microbial contamination).
- The evaluator also states that a single dose injection device may be possible. The sponsor has based the Ozempic dosing regimen on the established FlexTouch device platform;[3] which has been developed for ease of use for patients. A single dose pen is not considered a reasonable option at this time and is not considered as an appropriate conclusion in the context of the product development program and the available supporting data.

Conditions of registration

The evaluator has summarised the listed conditions of registration below for batch release testing and compliance with certified product details (CPD).

[2] The outstanding microbiology recommendation was resolved following compilation of the Delegate's Overview and prior to approval; see Section: *Delegate's update* in the *Risk-benefit analysis* later in this document.

[3] The **PDS290 / FlexTouch device** is a pre-filled multi-use pen developed by the sponsor currently in use for a range of sponsor products approved in Australia and registered on the ARTG.

- It is a condition of registration that all batches of Ozempic 0.25/0.5 mg semaglutide (rys) 1.34 mg/mL solution for injection pre-filled pen and Ozempic 1 mg semaglutide (rys) 1.34 mg/mL solution for injection pre-filled pen imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
- It is a condition of registration that each batch of Ozempic 0.25/0.5 mg semaglutide (rys) 1.34 mg/mL solution for injection pre-filled pen and Ozempic 1 mg semaglutide (rys) 1.34 mg/mL solution for injection pre-filled pen imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results; available at http://www.tga.gov.au/ws-labs-index.
- The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The sponsor must contact biochemistry.testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at https://www.tga.gov.au/publication/testing-biological-medicines.
- This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified Product Details:

- The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) (http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm), in portable document format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Nonclinical

The conclusions of the nonclinical evaluator are summarised below:

- the nonclinical dossier contained no critical deficiencies
- primary pharmacology studies offer support for the proposed use of the drug in the treatment of T2DM
- the combined safety studies indicate the following as potentially clinically-relevant:
  - transient acute effects (hypoactivity, suppressed appetite, reduced food consumption) at dose initiation
  - diuresis and natriuresis
  - gastrointestinal effects associated with delayed gastric emptying
- a risk for thyroid carcinogenicity cannot be completely dismissed but there is no greater risk with semaglutide compared with currently-registered long-acting GLP-1 receptor agonists
- there are no nonclinical objections to the registration of Ozempic semaglutide for monotherapy for the proposed indication. No studies were submitted in the nonclinical data to support combination therapy with one or more antidiabetic drugs.

The low potential for pharmacokinetic (PK) drug interactions and limited toxicity profile with semaglutide do not raise any obvious safety concerns for the proposed combination use. The PI is amended as directed.

Further to sponsor's acceptance of recommendations made by the nonclinical evaluator there are no further outstanding issues and the evaluator has confirmed that, *'no further comment is required from a nonclinical perspective.'*

Clinical

Pharmacology

Pharmacokinetics

The PK of semaglutide in patients with T2DM, in general, are adequately characterised during the clinical pharmacology programme. The maximum multiple dose tested was 1.5 mg once weekly and in T2DM patients, the maximum multiple dose tested was 1.6 mg once weekly. The PK profile is suitable for once weekly subcutaneous administration due to the prolonged release characteristics (for example, albumin binding, slow release from subcutis and reduced degradation by enzymes) of semaglutide.

The absolute bioavailability of semaglutide after a single dose, this was estimated to be 89% after subcutaneous injection into the abdomen. Based on the presented data it can be concluded that all three injection sites (thigh, upper arm and abdomen), can be used interchangeably.

The results of the studies and the analysis indicate a linear PK model within the dose range 0.25 mg to 1 mg. Steady state was reached between 4 to 5 weeks. Bodyweight is the only identified factor causing variability in the PK evaluation. The PK of semaglutide in patients with T2DM was similar to those in healthy subjects. The PK properties for the hepatically impaired subjects were similar to those of the subjects with normal hepatic function.

