Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for liraglutide

Proprietary Product Name: Saxenda

Sponsor: Novo Nordisk Pharmaceuticals Pty Ltd

March 2016

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
ACPM	Advisory Committee on Prescription Medicines
AE	adverse event
AHI	Apnea Hypopnea Index
ARC	arcuate nucleus
ASA	Australian Specific Annex
AUC	area under the plasma concentration time curve
BID	bis in die (twice daily)
BMI	Body Mass Index
Cmax	maximum (or peak) serum concentration of drug
CMI	Consumer Medicines Information
CV	cardiovascular
EMA	European Medicines Agency
FDA	Food and Drug Administration (US)
GI	gastrointestinal
GLP-1	glucagon like peptide-1
GLP-1R	glucagon like peptide-1 receptor
MACE	major adverse cardiac event
PD	pharmacodynamic
PI	Product Information
PK	pharmacokinetic
PO	per os (oral)
PSUR	Periodic Safety Update Report
PYE	patient years of exposure
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan

Abbreviation	Meaning
SAE	serious adverse event
SC	subcutaneous
T2DM	type 2 diabetes mellitus
TID	ter in die (three times daily)

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	23 December 2015
Date of entry onto ARTG	24 December 2015
Active ingredient:	Liraglutide
Product name:	Saxenda
Sponsor's name and address:	Novo Nordisk Pharmaceuticals Pty Ltd PO Box 7586 Baulkham Hills Business Centre NSW 2153
Dose form:	Solution for injection prefilled pen
Strength:	6 mg/mL
Container:	Glass cartridge (type I glass)
Pack sizes:	1, 3 or 5 prefilled pens (each containing 3 mL and is able to deliver doses of 0.6 mg, 1.2 mg, 1.8 mg, 2.4 mg and 3.0 mg)
Approved therapeutic use:	Saxenda is indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of • greater than or equal to 30 kg/m^2 (obese); or • greater than or equal to 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea. Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight. Long term use should be informed by the following: • Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (>12 months) might not have been identified in the clinical development program [refer CLINICAL TRIALS]. • Long term efficacy data are limited. The treatment effect has only been documented for 1 year [refer CLINICAL TRIALS].
Route of administration:	Subcutaneous

Dosage:	Starting from 0.6 mg followed by increments of 0.6 mg with at least one week intervals (ie. 0.6, 1.2, 1.8, 2.4 and 3.0 mg). Maintenance dose is 3.0 mg.
ARTG number:	225804

Product background

This AusPAR describes the application by Novo Nordisk Pharmaceuticals Pty Ltd to extend the indications of the registered Victoza (liraglutide (rys)), for a new good named Saxenda. Saxenda is a glucagon like peptide-1 (GLP-1) receptor (GLP-1R) analogue, classified as a GLP-1 agonist.

The approved indication for Victoza is as follows:

> *Victoza is indicated as an adjunct to diet and exercise for treatment of adults with T2DM to achieve glycaemic control:*
>
> - *in dual combination, added to metformin or a sulfonylurea, in patients with insufficient glycaemic control despite the use of maximally tolerated or clinically adequate doses of metformin or sulfonylurea monotherapy;*
> - *in triple combination, added to metformin and a sulfonylurea in patients with insufficient glycaemic control despite dual therapy.*

The recommended maximum daily dose approved in that submission was 1.8 mg daily.

The proposed changes for the new good Saxenda are:

- a new trade name (Saxenda);
- a new indication of weight loss;
- a recommendation of a new dose (3 mg once daily); and
- a new container type (prefilled pen).

The specific proposed additional indication for Saxenda is:

> *An adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial BMI of*
>
> - *30 kg/m^2 or greater (obese), or*
> - *27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity such as dysglycemia (pre-diabetes and T2DM), hypertension, dyslipidemia, obstructive sleep apnoea.*

The mechanism by which liraglutide treatment results in weight loss is not entirely understood. It may regulate the appetite by increasing feelings of fullness and lowering feelings of hunger, perhaps through delayed gastric emptying, but probably also other mechanisms, for example, the effects of GLP-1 on the brain.

Liraglutide also stimulates insulin secretion and lowers inappropriately high glucagon secretion, which results in a lowering of fasting and post-prandial glucose. The mechanism of blood glucose lowering also involves a delay in gastric emptying, which may contribute to the observed reductions in postprandial glucose.

In Australia, some pharmacological treatments for weight loss have previously been associated with adverse effects and have been withdrawn (for example, sibutramine); or were never approved/submitted (for example, rimonabant, taranabant). Loraserin and the fixed dose combination product phentermine-topiramate have been recently registered in

the US, but are not available in Australia. The fixed dose combination product naltrexone-bupropion (Mysimba) has recently been approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA), but is also not available in Australia.

Mono products (originator and generics) of phentermine (a nor-adrenaline agonist) are available in Australia. As per the Product Information (PI), it is indicated for use as a short term (for example, 3 month) adjunct to diet and exercise, under medical supervision. It works by suppressing hunger and possibly stimulating energy expenditure. As per the PI, it should be used with caution because it is associated with a range of side effects (for example, hypertension, tachycardia, insomnia). Also, some patients develop tolerance; and long term safety has not been tested; hence, the 'short term' indication.

Orlistat (Xenical) is available as an over the counter product. It is commonly associated with gastrointestinal adverse effects including, steatorrhoea, fatty faecal incontinence, and frequent or urgent bowel movements. These effects can be controlled by adhering to a low fat diet. Supplementation of fat soluble vitamins may be required if long term use is planned.

The following is from the current EMA guidelines from 2007,[1] which have been adopted by the TGA:

> *Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs.*

The EMA also released a draft updated guideline in 2014,[2] which has not yet been adopted by the TGA. The draft recommendations are similar to the 2007 guideline:

> *Weight loss should be documented both as absolute weight loss (kg) and percentage weight loss relative to baseline body weight. Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs.*

Regulatory status

At the time of this submission to the TGA, Saxenda for weight management (18 mg in 3 mL cartridge in prefilled pen) had been approved in a number of countries including Austria (23 March 2015), Belgium (23 March 2015), Bulgaria (23 March 2015), Canada (26 February 2015), Croatia (23 March 2015), Cyprus (23 March 2015), Czech Republic (23 March 2015), Denmark (23 March 2015), Estonia (23 March 2015), Finland (23 March 2015), France (23 March 2015), Germany (23 March 2015), Greece (23 March 2015), Hungary (23 March 2015), Iceland (23 March 2015), Ireland (23 March 2015), Italy (23 March 2015), Latvia (23 March 2015), Lithuania (23 March 2015), Luxembourg (23 March 2015), Malta (23 March 2015), Netherland (23 March 2015), Norway (23 March 2015), Poland (23 March 2015), Portugal (23 March 2015), Romania (23 March 2015), Slovakia (23 March 2015), Slovenia (23 March 2015), Spain (23 March 2015), Sweden (23 March 2015), United Kingdom (23 March 2015), and United States (23 December 2014).

[1] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[2] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014.

Product Information

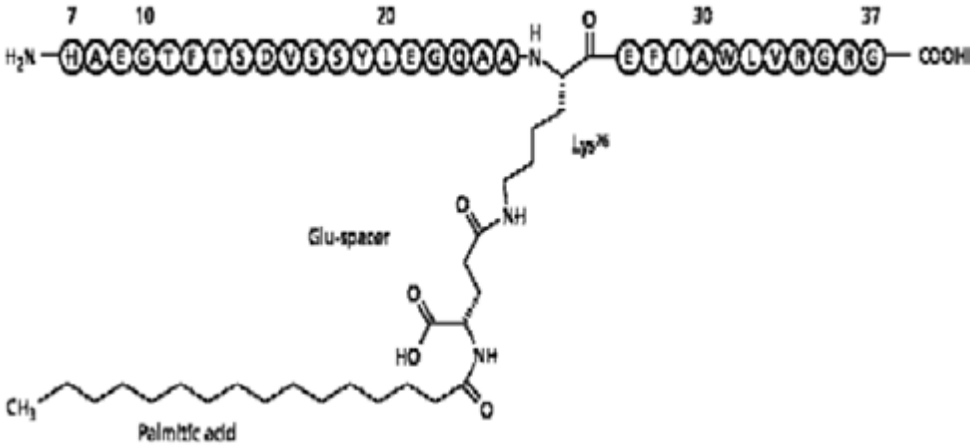
The approved PI current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Introduction (if applicable)

Liraglutide is an analogue of the naturally occurring human GLP-1 (GLP-1(7-37)). Liraglutide is an Arg34-GLP-1 analogue substituted on the ε-amino group of the lysine in position 26 with a Glu spaced palmitic acid. The structural formula is shown in Figure 1.

Figure 1. Chemical structure of liraglutide.



The analogue is produced as the polypeptide precursor by r-DNA technology with Saccharomyces cerevisiae strain YES2085 as the production strain. Substitution with the side chain is performed during downstream processing.

Drug substance (active ingredient)

The manufacturing process, physical and chemical properties of the drug substance, the specification of the drug substance, and the stability of the drug substance are all identical to that of the currently approved Victoza. No further details have been provided.

Drug product

The composition of liraglutide 6.0 mg/ml remains unchanged from that of the currently approved Victoza.

The primary packaging material is a 3 ml glass cartridge which is identical to that of the currently approved Victoza.

However, liraglutide 6.0 mg/ml, 3 ml cartridge for use in weight management is assembled in a prefilled pen injector **PDS290**. This pen injector is **different** to that of the currently approved Victoza.

The product is manufactured by Novo Nordisk and sterilised by filtration. The drug product manufacturing process is identical to that of the currently approved Victoza up until assembly, as they are assembled into two different pens. The specification of the drug

product is identical to that of the currently approved Victoza, except for dose accuracy of the new pen injector PDS290.

The stability studies documenting the shelf life and in use conditions for liraglutide 6.0 mg, 3 ml cartridge for use in weight management treatment are identical to the stability studies approved for Victoza, with the following exceptions:

- Stability study of liraglutide 6.0 mg/ml, 3 ml cartridge assembled in a pen injector compared to liraglutide 6.0 mg/ml, 3 ml cartridge assembled in PDS290 pen injector
- Photostability study of liraglutide 6.0 mg/ml, 3 ml cartridge assembled in PDS290 pen injector.

The results of the additional stability studies showed that **shelf life** and in use conditions of Victoza are applicable to Saxenda, that is, **30 months of long term storage at 2°C to 8°C** and **30 days at room temperature (below 30°C) after first use**.

Saxenda is light sensitive and needs to be protected from light during use.

Biopharmaceutics

Biopharmaceutic data are not required for this product because the route of administration is the same as that for the currently approved Victoza.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical, and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

All quality issues have been satisfactorily resolved. There is no objection to the registration of Saxenda on quality grounds.