The population pharmacokinetic (PopPK) analysis was a meta-analysis of data from five Phase IIIa clinical studies, comprising four global studies (Studies 3623, 3626, 3624, and 3744) and one study conducted in Japan (Study 4091). The analysis investigated the influence of age, race, ethnicity, body weight, renal impairment, and maintenance dose and injection site on the PK of semaglutide. Bodyweight was the only covariate that appeared to have a significant effect on exposure; the exposures of semaglutide decreased with increasing bodyweight and vice versa. The applicant conducted an additional analysis to evaluate the relationship between body weights and the safety and efficacy of semaglutide. There was no clear body weight related trend in safety across body weight categories and the efficacy (glycated haemoglobin (HbA1c);[4] change from Baseline response) appears to be similar across body weight. No dose adjustment is necessary based on age, sex, renal or hepatic function.

Semaglutide is homologous to endogenous GLP-1, thus it is anticipated that the potential for interaction is low as it undergoes protein degradation and has no effect on important enzyme systems. In specific interaction studies the only significant effect was the decrease in maximum concentration of atorvastatin (likely due to delayed gastric emptying), this is

[4] **HbA1c**, or **glycated haemoglobin**, is a form of haemoglobin chemically linked to a sugar via glycation. HbA1c is measured primarily to determine the three month average blood sugar level and is the most accepted method of measuring chronic glycaemia. Measurement can be used as a diagnostic test for diabetes mellitus and as an assessment test for glycaemic control in people with diabetes. An HbA1c of 48 mmol/mol (6.5%) or greater has now been recommended in Australia for the diagnosis of type 2 diabetes mellitus (T2DM).

not considered clinically relevant for a medicine such as atorvastatin that is administered long-term.

Pharmacodynamics

Semaglutide treatment, as compared with placebo, lowered fasting and postprandial blood glucose by improving multiple aspects of beta-cell function, including insulin secretion, and by reducing both fasting and postprandial glucagon concentrations, all in a glucose dependent manner. The glucose-dependent decrease in glucagon concentrations was observed with increasing concentrations of glucose in patients with T2DM was greater following treatment with semaglutide compared to placebo.

In general, the pharmacokinetics and pharmacodynamics of semaglutide have been sufficiently characterised.

Efficacy

The dose selection strategy was based on results of a Phase I and a Phase II study plus PK modelling across the Phase IIIa study program. Semaglutide was investigated at two dose levels (0.5 mg and 1.0 mg) in most Phase IIIa trials. This established the need for a slow dose escalation to increase tolerability by minimising gastrointestinal (GI) adverse events (AE). A dose response was seen between the proposed doses was small.

There were five key efficacy trials that evaluated the efficacy and safety of semaglutide as mono- and combination therapy (primarily combinations with metformin, a thiazolidinedione (TZD), a sulfonylurea (SU) and/or insulin). In addition, semaglutide was compared with insulin glargine, a DPP-4 inhibitor and another long acting GLP-1 receptor agonist. Two Phase IIIa trials evaluated semaglutide for treatment of T2DM in Japanese subjects (Trials 4092 and 4091). While safety was the primary endpoint for the Japanese trials, they were designed and conducted in a similar manner to the key efficacy trials. The last Phase IIIa trial (Trial 3744) was a 104 week cardiovascular outcomes trial (CVOT) in a T2DM population at high risk of CV events that investigated the effect of semaglutide on CV events as well as long-term safety and efficacy.

The studies that had markers of T2DM as primary endpoints were of similar design and had similar primary endpoints. There were a large number of secondary endpoints in each study; endpoints relevant to the proposed indication are presented in this report. Multiplicity was handled using a pre-specified hierarchical testing schemes. Of note, in the long term CV study superiority on time to major adverse coronary events (MACE); was not included in the predefined testing hierarchy.

In Study 3623 (SUSTAIN 1-Monotherapy trial) in drug naïve T2DM subjects, semaglutide was associated with a statistically significant decrease in HbA1c after 30 weeks (semaglutide 0.5 mg (1.43%); semaglutide 1.0 mg (1.53%)) compared to placebo. In addition, there were changes in bodyweight (semaglutide 0.5 mg (2.75 kg); semaglutide 1.0 mg (3.56 kg)).

Study 3626 (SUSTAIN 2 trial) was performed in T2DM subjects who had not achieved adequate glycaemic control on metformin, TZD or a combination of metformin/TZD. Compared to sitagliptin, semaglutide was associated with a statistically significant decrease in HbA1c after 56 weeks (semaglutide 0.5 mg (0.77%); semaglutide 1.0 mg (1.06%)). In addition, compared to sitagliptin, semaglutide was associated with a decrease in bodyweight (semaglutide 0.5 mg (2.35 kg); semaglutide 1.0 mg (4.20 kg)).

In Study 3624 (SUSTAIN 3 trial, combination with metformin or metformin with SU trial) after 56 weeks compared to exenatide (extended release (ER) formulation), semaglutide 1.0 mg was associated with statistically significant decrease in HbA1c of -0.62% and in bodyweight of 3.78 kg.

In Study 3625 (SUSTAIN 4 trial, combination with 1 or 2 oral antidiabetic drugs: metformin or metformin and SU trial) after 30 weeks compared to insulin glargine, semaglutide was associated with statistically significant decrease in HbA1c (semaglutide 0.5 mg (0.38%); semaglutide 1.0 mg (0.81%)) and in bodyweight (semaglutide 0.5 mg (4.62 kg); semaglutide 1.0 mg (6.33 kg)).

In Study 3627 (SUSTAIN 5 trial, combination with basal insulin trial) in subjects with T2DM on basal insulin, After 30 weeks compared to placebo, semaglutide was associated with statistically significant decrease in HbA1c (semaglutide 0.5 mg (1.35%); semaglutide 1.0 mg (1.75%)) and in bodyweight (semaglutide 0.5 mg (2.31 kg); semaglutide 1.0 mg (5.06 kg)).

In Study 3744 (SUSTAIN 6-CVOT; combination with SU monotherapy or premix insulin ± 1 or 2 oral antidiabetic drugs); the primary objective was to confirm that treatment with semaglutide does not result in an unacceptable increase in CV risk compared to placebo in T2DM subjects. The secondary objectives were to assess the long-term safety and efficacy of semaglutide 0.5 mg and 1.0 mg once weekly compared to placebo, both added on to standard of care, in T2DM subjects at high risk of CV events. The trial reached its primary objective and demonstrated non-inferiority of semaglutide versus placebo in terms of MACE. The composite primary outcome occurred in 108 of 1648 patients (6.6%) in the semaglutide group and 146 of 1649 (8.9%) in the placebo group (hazard ratio, 0.74; 95% confidence interval (CI), 0.58 to 0.95; $p < 0.001$ for non-inferiority). Superiority was tested post hoc without a statistical penalty for multiple testing. At Week 104, the mean HbA1c level in the semaglutide group, as compared with the placebo group, was 0.7% points lower in the group receiving 0.5 mg and 1.0% point lower in the group receiving 1.0 mg (estimated treatment difference) ($p < 0.001$ for both comparisons). At Week 104, the mean bodyweight in the semaglutide group, as compared with the placebo group, was 2.9 kg lower in the group receiving 0.5 mg and 4.3 kg lower in the group receiving 1.0 mg semaglutide ($p < 0.001$ for both comparisons). In addition, mean systolic blood pressure in the semaglutide group, as compared with the placebo group, was 1.3 mm Hg lower in the group receiving 0.5 mg ($p = 0.10$) and 2.6 mm Hg lower in the group receiving 1.0 mg ($p < 0.001$). Changes in diastolic blood pressure were similar across treatment groups. It is unknown if impact on CV endpoint was a primary effect of the drug or secondary effect of improvement in CV risk parameters (bodyweight, blood pressure, HbAc1 level).