III. Nonclinical findings

Introduction

Novo Nordisk Pharmaceuticals has applied to register Saxenda (6 mg/mL liraglutide solution for subcutaneous [SC] injection). This application represents an extension of indication and major variation (change in dosage) for liraglutide, plus a new trade name and container type. Saxenda is proposed to be used for chronic weight management in adult patients (as an adjunct to a reduced calorie diet and increased physical activity) at a maximum recommended dose of 3 mg/day (administered SC once daily). Liraglutide is currently registered by the sponsor as Victoza, approved for the treatment of adults with T2DM at a maximum recommended dose of 1.8 mg/day SC. Saxenda and Victoza are identical in formulation.

The nonclinical dossier was of acceptable quality and contained new data on primary pharmacology (relating to the proposed weight management indication), pharmacokinetics (assay validation), toxicity in juvenile animals, local tolerance, on mechanisms for thyroid C cell hyperplasia, and on the development of pancreatitis. The studies on local tolerance and thyroid C cell hyperplasia were Good Laboratory Practice compliant. Studies that were not Good Laboratory Practice were nevertheless well documented.

Pharmacology

The pharmacology studies investigated whether liraglutide, a GLP-1 receptor agonist, reduces weight gain by a central mechanism of action in male animals.

In previously evaluated studies (submitted for the original registration of liraglutide as a new chemical entity [Victoza]), reduced body weight gain, accompanied by decreased food consumption, was observed with liraglutide in the pivotal repeat dose toxicity studies in rats (6 months) and Cynomolgus monkeys (12 months), but only in male animals. Where seen in shorter toxicity studies, decreased body weight gain was less prominent and more transient in females compared to males. These studies were conducted in normal animals. Previously evaluated pharmacology studies involving obese female animals (rats and mini pigs) did show modest weight loss (≤5%) following treatment with liraglutide.

The studies identified that the GLP-1 receptor is present in the (non human) primate brain in regions known to be involved in the regulation of food intake; specifically, regions of the hypothalamus, brainstem and amygdala. In rodents, it was demonstrated that liraglutide localised to these brain regions after peripheral administration, and was able to activate neurons and induce changes in gene expression that are expected to result in reduced food intake.

Liraglutide was shown to activate neurons in the area postrema (AP), nucleus of the solitary tract (NTS), lateral parabrachial nucleus (lPBN) and central amygdala in rats after a single dose (100 µg/kg SC). In a 4 week study, treatment with liraglutide (100 µg/kg bis in die [BID]) reduced food intake and body weight in diet induced obese rats. Fat mass was reduced, with no change in lean body mass, body water content or energy expenditure. Liraglutide was found to increase CART gene expression in the arcuate nucleus (ARC) and paraventricular nucleus (PVN) of the hypothalamus; CART (cocaine and amphetamine regulated transcript) is an anorectic peptide neuromodulator involved in feeding and food related reward that acts as a satiety signal. As well, treatment with liraglutide inhibited the increase in Agouti related peptide and neuropeptide Y gene expression in the ARC that was seen in weight matched, diet restricted controls; mRNA levels in treated animals were equivalent to those of vehicle treated controls allowed ad libitum access to food. These neuropeptides are recognised as hunger signals, known to stimulate feeding behaviour.

In subsequent studies, regions of the hypothalamus and brainstem that play a role in food intake were separately ablated in an attempt to identify a central mechanism of action for liraglutide. While ablation of the area postrema and PVN caused expected effects on food intake and body weight (increased and decreased with ablation of the respective areas), these surgical procedures did not inhibit the effects of liraglutide, with decreased food intake, inhibition of gastric emptying and reduced body weight gain with liraglutide treatment maintained. This follows on from a previously evaluated study (submitted at the time of the drug's original registration) in which ablation of the ARC was also found not to prevent reduced food consumption and body weight with liraglutide treatment in rats. Also, de-afferentiation of the vagus nerve did not alter the effects of liraglutide.

Together, the studies show central effects of liraglutide, which is supported by a published study in which the inhibition of food intake by liraglutide was attenuated in mice lacking central expression of GLP-1R.[3] However, the studies in rats with lesioned or ablated brain regions have failed to provide compelling evidence to support an exclusive or predominant central mechanism for liraglutide's effects on food intake and body weight.

The effects of liraglutide on food intake and body weight may also be contributed to by inhibition of gastric emptying (observed with the drug in both normal and brain region ablated animals). The mechanism(s) whereby liraglutide reduces gastric emptying remain

[3] Sisley S, et al. (2014) Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J. Clin. Invest.* 124: 2456-2463.

to be defined. A peripheral site of action for liraglutide's effect on food intake and body weight is supported by a published study in which GLP-1 released from the intestine in response to ingested nutrients was found to act as a satiety signal, and with peripheral – but not central – inhibition of GLP-1R blocking the effects of peripherally administered GLP-1 on food intake.[4]

Toxicology

Relative exposure

Despite the higher maximum recommended dose of liraglutide with Saxenda cf. Victoza therapy, systemic exposure is not increased in patients. This reflects the different patient population and that exposure to liraglutide decreases with increased body weight. At the maximum recommended human doses, the clinical plasma Cmax and $AUC_{0\text{-}24h}$ are 13% and 8% lower, respectively, with Saxenda compared to Victoza (39 compared to 45 nM, and 743 compared to 809 nmol·h/L).

Exposure ratios achieved in nonclinical studies to be described in the PI document (Table 1) are calculated using a human reference AUC and measured in obese subjects administered the maximum recommended dose. Animal AUC values are from the final sampling day.

[4] Williams DL, et al. (2009) Evidence that intestinal glucagon-like peptide-1 plays a physiological role in satiety. *Endocrinology* 150: 1680-1687.

Table 1. Relative exposure in selected toxicity studies

Species	Study	Dose (mg/kg/day)	AUC0–24 h (nmol·h/L)				Exposure ratio #			
Mouse (CD-1)	2 year carcinogenicity [NN204229]	0.03	♂	203	♀	168	♂	0.27	♀	0.23
		0.2		1587		1415		2.1		1.9
		1		10090		6215		14		8
		3		36380		37280		49		50
Rat (SD)	Fertility & embryofoetal development; postnatal develop ment [NN990284; NN201109]	0.1	♂	754 a	♀	691 b	♂	1.0	♀	0.93
		0.25		3088 a		2693 b		4.2		3.6
		1		10698 a		9211 b		14		12
	2-year carcinogenicity [NN200240]	0.075	380				0.51			
		0.25	1785				2.4			
		0.75	6225				8			
Rabbit (NZW)	Embryofoetal development [NN990055]	0.01	148				0.20			
		0.025	233				0.31			
		0.05	383				0.52			
Monkey (Cynomolgus)	20 month mechanistic [NN203262]	0.25	7163				10			
		5	52120				70			
Human	Victoza (BMI: 20-30 kg/m2) [NN2211-1608]	1.8 mg/day	809				–			
	Saxenda (BMI: 30-40 kg/m2) [NN8022-3630]	1.8 mg/day	546				–			
		3 mg/day	743				–			

# = animal:human plasma $AUC_{0-24\,h}$; SC administration in all studies; the human reference dose is indicated in bold;
[a] = from Study NN980189; [b] = estimated from Study NN980186

Paediatric use

Liraglutide is not currently being proposed for use in paediatric populations, but a juvenile animal study has been conducted in rats, involving treatment for 5 weeks commencing from weaning. Liraglutide reduced weight gain and food intake over the treatment period in male rats at doses of 0.25 and 1 mg/kg/day SC (relative exposure, 2.9 and 12). Delayed sexual maturation was observed in these animals, but occurred secondary to the reduction in body weight. In female rats, there was an initial transient decrease in body weight and

food consumption at these dose levels, but no overall effect when considered over the entire treatment period. Sexual maturation of females was significantly delayed at ≥0.25 mg/kg/day, with vaginal opening not occurring until ~37 days of age (compared to 31 days for controls) and with body weight at sexual maturation almost 25% higher compared to controls. Body weight, food intake and sexual maturation were not affected in either sex with treatment at 0.1 mg/kg/day (relative exposure, 0.7).

Local tolerance

Previously submitted local tolerance studies with liraglutide did not use the commercial formulation. Newly submitted studies were conducted with the Saxenda/Victoza formulation, and examined local tolerance by the intended route (subcutaneous) and by various accidental routes (intravenous [IV], intramuscular [IM] and intraarterial [IA]) in pigs and rabbits, respectively. The product was well tolerated locally by all routes studied. Reactions at SC injection sites were only modestly greater cf. that seen with saline and attributable to the vehicle rather than liraglutide itself; similar observations were made for local reactions following IV and IM injection. IA administration was associated with a slight increase in the severity of reaction at liraglutide compared to vehicle injection sites.

Thyroid neoplasia

Thyroid C cell hyperplasia, adenoma and carcinoma were observed in mice and rats treated with liraglutide in studies evaluated for Victoza. Similar findings have been seen with other members of the pharmacological class in rodents. Previously evaluated mechanistic studies supported the involvement of GLP-1R activation in the development of C cell proliferative lesions in rats, the use of increased plasma calcitonin as a marker for their subsequent development, and that the rodent was particularly sensitive to these effects in comparison with primates. Newly submitted mechanistic studies in mice established that increased plasma calcitonin levels and thyroid C cell hyperplasia were dependent on the presence of a functional GLP-1R, and that these changes were reversible. The new data do not alter the previous conclusions drawn in the assessment of Victoza; that the human relevance of the observed thyroid C cell changes is likely to be low but cannot be completely excluded.

Another new mechanistic study demonstrated that liraglutide had neither agonist nor antagonist activity at recombinant human GLP-2, secretin, GHRH and VPAC2 receptors (expressed by Chinese Hamster Ovary [CHO] cells). This reinforced the specificity of liraglutide for the GLP-1 receptor.

Pancreatitis

Following marketing authorisation for Victoza, there have been some clinical reports of increased rates of pancreatitis. Two toxicology studies examined pancreatic changes associated with liraglutide administration. The first was a histopathological extension of a 20-month study in Cynomolgus monkeys that was previously considered in the Victoza submission. Microscopic examination of the pancreas found no treatment related changes (≤5 mg/kg/day SC; relative exposure, 70 for Saxenda patients and 64 for Victoza). The second study assessed markers of pancreatitis during 13 weeks of liraglutide treatment in diabetic rats (following on from existing toxicity studies that were all conducted in normal animals). Analysis of plasma protein markers (lipase, P-amylase) showed no evidence of pancreatitis (≤1 mg/kg/day SC; estimated relative exposure, ~8). Similarly, no treatment related abnormalities were found during histopathological review of the pancreas. These animal studies did not generate evidence of pancreatitis that had been suggested in clinical use.