Supportive studies

Studies 4091 and 4092 were both conducted in Japan. These studies are only considered supportive because they were performed in Japanese individuals only and efficacy was not a primary endpoint. In Study 4091, the primary objective was to compare the safety of once weekly dosing of semaglutide in monotherapy or in combination with 1 oral antidiabetic drug (either of a sulfonylurea, glinide, alpha-glucosidase or TZD) and in Study 4092 it was to compare the safety of once weekly dosing of semaglutide (0.5 and 1.0 mg) versus sitagliptin (100 mg) once daily, both as monotherapy during 30 weeks of treatment in Japanese T2DM subjects. In Study 4091, compared to additional oral antidiabetic drugs, semaglutide was associated with a decrease in HbA1c after 56 weeks (for semaglutide 0.5 mg (1.08%); for semaglutide 1.0 mg (1.37%)). In Study 4092, compared to sitagliptin, semaglutide was associated with decrease in HbA1c after 30 weeks (for semaglutide 0.5 mg (1.13%); for semaglutide 1.0 mg (1.44%)).

The results of Study 4216 (efficacy and safety of semaglutide versus dulaglutide as add on to metformin in subjects with T2DM) provide further support to Phase IIIa studies. Compared semaglutide was statistically superior to dulaglutide at reducing HbA1c. However, the treatment difference was small (0.4%) and unlikely to be clinically relevant.

In conclusion, the studies provided with this application (key efficacy and supportive) support the efficacy of semaglutide (for doses 0.5 mg and 1 mg once weekly) at achieving

glycaemic control (as evidenced by a reduction in HbA1c) when used as either a monotherapy or in combination with other oral antidiabetic drugs (discussed above). The observed decrease in HbA1c was supported by reductions in fasting blood glucose and there was reduction in body weight. Both the dose levels of semaglutide can be efficacious and should be based on individual needs. The proposed dosing in the PI is a stepwise progression depending on the patient need and tolerance. The SUSTAIN 6 trial (CVOT; Study 3744) reached its primary objective and demonstrated non-inferiority of semaglutide versus placebo in terms of MACE. However, occurrence of cardiovascular death was similar with semaglutide and placebo. Superiority was tested post hoc without a statistical penalty for multiple testing. The duration of the trial was relatively short. It is not possible to establish if there is any benefit effect of semaglutide on the individual components of MACEs.

Safety

The number of patients exposed in the Phase IIIa trials included a total of 8,093 patients of whom 4,792 patients received at least one dose of semaglutide. A total of 3,301 patients were included in comparator groups including 1,906 in placebo groups and 1,395 in active comparator groups (oral antidiabetic drugs: 120; sitagliptin: 510, exenatide ER: 405; insulin glargine: 360). A total of 1,321 patients were exposed to semaglutide for 18 months or longer.

The proportion of patients reporting at least one AE was higher with semaglutide (0.5 mg and 1.0 mg) than comparators in the Phase IIIa pool and similar with semaglutide (0.5 mg and 1.0 mg) and placebo in the 2-year CVOT (SUSTAIN 6 trial / Study 3744). The overall rate of AEs was higher with semaglutide than placebo and comparators across all Phase IIIa including the CVOT. The higher proportions and rates of AEs were mainly driven by GI disorders.

All safety issues identified among commonly reported AEs or serious adverse events (SAE) have previously been seen for other GLP-1 RA drugs, except for the adjudicated endpoint diabetic retinopathy complications in the CVOT. Systematic evaluation of diabetic retinopathy complications was only performed in the CVOT and not in the remaining Phase IIIa trials. Patients requiring active treatment for known proliferative retinopathy or maculopathy at Baseline were excluded from these trials, and overall no safety concerns related to retinopathy were observed.

The semaglutide safety profile in patients at high CV risk (CVOT) generally resembled that observed in the more broad T2DM population (Phase IIIa pool), albeit the incidences of especially deaths and CV events were higher reflecting a population at high risk of CV disease.

The most commonly reported AEs with semaglutide (0.5 mg and 1.0 mg) were GI disorders including nausea, diarrhoea, vomiting, constipation, dyspepsia, abdominal pain, abdominal distension, gastritis, gastro-oesophageal reflux disease, eructation and flatulence, which are known common side effects of GLP-1 RA drugs particularly at the start of treatment. In general, these reactions were mild or moderate in severity and of short duration.

Serious adverse events and deaths

In the Phase IIIa pool the proportion of patients with SAEs were generally low, and slightly higher with semaglutide (0.5 mg: 6.6%; 1.0 mg: 6.7%) than with comparator products (5.8%). This difference was mainly explained by more GI SAEs with semaglutide. In the CVOT (SUSTAIN 6 trial / Study 3744), the proportion of patients with SAEs was lower with semaglutide (0.5 mg: 32.1%; 1.0 mg: 29.3%) than with placebo (34.9%). In the CVOT the proportion of SAEs was slightly lower with semaglutide 1.0 mg than with 0.5 mg (0.5 mg: 32.1%; 1.0 mg: 29.3%).

Across the semaglutide development programme, a total of 140 patients died. In the CVOT, a total of 123 patients (3.7%) with T2DM and high risk of CV events died due to AEs that had onset during the 2 year in trial period of the trial; 62 with semaglutide and 61 with placebo. In the seven Phase IIIa trials in patients with T2DM, a total of 16 patients died; 10 (0.3%) randomised to semaglutide, and 6 patients (0.4%) randomised to comparator products. A review of the narratives did not reveal any significant concerns. There were no significant differences between semaglutide (0.5 mg and 1.0 mg pooled) and placebo (pooled) for external adjudication committee confirmed all-cause mortality or CV death.

Across the clinical development program there was a variable pattern of liver function testing results with overall a decrease in liver enzymes. The overall proportion of subjects with acute renal failure-related AEs and the corresponding rates were low with semaglutide (both doses) and comparators. There were no clinically relevant mean changes in haematology or biochemistry parameters.

Overall there does not appear to be a CV safety signal related to the use of semaglutide. There is no significant effect of semaglutide on cardiac repolarisation. There was a consistent small increase in mean resting pulse rate associated with the use of semaglutide. This is likely non-significant and of similar magnitude as seen with other GLP-1 RA drugs.

Overall the event rate for pancreatitis was low. Although the use of semaglutide is associated with an increase in pancreatic lipase and amylase there is no apparent association with the development of pancreatitis. Overall, across the study program, cholelithiasis was reported more frequently for subjects treated with semaglutide versus placebo or a comparator with the exception of dulaglutide in which the rates were similar. Cholelithiasis is a known effect of GLP-1 RA drugs.

Episodes of hypoglycaemia were generally infrequent with semaglutide treatment when used as monotherapy or in combination with oral antidiabetic drugs excluding sulfonylureas. Episodes of severe hypoglycaemia were infrequent when semaglutide was administered concomitantly with oral antidiabetic drugs excluding SU and primarily observed when semaglutide was used with a SU or insulin with no apparent differences between semaglutide and comparators.

There was no indication of an immunogenic response against semaglutide. Allergic reactions were reported by a low (4 to 6%) proportion of patients. Most of the allergic reactions were of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo/comparators were observed. Injection site reactions were reported by a low (approximately 1%) proportion of patients with semaglutide and were not recurrent in those individuals. Most injections site reactions were of mild or moderate severity, did not lead to premature treatment discontinuation and no differences between semaglutide and placebo and non-exenatide comparators was observed.

Overall the safety profile of semaglutide was generally similar to that for other GLP-1 RA drugs.

Risk management plan

The sponsor submitted EU risk management plan (EU-RMP) version 2.0 (26 June 2018; data lock point (DLP) 1 November 2017) and Australian-specific Annex (ASA) version 0.1 (11 July 2018) in support of this application. In its first round response the sponsor has updated these to EU-RMP version 3.1 (5 March 2019; DLP 31 May 2018) and ASA version 0.2 (20 March 2019).

The summary of safety concerns and their associated risk monitoring and mitigation strategies are summarised in Table 3.[5]

Table 3: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Diabetic retinopathy complications	ü	ü*	ü	–
Important potential risks	Acute pancreatitis	ü	–	ü	–
	Pancreatic cancer	ü	ü*	–	–
	Medullary thyroid cancer	ü	ü*	–	–
	Pregnancy and lactation	ü	–	ü	–
Missing information	Patients with severe hepatic impairment	ü	–	ü	–

* Planned pharmacovigilance studies

The RMP evaluator has summarised as follows:

- The sponsor has proposed routine pharmacovigilance for all safety concerns. The sponsor has proposed international, additional pharmacovigilance studies to address diabetic retinopathy complications, pancreatic cancer and medullary thyroid cancer pending marketing approval. This is considered acceptable.
- The sponsor has proposed routine risk minimisation activities for all safety concerns. The Consumer Medicines Information (CMI) will be included as a package insert. The sponsor has proposed no additional risk minimisation activities. This is considered acceptable.