Nonclinical summary and conclusions

- The nonclinical dossier contained data on primary pharmacodynamics, pharmacokinetics, toxicity in juvenile animals, local tolerance, mechanistic studies on thyroid C cell hyperplasia, and on the development of pancreatitis. The nonclinical studies were of acceptable quality.
- Liraglutide reduces food consumption and body weight gain in laboratory animal species (albeit to a significantly lesser extent in females compared to males). Animal pharmacology studies showed that the GLP-1R (the pharmacological target of liraglutide) is present in the brain in regions recognised to be involved in the regulation of food intake, and that peripherally administered liraglutide activates neurons and induces changes in gene expression (increased satiety and decreased hunger signals) in these regions. Ablation of these particular brain regions, however, did not alter the effects of liraglutide to reduce food consumption and body weight. While the submitted pharmacology studies show central effects of liraglutide, they do not establish a definitive brain region responsible for the central mechanism for the drug's effects on food intake and body weight. A peripheral mode of action, with liraglutide acting as a satiety signal in the intestine and inhibiting gastric emptying locally, may also contribute to weight loss.
- Despite the higher maximum recommended human dose, peak and overall clinical exposure (plasma Cmax and AUC) for liraglutide is not increased in the intended patient population with Saxenda compared to Victoza therapy, supporting safety.
- In juvenile rats, treatment with liraglutide was associated with delayed sexual maturation in both sexes, occurring at doses yielding low exposure ratios. This was secondary to reduced weight gain in males, but, importantly, not in females. As liraglutide is not approved or proposed for use in paediatric populations, this is of limited relevance currently.
- The commercial formulation was shown to be well tolerated locally with administration by the clinical route (SC) in pigs, and also by various accidental routes of exposure (IV, IM and IA) in rabbits.
- Thyroid C cell hyperplasia and neoplasia have been observed with liraglutide (and other GLP-1R agonists) in rodents previously. Newly submitted mechanistic studies showed that C cell hyperplasia in mice was dependent on a functional GLP-1R, and was reversible following cessation of liraglutide treatment. The clinical relevance of the thyroid proliferative changes observed in rodents is still considered to be low, but is unable to be completely excluded.
- Of relevance to post marketing concerns, the pancreas was not identified as a target for toxicity by liraglutide in diabetic rats (following 13 weeks treatment at ~8 times the clinical AUC), nor in Cynomolgus monkeys (20 months treatment at ≤64 times the clinical AUC).
- There are no nonclinical objections to the registration of Saxenda.

Comments on sponsor's response to nonclinical evaluation report

The sponsor provided a response to the Round 1 nonclinical evaluation report commenting on efficacy across sexes, the proposed mechanism of action, and study numbers given in the relative exposure table.

Efficacy across sexes

The nonclinical evaluator has considered the request to reword the statements regarding limited evidence of inhibition of weight gain in female animals. The statement in the summary is considered to accurately represent the data from studies in which the effects of liraglutide were studied in male and female animals. In the 'Pharmacology' section, the text has been modified to remove the potential interpretation that the use of male animals only in the current set of experiments was a deficiency, to note that previously evaluated repeat dose toxicity studies were conducted in normal (compared to obese) animals, and to report the modest weight loss observed in obese female rats and mini pigs in previously evaluated pharmacology studies.

Mechanism of action

The sponsor has restated their opinion that the ARC is "the primary site of action for the weight loss effect of liraglutide" and provided a published paper by Secher et al. (2014).[5] The publication described data already submitted to TGA; while some new electrophysiology data were included in the paper, it related to the effects of GLP-1 and not liraglutide.

The previously submitted data provides evidence of liraglutide acting centrally, and activating regions of the brain associated with food intake. In addition, the publication by Sisley et al. (2014)[6] supports a central mechanism of liraglutide inhibiting food intake. However, in the pivotal studies ablation or lesions in specific brain regions failed to inhibit the pharmacological effects of liraglutide. In particular, acute administration of liraglutide reduced food intake, and subchronic liraglutide administration led to weight loss to a similar extent in ARC intact and ARC lesioned rats (Study PJL90-1170). It is acknowledged that the monosodium glutamate model that was used may not completely remove all pro-opiomelanocortin (POMC) neurons from the ARC. However, if the ARC is central to the actions of liraglutide it is expected that extensive damage to this brain region would at least attenuate the effects of liraglutide. Given the similar magnitude of effect of liraglutide in ARC lesioned and ARC intact rats, it is reasonable to conclude that the ARC is not critical for the pharmacological effects of liraglutide on body weight.

Therefore, while the nonclinical evaluator agrees that the mechanism of action involves the brain, the data provided are insufficient to determine which region of the brain is critical. As such, the sponsor's conclusion that the arcuate nucleus is central to the mechanism of action is not supported by the data provided. Minor modifications to the nonclinical report have been made to reflect the likelihood of a central mechanism, but uncertainty about the brain regions involved.

The sponsor cites Jelsing et al. (2012)[7] to support that the effect of liraglutide on gastric emptying is ameliorated with chronic dosing in SD rats. However, the opposite was reported in a chronic study in Göttingen minipigs (Study ULR8.001103 [/ULR8.00103]). In that study, liraglutide (3.3 µg/kg/day SC) inhibited gastric emptying by ~20% after 2 weeks, which was further inhibited to ~50% after 4 weeks. In clinical trial 3630 there was no significant difference in the primary measure of gastric emptying after 5 weeks dosing, which was paracetamol $AUC_{0-300min}$. However, there was a 23% reduction in paracetamol $AUC_{0-60min}$ in subjects that received 3 mg liraglutide daily for 5 weeks. This suggests that

[5] Secher A, et al. (2014) The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. *J. Clin. Invest.* 124: 4473-4488.
[6] Sisley S, et al. (2014) Neuronal GLP1R mediates liraglutide's anorectic but not glucose-lowering effect. *J. Clin. Invest.* 124: 2456-2463.
[7] Jelsing J, et al. (2012) Liraglutide: short-lived effect on gastric emptying — long lasting effects on body weight. *Diabetes Obes. Metab.* 14: 531-538.

the delayed gastric emptying immediately after a meal may contribute to the improved satiety signals reported clinically.

Based on these considerations, the nonclinical evaluator considers that the effects of liraglutide on gastric emptying may contribute to reduced food intake and body weight. Therefore, these comments have been retained in the evaluation report.

Study references

Study numbers for the rat reproductive toxicity studies given in the relative exposure table have been corrected.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

In the clinical trial development programme for Victoza, it was noted that patients developed nausea and weight loss, with an apparent dose response profile. As obesity is a large and increasing public health issue, the development of this drug as a weight loss agent was pursued.

Guidance

In addition to the information submitted in this submission, guidance on the drug class as a whole and on previous liraglutide submission was sought from the Victoza AusPAR.

The key Australian regulatory guideline in place at the time of this application was the TGA adopted 2007 EMA guideline on weight loss.[8] The clinical relevance of weight loss and the translation of weight loss into a health improvement were appraised in the context of the guideline.

This guideline states:

> *An important goal of the treatment of obesity is to prevent associated morbidity and mortality. Although no studies have as yet confirmed an effect on mortality or morbidity, weight reduction has been associated with reduction in blood pressure in both normotensive and hypertensive individuals, improvement in lipid profiles, and improved glycaemic control in both patients without diabetes and patients with type 2 diabetes. Relevant decreases in certain risk factors associated with obesity have been seen with loss of at least 5 to 10% of initial weight. Hence, the main objective of promoting weight loss in obese patients is to reduce these risk factors, which otherwise ultimately lead to increased morbidity and mortality.*

This is to say that although weight loss from a specific method (or drug treatment) may have different effects on morbidity and mortality, the nature of the relationship was not clear at the time the guidelines was written. With regard to the former, the guideline states that:

[8] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

> *Weight loss is the primary endpoint. Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.*
>
> *Weight loss should be documented both as absolute weight loss and by other appropriate measures (such as percentage body weight loss). Appropriate covariates should be included in the model, including but not limited to the baseline body weight, if clinically justified.*

The guideline also states:

> *Measurements using accepted methods selected and justified by the applicant should demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water). Measurement of changes in body composition and in fat distribution can be useful to better define weight loss. Methods such as waist circumference measurement, waist to hip ratio, magnetic resonance imaging and computer tomography may be used to assess abdominal fat content.*

The guideline also states:

> *Long term studies are required to demonstrate treatment associated benefits and risks and are particularly useful in documenting any changes in or loss of drug effect. Since the physiological response to dieting and reduced food intake can suggest a reduction in drug effect, it is important to remember that drug effect can be continuing despite a reduction in the rate of weight loss and may even be manifest as a failure to regain weight lost. At present, trials documenting the effect of treatment for at least one year are required but an applicant intending to demonstrate the effect of weight loss on morbidity and mortality would require a longer prospective study.*

A new EMA guideline[9] (currently out for public consultation) has been drafted because two weight control products have been pulled from the market since publication of the 2007 guideline. This new draft guideline was also considered during the evaluation because it will be considered for adoption by the TGA when it is finalised by the EMA. It states:

> *Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period)….*
>
> *….Further, the predictive value of weight loss after e.g. 3 months treatment with respect to long term effects should be documented in order to identify a population with expected long term benefit. Measurements of central adiposity (e.g. waist circumference or waist to hip ratio) should always be documented. Measurements using accepted and validated methods (i.e. DEXA, magnetic resonance imaging or computer tomography) should demonstrate that weight loss is associated with appropriate loss of body fat (as distinct from muscle or body water).*

[9] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014.

Contents of the clinical dossier

The submission included data from four new Phase III trials submitted in support of the new indication as well as data from studies previously evaluated by the TGA for the registration of Victoza that was relevant to this application.

The submission contained the following clinical information:

- 4 pivotal efficacy studies (Phase III)
  - SCALE Obesity and prediabetes (NN8022-1839 [at times referenced as "1839" in this report]): one year double blind weight loss trial, conducted in 3731 subjects with BMI ≥30 kg/m^2, or ≥27 kg/m^2 with dyslipidaemia and or/hypertension.
  - SCALE Diabetes (NN8022-1922 [at times referenced as "1922" in this report]): one year double blind weight loss trial conducted in 846 subjects with BMI ≥27 kg/m^2 and with an established diagnosis of T2DM.
  - SCALE Sleep apnoea (NN8022-3970 [at times referenced as "3970" in this report]): a six month double blind trial conducted in 359 subjects with BMI ≥30 kg/m^2 and moderate or severe obstructive sleep apnoea
  - SCALE Maintenance (NN8022-1923 [at times referenced as "1923" in this report]): a one year double blind weight loss and weight maintenance trial conducted in 422 subjects with BMI ≥30 kg/m^2, or ≥27 kg/m^2 with dyslipidaemia and/or hypertension. Subjects achieving ≥5% weight loss during the 4-12 week run in period on low calorie diet were randomised to treatment.
- 1 clinical pharmacology study (NN8022-3630 [at times referenced as "3630" in this report]) providing pharmacokinetic (PK) and pharmacodynamic (PD) data from a 35 day study in obese but otherwise healthy patients receiving the 1.8 and the 3 mg dose of liraglutide. This study was considered during the evaluation so as to understand the pharmacokinetics with the higher dose in an obese population, the pharmacokinetic-pharmcodynamic relationship and the toxicity data.
- Two population pharmacokinetic analyses: predominantly using data from trials NN8022-1839 and NN8022-1922. These were used to simulate exposure in special populations and groups not included in the clinical trials.
- One dose finding study (NN8022-1807 [at times referenced as "1807" in this report]): liraglutide 1.2, 1.8, 2.4, or 3 mg, dose escalated in weekly steps of 0.6 mg and orlistat: ter in die (TID) per os (PO) doses of 120 mg. This study had previously been evaluated but new extension (observational) data was used from this study to examine weight rebound and toxicity.
- Other efficacy/safety studies: extension of NN2211-1573 in T2DM with lower doses of liraglutide than requested in this application (1.2 and 1.8 mg – updated study report); NN2211-1700 including extension (also T2DM extension with doses of 0.9 mg liraglutide), NN2211-1701 including extension (also T2DM and also lower doses than in application – up to 0.9 mg in combination with sulfonylurea); NN2211-1796 (also T2DM and with liraglutide doses up to 1.8 mg); NN2211-1797 extension (also T2DM and with liraglutide doses up to 1.8 mg); NN2211-1799 (also T2DM with liraglutide 1.8 mg); NN2211-1860 (with extension – also T2DM and liraglutide 1.2 or 1.8 mg); NN2211-3924 (T2DM with liraglutide 0.9 mg); NN2211-3925 (T2DM and liraglutide 0.9 mg); NN9535-1821 (T2DM and liraglutide 1.2 or 1.8 mg versus semaglutide + metformin); NN1250-3948 T2DM and liragutide 1.2 mg daily); NN9068-3697 (T2DM and liraglutide 1.8 mg); NN9068-3697 T2DM and liraglutide 1.8 mg); NN9068-3912 T2DM and liraglutide 1.8 mg). While the extension phases of these studies provided safety data out to a year (56 weeks [+ 104 weeks of extension in Study MM2211-1573]), most did not provide efficacy or safety data for either the population or the

dose requested in this application. However, data from the following three study reports was considered relevant to the examination of safety:

  - Study report for NN2211-1573: Extension 3 Year Data Liraglutide Effect and Action in Diabetes (LEAD 3): Effect on Glycemic Control of Liraglutide versus Glimepiride in Type 2 Diabetes. This report covers the 52 week double blind period and the 52 week open label extension plus an additional 52 week open label extension for the 1 year double blind plus 6 month open label extension originally assessed in the Victoza submission.
  - Study report NN2211-1797 Extension 2 Liraglutide Effect and Action in Diabetes: LEAD-6 Effect on Glycaemic Control of Liraglutide or Exenatide Added to Metformin, Sulphonylurea, or a Combination of Both in Subjects with Type 2 Diabetes. A 26 week randomised, open label, active comparator, two armed, parallel group, multicentre, multinational trial with a 14 week non randomised extension period followed by an additional 38 week non randomised extension period. Study reports for the original 26 week randomised period had previously been assessed in Victoza; the data in this application includes new report data from a further 28 week extension.
  - Study report NN2211-1860 Extension 2 The Effect of Liraglutide Compared to Sitagliptin, Both in Combination with Metformin in Subjects with Type 2 Diabetes. A 26 Week, Randomised, Open label, Active Comparator, Three Armed, Parallel Group, Multicentre, Multinational Trial With a 52 Week Extension. This Clinical Trial Report covers the main and the 52 Week extension (corresponding to 78 Weeks of Treatment) previously assessed in liraglutide (Victoza).

- Reports of Post Marketing Experience: specifically the PSUR/PBRER liraglutide (1 July 2012 - 30 June 2013) which was submitted to TGA on 29 August 2013 as routine post approval PSUR commitment to liraglutide new biological entity application. This was reviewed in the safety part of this application.
- Integrated summary efficacy and safety data from the weight management pivotal trials including 1922 was provided. This enabled confirmatory testing of specific pre specified secondary endpoints to confirm the results seen in the individual trials and was summarised.
- A literature review (predominantly of publications and guidelines on the use of liraglutide in the T2DM area) provided general information about the clinicaluse of and experience with this therapy.

Paediatric data

The submission did not include paediatric data.

Novo Nordisk has an agreed Paediatric Investigation Plan (PIP) in Europe with 2 waivers: 0-2 and 2-6 years. Novo Nordisk has also submitted the PSP (Paediatric Study Plan) to the FDA as part of the new drug application. To date, no feedback has been received on this PSP.

Good clinical practice

Good Manufacturing Practice clearance for overseas manufacturing sites was provided. Good Clinical Practice was required and obtained by ethics committees for the clinical trial programme (detailed at the end of each study report).

Pharmacokinetics

Studies providing pharmacokinetic data

Study NN8022-3630 provided PK and PD data from 49 obese but otherwise healthy subjects who received 1.8 and/or the 3 mg doses of liraglutide in a placebo-controlled, double-blind, 6 sequence cross-over study.

Previous pharmacokinetic data has already been evaluated in the 2008 submission for Victoza. Table 2 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 2. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID
PK in healthy adults	General PK - Single dose	Previously evaluated
	- Multi dose	
	Bioequivalence † - Single dose	Previously evaluated
	- Multi dose	
	Food effect	
PK in special populations	Target population § - Single dose	NN8022-3630
	- Multi dose	
	Hepatic impairment	Simulated data using concentration data from 1839, 1807 and 1922
	Renal impairment	
	Neonates/infants/children/adolescents	
	Elderly	
Genetic/gender related PK	Males versus females	
PK interactions		Drug interaction work previously submitted with 1.8 mg. As trial 3630 showed a delayed gastric emptying and effects on AUC with the 3 mg dose, extrapolation were made by the evaluator of possible clinically relevant interactions
Population PK analyses	Healthy subjects	
	Target population	Data from 1839, 1807 and 1922
	Other	

† Bioequivalence of different formulations.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

The sponsor states that the liraglutide formulation used in the trials conducted in the weight management clinical development programme for this indication is both the same as that intended for the market and identical to the currently registered and marketed commercial formulation of Victoza, so standard pharmacokinetic work around bioavailability and bioequivalence is not needed for Saxenda.

However, the PK for many drugs alters as the dose increases, due to saturable processes and competitive binding. Further as this drug has a known effect on absorption, known to affect exposure, pharmacokinetic knowledge of all drugs being used with liraglutide as well as monitoring should be undertaken. This is particularly pertinent in obese patients who often have at least one other comorbidity. Importantly, PK is often complex in an obese population (much of the data above is drug interactions of a smaller dose and in a more healthy population) and has different effects on different drugs depending on their own PK and physicochemical properties. The fact there is a 24% lower AUC with liraglutide 3 mg versus 1.8 mg in study NN8022-3630 when taken over 60 mins is a case in point. Therefore, the lack of PK data for this higher dosage in this complex population is an issue of potential clinical concern.

It is noted that sex and body weight were the main covariates for liraglutide exposure in the modelling study so PK data of the 3 mg dose in these groups would be helpful. Although there was no observed effect on teratogenicity in the observational studies, teratogenicity has been observed in animals with less exposure than that expected (from the modelling studies) in people taking the 3 mg dose and is appropriately reflected in the PI. There are changes to the PI recommended from the lack of knowledge about the PK in the higher dose and in the obese population.

Pharmacodynamics

Studies providing pharmacodynamic data

Study NN8022-3630 provided PK and PD data from 49 obese but otherwise healthy subjects who received 1.8 and/or the 3 mg doses of liraglutide in a placebo controlled, double blind, 6 sequence crossover study. Table 3 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 3. Submitted pharmacokinetic studies.

PD Topic	Subtopic	Study ID
Primary Pharmacology	Effect on weight loss and mechanism	NN8022-3630

Evaluator's conclusions on pharmacodynamics

Pharmacodynamic data previously submitted (in the 2008 and 2012 submissions) clearly demonstrate an effect of liraglutide (at lower doses) on HbA1c. Effects on weight loss are also seen in these T2DM studies and discussed further in the clinical section.

Dosage selection for the pivotal studies

The dose for the pivotal studies was chosen based on data from trial 1807, the Phase II dose finding trial, evaluated previously but included also in the submission with open label extension data (Table 4). It included liraglutide doses of 1.2, 1.8, 2.4 and 3 mg. Trial 1922 (included in the evaluated pivotal studies, undertaken in subjects with T2DM), included both the 1.8 and 3 mg doses. The dose related efficacy and non dose related (apart from gastrointestinal) safety results obtained in this trial suggested that liraglutide 3 mg dose was the optimal clinical dose compared to 1.8 mg in weight management for overweight or obese subjects with T2DM.

Table 4. Dosage selection for the pivotal studies.

Trial 1807 (52 weeks)					
	1.2 mg N=89	**1.8 mg N=89**	**2.4 mg N=85**	**3.0 mg N=88**	**p-value for dose response**
Body weight change in %	-2.19*#	-3.72*#	-4.36*	-6.08*	<0.0001
Body weight change in kg	-1.97*#	-3.51*#	-4.22*	-5.82*	<0.0001
% of subjects losing ≥5% of baseline body weight	20.7*#	26.4*#	28.4*#	48.4*	0.0004
% of subjects losing >10% of baseline body weight	7.9*#	17.0*	19.4*	26.2*	0.0085
Trial 1922 (56 weeks)					
	–	**1.8 mg N=202**	–	**3.0 mg N=411**	–
Body weight change in %	–	-2.62*#	–	-3.97*	–
Body weight change in kg	–	-2.65*#	–	-4.11*	–
% of subjects losing ≥5% of baseline body weight	–	22.3*#	–	37.2*	–
% of subjects losing >10% of baseline body weight	–	9.5*#	–	18.3*	–

*Indicates significantly better than placebo. #Indicates 3.0 mg is significantly better than the specified dose.

It can be seen that there is a clear dose-response relationship with maximal weight loss being seen in the 3 mg dose. 1807 had an open label extension period which provided observational data up to 104 weeks of treatment.

As well as a dose response relationship for weight loss, in both trials 1807 and 1922, liraglutide 3 mg also had the most beneficial effects on a wide range of secondary endpoints. These include glycaemic control parameters, blood pressure, fasting lipids, cardiovascular biomarkers and quality of life.

In addition, an exposure response relationship was also seen across all subgroups which began to flatten off at the highest exposure achieved with liraglutide 3 mg.

Efficacy

The development programme for weight loss efficacy (as opposed to diabetes efficacy) includes one clinical pharmacology trial (trial NN802-3630), one Phase II trial (trial 1807 plus extension) and four Phase III trials (trials 1839, 1922, 3970 and 1923). The trial population includes more than 5500 obese or overweight subjects with one or more comorbidities such as pre-diabetes/T2DM, hypertension, dyslipidaemia or obstructive sleep apnoea (OSA).