The RMP evaluator has confirmed there are no new or outstanding recommendations and has suggested the following wording for conditions of registration (see following section).

Wording for conditions of registration regarding the risk management plan

The following are the suggested wordings for conditions of registration:

- Any changes to which the sponsor has agreed should be included in a revised Risk Management Plan (RMP) and Australia specific Annex (ASA). However, irrespective of

[5] *Routine risk minimisation* activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.
Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

- The Ozempic EU- RMP (version 3.1, dated 5 March 2019, data lock point 31 May 2018), with ASA (version 0.2, dated 20 March 2019), included with submission PM-2018-02748-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

The following wording is recommended for the periodic safety update reports (PSURs) requirement:

- An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.
- Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of this approval letter.
- The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on Good Pharmacovigilance Practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.

As Ozempic is a new chemical entity it should be included in the Black Triangle Scheme;[1] as a condition of registration. The following wording is recommended for the condition of registration:

- Ozempic (semaglutide) is to be included in the Black Triangle Scheme. The PI and CMI for Ozempic must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.

Other advice to the delegate

The sponsor has committed to including the CMI as a package insert. It is recommended that the Delegate consider wording in the conditions of registration for inclusion of the CMI in the package.

Risk-benefit analysis

Delegate's considerations

In relation to quality, there is still an outstanding microbiology issue regarding the open shelf life of Ozempic pen.[2]

There are no outstanding issues from the nonclinical evaluation of data.

In relation to efficacy, semaglutide was effective at achieving glycaemic control as evidenced by a reduction in HbA1c when used as either a monotherapy or in combination with other oral antidiabetic drugs. The efficacy trials evaluated the efficacy of semaglutide as mono- and combination-therapy (primarily combinations with metformin, a TZD, a SU and/or insulin). In addition, semaglutide was compared with insulin glargine, a DPP-4 inhibitor and another long acting GLP-1 receptor agonist. No trials with combination therapy with DPP-4-inhibitors have been carried out which is acceptable as they have similar mechanism of action. As there were a few patients in the CVOT (SUSTAIN 6 trial / Study 3744) with SGLT2-inhibitors added as standard of care treatment and as no

interactions are expected between semaglutide and SGLT2-inhibitors, concomitant use is considered acceptable.

In relation to safety, semaglutide does not increase the risk of hypoglycaemia unless combined with either a sulfonylurea or insulin. The AE profile is consistent with other drugs in this class and risks are described in the PI. The proposed summary of safety concerns and their associated risk monitoring and mitigation strategies are considered acceptable. Overall the safety profile of semaglutide was generally similar to that for other GLP-1 RA drugs.

The Delegate considers that the benefit-risk profile of Ozempic to be used:

> *'For the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise;*
>
> - *as monotherapy when metformin is not tolerated or contraindicated.*
> - *in addition to other medicinal products for the treatment of type 2 diabetes'.*

as favourable and approvable subject to sponsor's acceptance for below recommendations, conditions of registration and upon resolution of the outstanding microbiology issue on open shelf life of the Ozempic pen.

However, the benefit-risk profile Ozempic to be used to prevent cardiovascular events in adults with type 2 diabetes mellitus and high cardiovascular risk, as an adjunct to standard treatment of cardiovascular risk factors is unfavourable and not approved because of the following reasons.