Studies providing efficacy data

There are four pivotal studies submitted (1922, 1839, 3970 and 1923). Trials 1839, 3970 and 1923 and a non pivotal study (1807) were conducted in obese or overweight subjects without T2DM. Trial 1922 was conducted in subjects with T2DM. NN802-1807 was a Phase II study. Trial 1839 stratified subjects according to whether or not they had pre-diabetes at screening (according to ADA 2010 criteria). Trial 3970 was conducted in obese subjects with moderate or severe OSA. Trial 1923 was a weight loss and weight maintenance trial conducted in subjects who had achieved ≥5% weight loss during a pre-randomisation 4-12 week run in period on a low calorie diet (1200-1400 kcal).

The four pivotal studies were randomised, double blind placebo controlled trials that used liraglutide doses ranging from 1.8 mg to 3.0 mg. The studies spanned 32-56 weeks (including a 4 week dose escalation period) and included 5358 patients as follows:

- The SCALE Obesity and Pre diabetes (NN8022-1839): this examined one year weight management trial in 3731 overweight patients with at least one comorbid condition, or obese adult patient, with or without pre-diabetes. The dose used was 3 mg.
- Scale diabetes (NN8022-1922): one year weight management trial in 846 obese or overweight patients with T2DM. The doses used were the 1.8 and 3 mg.
- SCALE Sleep Apnoea (NN8022-3970): six months weight management trial in 359 obese patients with moderate or severe obstructive sleep apnoea. The dose used was 3 mg.
- SCALE Maintenance (NN8022-1923): one year additional weight loss in 422 overweight people, with at least one comorbid condition, or obese patients after initial >5% weight loss on low caloric diet. This trial assessed the ability of Saxenda to maintain prior weight loss induced by diet and exercise alone and to examine if additional weight loss could be achieved, as a secondary objective. The dose used was 3 mg.

Evaluator's conclusions on efficacy

In each of the four Phase III randomised control trials here is evidence of a statistically significant weight loss difference between placebo and Saxenda, maintained out to one year. In the pooled analysis, weight loss is around 4.2-6.1% of total body weight (compared to placebo after adjustment for baseline). The clinical relevance of the statistically significant percentage is not discussed, although the EMA guideline states:[10]

> *Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs.*

This criterion was not met for 2 of the 5 studies: 3.95% (1922), 4.15% (3970) and just met for three others: 5.39% (1839), 6.06% (1923) and 6.08% (1807).

The guideline also states:

> *Measurements using accepted methods selected and justified by the applicant should demonstrate that weight loss is associated with appropriate loss of body fat … Methods such as waist circumference measurement, waist to hip ratio, magnetic*

[10] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

> *resonance imaging and computer tomography may be used to assess abdominal fat content.*

Waist circumference was reported in the studies (see below).

The guideline also states:

> *Long-term studies are required to demonstrate treatment associated benefits and risks and are particularly useful in documenting any changes in or loss of drug effect. Since the physiological response to dieting and reduced food intake can suggest a reduction in drug effect, it is important to remember that drug effect can be continuing despite a reduction in the rate of weight loss and may even be manifest as a failure to regain weight lost. At present, trials documenting the effect of treatment for at least one year are required but an applicant intending to demonstrate the effect of weight loss on morbidity and mortality would require a longer prospective study.*

In all studies there was a plateau with no clinically relevant further weight gain after the initial 3-4 month weight loss. In the studies where rebound was examined, patients were regaining lost weight – based on the trend it could be presumed that this group would return back to baseline, although it is noted that at the time of end of the relatively short study follow-up the weight had not returned to baseline.

It was noted that Saxenda had positive statistically significant effects on BMI and waist circumference in all 4 Phase III and the Phase II 1870 trial (Table 5). It also reduced neck circumference in the OSA trial 3970.

Table 5. Effects on BMI and waist circumference.

Trial	BMI (kg/m^2) Mean estimates and treatment differences (ANCOVA)			Waist circumference (cm) Mean estimates and treatment differences (ANCOVA)		
	Liraglutide 3.0 mg	Placebo	Lira - placebo	Liraglutide 3.0 mg	Placebo	Lira - placebo
1839	-3.04	-1.00	-2.04*	-8.17	-3.97	-4.20*
1922	-2.24	-0.74	-1.50*	-6.02	-2.81	-3.21*
3970	-2.21	-0.62	-1.59*	-6.35	-3.14	-3.22*
1923	-2.07	-0.02	-2.05*	-4.68	-1.19	-3.49*
1807	-3.09	-1.02	-2.07*	-9.43	-4.72	-4.72*

*p<0.0001.

The clinical significance of a reduction in BMI or waist circumference of 3.2-4.7 cm was not discussed, although this was noted to be an important endpoint in the EMA guidance. The Guidance recommended these endpoints as weight loss is important for the effects it has on clinical outcomes, such as myocardial infarction and metabolic syndrome. Some of these clinical outcomes were included as secondary or safety outcomes in this Application but the relationship for the effects of this drug on those outcomes were not made clearly. As it is presented in this application, weight loss appears to be discussed as a surrogate biomarker.

Examining the graphs of the weight loss in the trial individually and the pooled data, one can see a relatively quick weight loss with Saxenda in the first 12 weeks. After 24 weeks there is no apparent weight loss in either placebo or Saxenda groups.[11] This suggests that the 4-6% weight loss does not continue (data presented in SCALE-Maintenance suggests

[11] Sponsor comment: "This does not hold for all trials (1839, 1922)."

some of the weight loss may be maintained if Saxenda is continued but not if discontinued). Long term data and follow-up for people on the drug and those who stopped as recommended in the current 2007 guideline is warranted. At present the optimum duration of treatment is unknown. To date all studies suggest an immediate cessation of treatment effect as soon as treatment is stopped. Long term therapy for obesity is, therefore, likely to be required to show that weight loss can be achieved and maintained. Long term studies are required to demonstrate treatment associated benefits and risks and will be particularly useful in documenting any changes in or loss of drug effect. Since the physiological response to dieting and reduced food intake can suggest a reduction in drug effect, it is important to remember that drug effect can be continuing despite a reduction in the rate of weight loss and may even be manifest as a failure to regain weight lost.

At present, trials documenting the effect of treatment for at least one year are required but an applicant intending to demonstrate the effect of weight loss on morbidity and mortality would require a longer prospective study.

The information around the mechanism also requires discussion. Does this drug cause weight loss by inducing nausea? Were the patients developing adverse events those who had the greatest weight loss. Does the mechanism that causes nausea and early satiety lose its effectiveness in time?

Of further interest is that in some studies only 1/3 subjects had 10% or greater weight loss, in some studies half of the patients taking Saxenda had difficulty even reaching a 5% weight loss. The proportion of 5% responders in the Saxenda group at the end of the trials was 46-78%. Even in the placebo arm there was a response rate in this 5% weight loss group of 14-30%. The proportion achieving at least 10% weight loss was 22 -36% in the liraglutide compared with 2-10% in the placebo group. Does the sponsor have a method of predicting who will get benefit as there is a large number of people who will be treated for no benefit, yet exposed to potential toxicity?

Differential responders are also evidenced in the 10% weight loss group. Similarly the mechanism of 'early response' was not discussed and whether this is a mechanism for identifying patients who are likely to benefit (as seen in SCALE-Maintenance). For example, the submission calculates that in the SCALE-obesity and pre-diabetes and SCALE-Diabetes studies combined, 65.0% of the Saxenda group achieved ≥5% weight loss after four months. Yet overall mean change from baseline in body weight was <5%; for the 'early responders' it was -11.2 % after one year (excluded the non-early responders); however, when adjusting for response in the placebo group which was around 2% in the total group (early responders and overall responders) the value is likely to be less than 10%.

It is noted than in the obese people with T2DM (1922 study) there is a statistical and clinically significant lowering of glycated haemoglobin. A clinically significant reduction is not seen in non diabetic patients, therefore the relevance for the indication which is obesity is not clear.

There is a 2-3 mmHg reduction in systolic blood pressure with Saxenda in all trials.

In patients with sleep apnoea, there is a statistically different difference between Saxenda and placebo in number of events per h; but the clinical significance of a reduction from 49 events/h to 43 events/h is not discussed.

There is statistical significance in some of the patient reported outcomes (PRO), although their clinical significance is not discussed. For example, liraglutide 3 mg (but not the 1.8 mg) treatment resulted in a higher (better) total score (estimated treatment difference: 2.75, p = 0.0136 in the Impact of Weight on Quality of Life [IWQoL]-Lite), and higher score in 'physical function' (estimated treatment difference 4.92, p = 0.0006) at Week 56

compared with placebo. For the Diabetes Treatment Satisfaction Questionnaire (DTSQ), liraglutide 3 mg but not 1.8 mg treatment was associated with a higher total score (estimated treatment difference: 1.44, p = 0.0066) compared with placebo.

Safety

Studies providing safety data

As well as summary data from studies submitted for earlier applications and their extension data, which was provided in the submission, the following new studies provided evaluable safety data on the proposed indication.

The four pivotal randomised controlled trials of Saxenda versus placebo were as follows:

- SCALE Obesity and pre-diabetes (NN8022-1839) one year double blind weight loss trial, conducted in 3731 subjects with BMI ≥30 kg/m^2, or ≥27 kg/m^2 with dyslipidaemia and or/hypertension.
- SCALE Diabetes (NN8022-1922): one year double blind weight loss trial conducted in 846 subjects with BMI ≥27 kg/m^2 and with an established diagnosis of T2DM.
- SCALE Sleep Apnoea (NN8022-3970): a six month double blind trial conducted in 359 subjects with BMI ≥30 kg/m^2 and moderate or severe obstructive sleep apnoea.
- SCALE Maintenance (NN8022-1923): a one year double blind weight loss and weight maintenance trial conducted in 422 subjects with BMI ≥30 kg/m^2, or ≥27 kg/m^2 with dyslipidaemia and/or hypertension. Only subjects achieving ≥5% weight loss during the 4-12 week run-in period on low calorie diet were randomised to treatment.

Pivotal efficacy studies

- The pivotal Study 1922 provided data on comparable toxicity across the 1.8 and 3 mg dose.
- The pivotal Study 1839, 1923 and 3970 provided comparative safety data

In these pivotal efficacy studies, the following safety data were collected:

- General adverse events (AEs) were assessed by self report and direct questioning at study visits. AEs of particular interest, including hypoglycaemia, pancreatitis and events of the gastrointestinal system, were assessed at each visit. Hypoglycaemia was assessed based on self reported symptoms by patients and not confirmed by blood glucose measurements in patients without T2DM.
- Laboratory tests, including full blood examination, thyroid and liver and renal tests, were performed at study visits as documented in the protocol.
- Electrocardiograms and physical examinations were also undertaken.

All four pivotal studies clearly documented the safety parameters collected and any protocol violations that resulted. The overall summary data is provided below, and apart from 1839, System Organ Class (SOC) are not specifically reported if there was no differences between the liraglutide and placebo study groups.

Patient exposure

Patient exposure is shown in Table 6.

Table 6. Summary of duration of exposure (days) by randomised treatment – Safety analysis set (Study 1807).

	Placebo	Lira 1.2 mg	Lira 1.8 mg	Lira 2.4 mg	Lira 3.0 mg	Orlistat
Duration of Treatment (days)						
N	98	95	90	93	93	95
Mean (SD)	484.4 (297.0)	502.3 (289.7)	455.1 (290.3)	473.7 (293.4)	520.7 (273.2)	468.1 (289.0)
Median	725.5	728.0	511.5	672.0	734.0	575.0
Min : Max	21 : 759	1 : 751	1 : 759	4 : 762	5 : 772	4 : 762
Total exposure in subject years *	130.0	130.6	112.1	120.6	132.6	121.8

Safety issues with the potential for major regulatory impact

Liver toxicity

A mean increase from baseline to end of study was seen in lipase and amylase in the liraglutide arm 3 mg whereas a decrease was seen with placebo. Mean concentrations were reversed to baseline levels after 12 weeks without liraglutide 3 mg supporting this AE being related to drug exposure.

Haematological toxicity

Nil

Serious skin reactions

Nil. Skin irritation from the SC injections were reported in all trials but these were not serious (liraglutide 3 mg [13.9%, 22.9 events per 100 patient years of exposure {PYE}] versus placebo [10.5%, 15.7 events per 100 PYE]).

Cardiovascular safety

Retrospective meta analyses of major adverse cardiac events (MACEs) across clinical development programmes with GLP-1R agonists in a different population to this indication (that is, T2DM), which include randomised trials of at least 24 weeks duration did not indicate an increased cardiovascular risk with this class, to date. There are ongoing cardiovascular outcome trials (including with liraglutide in T2DM) which will help understand the long term cardiovascular risk of GLP-1R agonists.

In the weight management pool, the proportion of subjects with events identified by the medical dictionary for regulatory activities (MedDRA) search for cardiovascular events was similar with liraglutide 3 mg (8.7%, 12.3 events per 100 PYE) and placebo (9.2%, 13.8 events per 100 PYE).

Tachycardia was reported by statistically significantly more subjects on liraglutide 3 mg than on placebo (0.6% on liraglutide 3 mg versus 0.1% on placebo). One AE with tachycardia was reported as a serious adverse event (SAE). The estimated treatment difference (2.5 beats/min) between liraglutide 3 mg and placebo at end of treatment in the weight management pool was statistically significant ($p<0.0001$, ANCOVA). The proportion of subjects with MACE confirmed by the external event adjudication committee (defined as a composite of non fatal myocardial infarction, non fatal stroke and cardiovascular death) and the rate of events was lower with liraglutide 3 mg (0.1%, 0.2 events per 100 PYE) than with placebo (0.5%, 0.6 events per 100 PYE) and consistent across the 3 components of the composite endpoint. There were no trends for higher pulse or pulse increases in subjects with events as compared to those without MACE, or between treatment groups (Table 7). Increased resting pulse has been detected as well as with other GLP-1R agonists.

Table 7. Confirmed MACE in the weight management pool.

	Lira 3.0 mg N	(%)	E	R	Total lira N	(%)	E	R	Placebo N	(%)	E	R
Number of subjects	3304				3872				1941			
Years of exposure	2974.3				3372.7				1600.9			
EAC Confirmed Events	5	(0.1)	5	0.2	8	(0.2)	8	0.2	9	(0.5)	9	0.6
Non-fatal Myocardial Infarction	3	(<0.1)	3	0.1	5	(0.1)	5	0.1	5	(0.3)	5	0.3
Non-fatal Stroke	1	(<0.1)	1	<0.1	2	(<0.1)	2	<0.1	2	(0.1)	2	0.1
Cardiovascular Death	1	(<0.1)	1	<0.1	1	(<0.1)	1	<0.1	2	(0.1)	2	0.1

EAC: (external) event adjudication committee. MACE: Major cardiovascular event. N: Number of subjects. %: Percentage of subjects. E: Number of events. R: Event rate per 100 years of exposure
Events were treatment emergent and belonged to the main treatment period of the individual trials.
Data are based on trials 1839, 1922, 3970, 1923, 1807 and 1807-ext-1
Cardiovascular death includes cases adjudicated as unknown cause of death

Unwanted immunological events

Liraglutide is a protein based drug and therefore has the potential to cause immunogenic reactions. It has 97% homology to endogenous GLP-1 so there has been concern regarding cross reactivity to native GLP-1R. Cases of anaphylactic reactions with additional symptoms such as hypotension, palpitations, dyspnoea and oedema have been reported with marketed use of liraglutide in T2DM.

Overall, the frequency and rate of 'allergic reactions', as defined by the MedDRA search, reported with liraglutide 3 mg (2.0%, 2.5 events per 100 PYE) were comparable to those in the placebo group (2.4%, 3.5 events per 100 PYE). The most frequently reported immunological events were asthma and urticaria and most were of moderate severity.

Overall, up to 3% developed anti liraglutide antibodies in the Phase II and III weight management trials. With liraglutide 3 mg, neutralising antibodies were found in 1.1% of subjects and cross reacting antibodies in 0.5%. In 1839, at Week 58, less than 3% (17 subjects) had developed anti liraglutide specific antibodies; less than 1% cross reacted with native GLP-1 and less than 1% had in vitro neutralising effect to liraglutide. However, at the follow up visit (Week 70), 3 of the 13 subjects switched from liraglutide 3 mg to placebo were still anti liraglutide antibody positive.

Three cases of anaphylactic reactions were reported in subjects treated with liraglutide 3 mg (1 SAEs): two during the main treatment period, and one during the second year of trial 1807. There were no anaphylactic reactions in the placebo groups.

Evaluator's conclusions on safety

Liraglutide has been in clinical use in Australia for 5 years, at a dose of 1.8 mg as compared to the 3 mg requested in this application and PSUR data to date has not revealed any new signals. However, this is a drug that binds almost 24 h to stimulate a receptor and because obesity is a chronic problem may be taken long term. Therefore, long term pharmacovigilance data is paramount.

Apart from gastrointestinal (GI) events which were reported in an increasing amount to the 1.8 mg dose (up to 50% had nausea in one study); overall, a dose response relationship was not able to be ascertained for other safety events.

The clinical significance of a pulse rate increase of 2-3 beats/minute was not discussed however there are agents registered in Australia to lower heart rate based on translational evidence showing that higher heart rates are associated with higher death rates. Results of multiple ongoing cardiovascular outcome trials (including LEADER with liraglutide in T2DM) will help clarify the long term CV risk of liraglutide. The CV trial data is awaited

from studies currently underway and observation for thyroid disease, hepato-biliary disease, thyroid cancers and hypoglycaemia continues.

There were a number of AEs seen in the liraglutide 3 mg group in this application that occurred at a higher rate than the placebo group. These include pancreatitis and gallbladder disease. Amylase and lipase concentrations were consistently elevated across the trials in the liraglutide 3 mg arm; this resolved on drug cessation supporting the drug-event relationship.

The risk of hypoglyacemia was reported in the liraglutide group even in the non T2DM group. A total of 8 severe treatment emergent hypoglycaemic episodes were reported, 5 events by 3 subjects (0.7%) with liraglutide 3 mg, and 3 events were reported by 2 subjects (1.0%) with liraglutide 1.8 mg; all subjects were taking sulfonylurea (SU) as background diabetes medication.

Safety was not examined in groups excluded from partaking in the study but whom may be eligible to take the drug if marketed, depending in the listing. 93% of the exposure was in subjects in the age group 18 to 65 years. Similarly, few subjects with renal impairment were included in the trials.

A total of 11 of the 46 pregnancies that occurred in the trial 1839 resulted in spontaneous abortion (9 of 31 with 3 mg liraglutide and 2 of 15 with placebo).

First round benefit-risk assessment

First round assessment of benefits

The benefits of Saxenda in the proposed usage are:

- For some patients there was a reduction in body weight around 5% which was seen early and maintained whilst still taking the therapy. Some subjects achieved up to 10% body weight reduction.
- This reduction was short term, however the weight loss was maintained for the duration of the studies.
- There was a mild but clinically significant reduction in systolic blood pressure.

First round assessment of risks

The risks of Saxenda in the proposed usage are:

- Population group need to be taking a reduced calorie diet and on an exercise plan to achieve benefits seen in the trial.
- If they do this and take Saxenda, then some will lose 5-10% of body weight, but many will not.
- All will be exposed to the risk of toxicity, which is predominantly symptomatic (for example, gastrointestinal side effects) but can also be serious (hypoglycaemia, immunogeneticity, pancreatitis).
- Long term data is lacking: side effects are possible for all users but also rebound weight gain is likely (see in the studies of cross over and observational data)

First round assessment of benefit-risk balance

The benefit-risk balance of Saxenda, given the proposed usage, is unfavourable.

The data meets the 2007 EMA criteria[12] for weight loss for 3 of the 5 studies. The weight loss is maintained short term but no further weight loss occurs. Stopping the drug appears to cause weight regain.

First round recommendation regarding authorisation

Saxenda gives a small, clinically relevant weight loss in some patients who are concomitantly on a lifestyle weight loss programme. It is difficult to predict which patients will benefit but all need to be on a diet and exercise programme; this will be difficult to manage in the population outside the clinical trial, and also long term. Therefore, the efficacy in the real world setting is likely to be reduced from the relatively short term clinical trial findings. There are side effects with the treatment (mainly GI) and long term safety data from chronic stimulation of the GLP-1R is unknown, especially from this 3 mg dose.

Further, after an initial weight loss, continual treatment in the manner seen in the trial (90% compliance) is required to maintain the weight loss. Stopping the therapy, and even without stopping in some patients, weight was regained.

The sponsor does not attempt to translate the short term and small weight loss benefit to clinically meaningful outcomes such as reduction in myocardial infarctions.

Clinical questions

The sponsor's answers to the clinical questions were considered by the Delegate during preparation of the request for Advisory Committee on Prescription Medicines (ACPM) advice.

Pharmacokinetics

Nil required. Ideally, some real concentration and AUC data relating those to efficacy and toxicity would have been helpful (in addition to the simulated data). This is because some of the patients with the greatest weight loss had lower BMI and were female. It is also important because there was more weight loss in the 3 mg than in the other doses. Therefore, it is possible that side effects are concentration related also, or maybe related also to other phenotypic factors.

Pharmacodynamics

Nil required.