- For a drug that is intended for long term diabetes treatment, the duration of the CVOT (2 years) is relatively short (also in comparison to several other cardiovascular outcome trials). Longer term safety is uncertain.
- In the CVOT trial semaglutide had a favourable effect on non-fatal myocardial infarction and non-fatal stroke, but the occurrence of CV death was similar with semaglutide and placebo. Although the three individual components of the composite endpoint are clinically meaningful, CV death is considered more clinically relevant than non-fatal myocardial infarction and non-fatal stroke.
- The effect of semaglutide on several other important outcome measures was negative. Hospitalisation for heart failure, all-cause mortality, SAEs of coronary artery disease, SAEs of cardiac failure and vascular therapeutic procedures (particularly cardiac interventions) were higher with semaglutide than with placebo. The lack of concordance between primary and secondary endpoints and components of the MACE makes one question if the improvement in MACE may have occurred by chance.
- In the CVOT superiority on time to MACE (semaglutide versus placebo) was not included in the predefined testing hierarchy and was only demonstrated in a post hoc analysis. However, the superiority test for MACE was performed as one of a range of *post-hoc* tests. This means that the sponsor had the chance to choose any statistically significant test from the *post-hoc* analyses, which will lead to inflation of the type I error. This should analysis should have been pre-specified to avoid bias thus superiority cannot be claimed.
- Single pivotal study and its problem; improvement in MACE is not a class effect, seen with liraglutide but no other drugs in this class.
- Unknown if impact on CV endpoint was a primary effect of the drug or secondary effect of improvement in CV risk parameters (bodyweight, blood pressure, HbA1c).

Outstanding microbiology recommendation

The in use shelf life is 6 weeks (as proposed by the sponsor) versus 4 weeks (recommended by the microbiology evaluator).[2]

Proposed action

The Delegate considers that the benefit-risk profile of Ozempic to be used:

> *For the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise;*
>
> - *as monotherapy when metformin is not tolerated or contraindicated.*
> - *in addition to other medicinal products for the treatment of type 2 diabetes*

as favourable and approvable subject to sponsor's acceptance for below recommendations, conditions of registration and upon resolution of the outstanding microbiology issue on open shelf life of the Ozempic pen.

Delegate's update

As of 15 August 2019:

- the sponsor agreed to all the above recommendations and PI/CMI was amended; and
- the microbiology evaluation area at the TGA reconsidered their decision and accepted the open shelf life of 42 days as proposed by the sponsor and had no objections from a microbiological perspective to the approval of this application.

Advisory Committee considerations[6]

The Delegate did not refer this application to the Advisory Committee on Medicines (ACM) for advice.

Outcome

Based on a review of quality, safety and efficacy, the TGA approved the registration of Ozempic 0.25/0.5 mg and 1 mg semaglutide 1.34 mg/mL solution for injection pre-filled pen for the following indication:

> *Ozempic is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise;*
>
> - *as monotherapy when metformin is not tolerated or contraindicated.*
> - *in addition to other medicinal products for the treatment of type 2 diabetes*

[6] The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines.
The Committee is established under Regulation 35 of the Therapeutic Goods Regulations 1990. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific conditions of registration applying to these goods

- Ozempic semaglutide (rys) is to be included in the Black Triangle Scheme. The PI and CMI for Ozempic must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the products.
- Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

  The Ozempic EU-RMP, version 3.1, dated 5 March 2019 (data lock point 31 May 2018), with ASA, version 0.2, dated 20 March 2019, included with submission PM-2018-02748-1-5, and any subsequent revisions, as agreed with the TGA will be implemented in Australia. An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of PSURs.

  Reports are to be provided in line with the current published list of EU reference dates and frequency of submission of PSURs until the period covered by such reports is not less than three years from the date of the approval letter.

  The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on GVP Module VII-Periodic Safety Update Report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration.
- The CMI must be included with the products as a package insert. The CMI should have a link to the full version of the PI on the TGA website.
- Batch Release Testing and Compliance with CPD
  - All batches of Ozempic (semaglutide (rys)) 1.34 mg/mL solution for injection pre-filled pen imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - Each batch of Ozempic (semaglutide (rys)) 1.34 mg/mL solution for injection prefilled pen imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results (http://www.tga.gov.au/ws-labs-index).

  The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories Branch.

Attachment 1. Product Information

The PI for Ozempic approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au