Efficacy

- What is the clinical relevance of the change in the AHI (Apnea Hypopnea Index) in the SCALE-Apnoea study?
- What is the clinical relevance of a change in the IWQoL-Lite (of 2.73-3.8) and SF 36 for overall physical health (0.86-1.73) and mental health of 0.59-0.9?
- What is the clinical significance of the change in metabolic parameters, that is, changes in LDLc, HbA1C and systolic blood pressure?

[12] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

- In Study 1923, please confirm if the re-randomised liraglutide patients were included in the original assignment group for the 68 week analysis; if not, and as the majority of weight loss occurs in the first 3-4 months of liraglutide treatment, then the original placebo group may have confounded the benefit of the liraglutide treatment seen in Weeks 56-68.
- In the pooled summary, please confirm for the early responders what the overall comparative weight loss is (that is, in the liraglutide early responders minus the placebo early responders); for the 'early responders' in liraglutide group, it was -11.2 % without comparison to placebo group.
- Please comment on the effect of dropouts/loss to follow up/discontinuations (~20% across the four Phase III studies) on adding additional uncertainty to the results.
- Please comment on concerns about weight gain on discontinuation and advice to prescribers and patients about duration of treatment.
- Please comment on advice to prescribers and patients about when to stop liraglutide, if there is no initial weight loss.

Safety

Please comment on safety concerns around:

- increased resting pulse rate
- cholecystitis
- pancreatitis
- neoplasms

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted an EU-Risk Management Plan (RMP), edition 19, version 2, dated 9 December 2013 and Australian Specific Annex (ASA), version 1.0, dated 30 June 2014 and EU-RMP version 8, edition 20, date 11 February 2015 and ASA version 3.0, dated 19 February 2015

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 8.

Table 8: Ongoing safety concerns.

Ongoing safety concerns	
Important identified risks	Hypoglycaemia in combination with other anti-glycaemic patients Gastrointestinal adverse events Altered renal function Allergic reaction Acute gallstone disease
Important potential risks	Hyperglycaemia due to discontinuation of insulin Medullary thyroid cancer Neoplasm Pancreatitis Anti liraglutide antibody formation
Missing information	Children and adolescents < 18 years Pregnant and lactating women Patients with hepatic impairment Patients with severe renal impairment Patients with congestive heart failure NYHA III-IV Patients with a history of major depression or other severe psychiatric disorders Concomitant use of other weight lowering products Overdose Off-label use Drug-drug interaction with warfarin

NYHA = New York Heart Association

OPR reviewer comment

Notwithstanding the evaluation of the nonclinical and clinical aspects of the Safety Specification, the following changes to the list of ongoing safety concerns are recommended.

- As the product will be administered by patients in a home treatment setting, it is recommended that "medication error", which should include "medication error in a home treatment setting", be added as potential risk to the table of ongoing safety concerns.
- It is noted that "Use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)" is included as contraindication in the US PI and the Canada Product Monograph. It is recommended this be included as potential risk in the table of ongoing safety concerns.
- It is recommended that "Rapid weight loss" be added as potential risk.
- It is noted that "Cardiovascular disorders" is listed as potential risk in the table of ongoing safety concerns for Victoza but not for Saxenda. Furthermore, in clinical trials

tachycardia was reported in 0.6% of patients treated with Saxenda and in 0.1% of patients treated with placebo. It is recommended that "Cardiovascular disorders", which should include tachycardia, be added to the table of ongoing safety concerns for Saxenda.

Pharmacovigilance plan

Proposed pharmacovigilance activities

The sponsor proposes routine pharmacovigilance activities for all ongoing safety concerns. This also includes targeted safety surveillance for the following ongoing safety concerns: Altered renal function, Immunogenicity related events (allergic reactions), Acute gallstone disease, Hyperglycaemia due to discontinuation of insulin, Medullary thyroid cancer, Neoplasm, Pancreatitis and Anti liraglutide antibody formation.

In addition, various studies are ongoing to address certain ongoing safety concerns, and some of these studies include Australian patients.

The following safety concerns for the indication of weight management are addressed by ongoing studies (Table 10).

Table 10: Ongoing studies for the indication of weight management.

Areas requiring confirmation or further investigation	Proposed routine and additional PhV activities	Objectives
Safety concern: Hyperglycaemia due to discontinuation of insulin		
Investigate any potential causal relationship between MTC and liraglutide	Database studies (NN2211-3784 and NN2211-3880)*	To identify any causal relationship between MTC and liraglutide.
Investigate risk factors	Medullary thyroid carcinoma registry (MTC-22341)**	To identify any causal relationship between MTC and liraglutide.
Safety concern: Neoplasms		
Investigate any potential causal relationship between neoplasms and liraglutide	Database studies (NN2211-3784 and NN2211-3880)* Cardiovascular outcome trial LEADER®*	To identify any causal relationship between neoplasms and liraglutide.
Safety concern: Pancreatitis		
Investigate any potential causal relationship between pancreatitis and liraglutide	Database studies (NN2211-3784 and NN2211-3880)* Cardiovascular outcome trial LEADER®*	Investigate any potential causal relationship between pancreatitis and liraglutide.
Safety concern: Anti-liraglutide antibody formation		
Investigate any potential causal relationship between anti-liraglutide antibody formation and liraglutide	Cardiovascular outcome trial LEADER®*	Investigate any potential causal relationship between anti-liraglutide antibody formation and liraglutide.
Safety concern: Children and adolescents < 18 years		
Investigate safety and tolerability in obese adolescents	Clinical trial (NN8022-3967) which includes obese adolescents ≥12 years and <18 years	Investigate safety and tolerability in adolescents (12-17 years)
Safety concern: Patients with congestive heart failure NYHA III-IV		
Investigate any potential risk of liraglutide treatment in high-risk CV patients	Cardiovascular outcome trial LEADER®*	Investigate any potential risk of liraglutide treatment in high-risk CV patients

* These studies are conducted in patients with T2DM treated with liraglutide 1.8 mg. The results are considered relevant for all doses of liraglutide although not specifically designed for the weight management indication.

** MTC-22341 is set up to identify incident cases of MTC in patients treated with exenatide or liraglutide, irrespective of dose, indication or trade name.

Abbreviations: MTC = medullary thyroid cancer; NYHA = New York Heart Association; PhV = pharmacovigilance.

The sponsor provided the following relevant details regarding the ongoing and planned pharmacovigilance program (Table 11).

Table 11: Ongoing studies for the indication of weight management.

Study/activity type, title and category (1–3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
NN2211-3784* Optum Database study Category 3	Post-marketing safety surveillance to observe the safety profile of liraglutide when used in a real-life setting in the U.S. To describe and monitor the safety profile of liraglutide and compare the incidence of adverse events with other antidiabetic medications commonly in use	Neoplasms (including thyroid cancer, MTC, pancreatic cancer and overall malignant neoplasms), serious hypoglycaemia, acute pancreatitis, acute renal failure, macrovascular conditions, micro-vascular conditions, thyroid events and hypersensitivity reactions	Ongoing	Final study report 31 Jan 2016
EX2211-3748* LEADER® Category 3	A long-term, multi-centre, international, randomised double-blind, placebo-controlled trial to determine liraglutide effects on cardiovascular events.	Cardiovascular disorders/neoplasms/pancreatitis/anti-liraglutide antibody formation/congestive heart failure	Ongoing	Final study report 30 Mar 2016
NN2211-3880*, CPRD study Category 3	To evaluate the safety of liraglutide in the U.K. population To compare safety outcomes during current use of liraglutide with the safety outcomes during the use of other non-insulin antidiabetic drugs (NIADs). *Addendum study in 3880:* A substudy evaluating the potential risk of neoplasms in patients treated with liraglutide in combination with metformin and insulin	Neoplasms (including malignant neoplasms and thyroid cancer, including MTC), acute pancreatitis and macrovascular conditions	Ongoing	Final study report 30 Jun 2015
MTC registry** MTC- 22341 Category 3	A medullary thyroid cancer case series registry of at least 15 years duration to systematically monitor the annual incidence of medullary thyroid carcinoma in the U.S. and to identify any increase related to the introduction of Victoza® injection into the marketplace.	Medullary thyroid cancer	Ongoing	Final report 15 Sep 2026
NN212291 Nonclinical study Category 3	10-week juvenile toxicity study in the Crl:CD(SD) rat by subcutaneous administration with a 4-week recovery period	Sexual maturation	Ongoing	Final study report 08 Aug 2014

* These studies are conducted in patients with T2DM treated with liraglutide 1.8 mg. The results are considered relevant for all doses of liraglutide although not specifically designed for the weight management indication.

** MTC-22341 is set up to identify incident cases of MTC in patients treated with exenatide or liraglutide, irrespective of dose, indication or trade name.

Abbreviations: MTC = medullary thyroid cancer; NIAD = non-insulin antidiabetic drug; T2DM = type 2 diabetes mellitus.

Australian patients are participating in the LEADER trial.

The sponsor states in the ASA: NN8022-3967: A trial investigating safety and tolerability of liraglutide 3.0 mg in obese adolescents. This study is currently ongoing and in being conducted in Germany; the study started in February 2013 and is expected to be

completed in mid 2014. Australia will not be participating directly in the study but it is expected that the results will be applicable to the Australian clinical setting.

OPR reviewer comment

In all studies except Study NN8022-3967, liraglutide is used at the currently highest approved dose of 1.8 mg, although it is noted that the Medullary Thyroid Carcinoma Surveillance Study (MTC-22341) will collect data of use of liraglutide in all indications. However, at present the indication of weight management is not approved in the USA and consequently, only information is collected related to the currently highest registered dose of 1.8 mg. Should the weight management indication not be approved in the USA then there will be no safety data collected relating to the higher dose of 3 mg for weight management in Study MTC-22341, and the only safety data related to the higher dose of 3 mg will be collected in Study NN8022-3967. **Consequently, it is questioned as to whether these studies will provide safety data which is sufficiently relevant to the weight management indication. It is recommended that the sponsor elaborates on this issue in their Section 31 response, and explains how safety data relevant for the 3 mg dose will be collected if the weight management indication is not be approved in the USA.**

The study protocols for these studies have not been reviewed in detail, as all studies are ongoing at the time of this evaluation and therefore are not considered part of the planned pharmacovigilance program of the RMP.

The sponsor states in the ASA that study NN8022-3967 is expected to be completed in mid 2014. **As this has now passed, it is recommended that the sponsor provides an updated RMP to include any relevant information gathered in this study.**

The final study report for the nonclinical juvenile toxicity Study NN212291 was available on 8 August 2014. **As this has now passed, it is recommended that the sponsor provides an updated RMP to include any relevant information gathered in this study.**

Of note, a clinical development program is ongoing for liraglutide, 1.2 mg and 1.8 mg as an adjunct to insulin in patients with type 1 diabetes. Australia is participating in the largest trial in this multinational trial program (planned patients globally: 1850). However, information gathered in this trial will only be of limited use for the indication of weight management as the dose used in this trial is lower than the proposed dose for weight management.

Risk minimisation activities

The sponsor concludes that no further activities beyond product labelling are required for the product used in weight management at the dose of 3 mg.

OPR reviewer comment

In principle there are no objections to implementing only routine risk minimisation activities, although it is considered that there is a high potential for off label use to achieve weight loss in patients with a BMI below 27 and for off label use in paediatric patients. Further, as the product will be administered by patients at home there is a potential for medication errors and over dose.

As the product is a prescription only medicine, the risk of off label use should be minimised. The combination of information provided in the Consumer Medicines Information (CMI), PI, and Instructions For Use (IFU) appears to be sufficient to reduce the risk of medication errors and over dose to a minimum. However, it is recommended that medication error be added as potential risk to the table of ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

The following section summarises the OPR's first round evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation #1 in RMP evaluation report

Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated Section 31 request and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

Please provide information that is relevant and necessary to address the recommendations made in the RMP evaluation report.

Sponsor response

Novo Nordisk is of the opinion that the RMP adequately reflects the safety concerns addressed in the nonclinical and clinical evaluations.

Evaluator's comment

The sponsor's response has been noted.

Recommendation #2 in RMP evaluation report

As the product will be administered by patients in a home treatment setting, it is recommended that medication error", which should include "medication error in a home treatment setting", be added as potential risk to the table of ongoing safety concerns.

Sponsor response

The sponsor provides a detailed response and concludes that inclusion of "medication error in a home treatment setting" is not warranted.

Evaluator's comment

This is considered acceptable in this instance.

Recommendation #3 in RMP evaluation report

It is noted that "Use in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)" is included as contraindication in the US-PI and the Canada Product Monograph. It is recommended this be included as potential risk in the table of ongoing safety concerns.

Sponsor response

The sponsor provides a detailed response and concludes that inclusion of these potential risks in the table of ongoing safety concern is not warranted.

In particular the sponsor refers to their routine and additional pharmacovigilance activities, which the sponsor claims will "identify any causal relationship between MTC and liraglutide".

Furthermore, the sponsor refers to targeted safety surveillance in their routine pharmacovigilance program.

Evaluator's comment

Whether cases of MTC will be sufficiently examined for personal or family history of MTC MEN 2 has not been sufficiently established.

The targeted safety surveillance appears to refer to targeted follow-up questionnaires. Of note, no follow-up questionnaires have been provided as annex to the RMP.

The sponsor should further clarify how detailed investigations into cases of MTC as a possible consequence of personal or family history of MTC or MEN 2 will be ensured. Follow-up questionnaires should be provided for review.

Recommendation #4 in RMP evaluation report

It is recommended that "Rapid weight loss" be added as potential risk.

Sponsor response

Novo Nordisk believes that "rapid weight loss" is an important risk factor for the development of acute gallstone disease, and it should be highlighted as such in the RMP. Rapid weight loss is a risk factor for the development of clinically important risk of acute gallstone disease. Novo Nordisk has included the risk of acute gallstone disease as an important identified risk in the RMP.

In particular, the sponsor refers to their routine and additional pharmacovigilance activities. Further, the sponsor refers to targeted safety surveillance in their routine pharmacovigilance program.

Evaluator's comment

Whether cases of acute gallstone disease will be sufficiently examined for the possible causality of rapid weight loss **has not been sufficiently established**.

The targeted safety surveillance appears to refer to targeted follow-up questionnaires. Of note, **no follow-up questionnaires have been provided as annex to the RMP**.

The sponsor should further clarify how detailed investigations into cases of acute gallstone disease as a possible consequence of rapid weight loss will be ensured. Follow-up questionnaires should be provided for review.

Recommendation #5 in RMP evaluation report

It is noted that "Cardiovascular disorders" is listed as potential risk in the table of ongoing safety concerns for Victoza but not for Saxenda. Furthermore, in clinical trials tachycardia was reported in 0.6% of patients treated with Saxenda and in 0.1% of patients treated with placebo. It is recommended that "Cardiovascular disorders", which should include tachycardia, be added to the table of ongoing safety concerns for Saxenda.

Sponsor response

Novo Nordisk has included the important potential risk of cardiovascular disorders, including tachycardia, in the RMP for Saxenda. Appropriate pharmacovigilance and risk minimisation activities have also been included.

Evaluator's comment

This is considered acceptable.

Recommendation #6 in RMP evaluation report

In all studies except Study NN8022-3967, liraglutide is used at the currently highest approved dose of 1.8 mg, although it is noted that the Medullary Thyroid Carcinoma Surveillance Study (MTC-22341) will collect data of use of liraglutide in all indications. However, at present the indication of weight management is not approved in the USA and consequently, only information is collected related to the currently highest registered dose of 1.8 mg. Should the weight management indication not be approved in the USA then there will be no safety data collected relating to the higher dose of 3 mg for weight management in Study MTC-22341, and the only safety data related to the higher dose of 3 mg will be collected in Study NN8022-3967. Consequently, it is questioned as to whether

these studies will provide safety data which is sufficiently relevant to the weight management indication. It is recommended that the sponsor elaborates on this issue in their Section 31 response, and explains how safety data relevant for the 3 mg dose will be collected if the weight management indication is not be approved in the USA.

Sponsor response

Saxenda has been approved in the USA (23 December 2014); therefore, the proposed studies should provide sufficient data to characterise the risk of MTC with the higher 3 mg dose.

Evaluator's comment

The sponsor's response has been noted.

Recommendation #7 in RMP evaluation report

The sponsor states in the ASA that Study NN8022-3967 is expected to be completed in mid 2014. As this has now passed, it is recommended that the sponsor provides an updated RMP to include any relevant information gathered in this study.

Sponsor response

Novo Nordisk will do a full update of the RMP in May 2015. This update will include the completed study NN8022-3967. In summary, the results from NN8022-3697 do not provide new information that impacts the benefit-risk balance of Saxenda. The main conclusions from the trial were:

- Treatment with liraglutide was well tolerated in the present obese adolescent trial population and no unexpected safety and tolerability issues were identified compared to adults.
- The pharmacokinetic properties in the adolescent population were found to be consistent with those observed in adults.

Although most of the explorative PD endpoints tended to be numerically in favour of liraglutide, no statistically significant treatment effect was demonstrated for the BMI Z-score, body weight, fasting plasma glucose, HbA1c and serum insulin after 5 weeks of treatment (including dose escalation).

Evaluator's comment

The sponsor's response has been noted.

Recommendation #8 in RMP evaluation report

The final study report for the nonclinical juvenile toxicity Study NN212291 was available on 8 August 2014. As this has now passed, it is recommended that the sponsor provides an updated RMP to include any relevant information gathered in this study.

Sponsor response

Novo Nordisk will update the RMP in May 2015. This update will include the completed nonclinical Study NN212291. In summary, the results from NN212291 did not provide new information that impacts the benefit-risk balance of Saxenda. Safety related findings from this study do not provide any new information from that already included in the RMP. A summary of the relevant conclusions is provided below.

It was concluded that daily SC administration of liraglutide to juvenile Sprague Dawley rats for 10 Weeks produced adverse signs of toxicity among females at a dose level of 0.25 and above, resulting in a marked delay in the attainment of sexual maturation at 0.25 and 1 mg/kg/day and slightly low implantation counts and post partum litter size following mating at 1 mg/kg/day, for which a relationship to treatment could not be discounted. The No Observed Adverse Effect Level (NOAEL) for juvenile female rats was therefore

considered to be 0.05 mg/kg/day. There were no toxicologically significant changes observed among liraglutide treated males, and it was therefore considered that the NOAEL for juvenile male rats was 1 mg/kg/day.

Evaluator's comment

It is brought to the Delegate's attention that study results of the juvenile toxicity study NN212291 are available.

Recommendation #9 in RMP evaluation report

The sponsor should provide a table summarising the planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.

Sponsor response

The TGA Q&A document quoted by the RMP evaluator only requires comparison between the SmPC and PI text and does not require inclusion of the CMI text in the risk management comparison. The TGA requires that the PI and CMI are maintained in parallel so that the information is consistent between those two documents. Therefore, the table in the ASA has been updated to include only the SmPC and PI text.

Evaluator's comment

This is considered acceptable in this instance.

Recommendation #10 in RMP evaluation report

The ASA should be revised to include a risk minimisation activities table detailing all planned risk minimisation measures in the Australian context and the EU-RMP context. This table should include a comparison of the actual content and wording of the EU Summary of Product Characteristics (SmPC) and the proposed Australian PI and CMI for all of the specified ongoing safety concerns and missing information to identify and provide reasons for any observed differences, particularly where it appears the EU SmPC is more restrictive.

Sponsor response

As included in the draft ASA, neither documents (SmPC or PI) are approved and are at different stages of review and negotiation. Novo Nordisk has included a commitment in the ASA to update the risk minimisation comparison table to complete this comparison when the SmPC and the Australian PI are finalised, as per advice from the OPR.

Evaluator's comment

The sponsor's response has been noted.

Recommendation #11 in RMP evaluation report

The sponsor states:

> *It is recommended in the IFU that patients with severe visual impairment should get help from people who are able to read the dose counter. The following statement is included in the IFU. "If you are blind or have poor eyesight and cannot read the dose counter on the pen, do not use this pen without help. Get help from a person with good eyesight who is trained to use the Saxenda prefilled pen."*

It is recommended that this statement also be included in the PI, this will enable physicians to communicate this information to patients prior to patients obtaining the product.

Sponsor response

Novo Nordisk agrees to include the following sentence in the "Dosage and Administration" section of the PI:

> *A patient who is blind or has poor vision, must be instructed to always get help/assistance from another person who has good vision and is trained in using the Saxenda prefilled pen.*

Evaluator's comment

Pending the Delegate's approval this is considered acceptable.

Summary of recommendations

It is considered that the sponsor's response to the TGA Section 31 Request **has not adequately addressed** all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

- The sponsor should further clarify how detailed investigations into cases of MTC as a possible consequence of personal or family history of MTC or MEN 2 will be ensured. Follow-up questionnaires should be provided for review.
- The sponsor should further clarify how detailed investigations into cases of acute gallstone disease as a possible consequence of rapid weight loss will be ensured. Follow-up questionnaires should be provided for review.
- The following statement or a statement to this effect should be included in the PI: The treating physician should determine if self administration is appropriate for the individual patient.
- A statement describing that a personal or family history of MTC or MEN 2, are risk factors for the development of MTC, should be included in the PI.
- A statement describing that the product is produced in yeast cells, as it is included in the PI, should be included in the CMI.
- The amended CMI should be provided prior to approval (see 18 section 5).

Issues arising following the sponsor's Section 31 response

- It is brought to the Delegate's attention that study results of the juvenile toxicity study NN212291 are available.

Comments on the safety specification of the RMP

Clinical evaluation report

The Safety Specification in the draft RMP is satisfactory.

Nonclinical evaluation report

Results and conclusions drawn from the nonclinical program for liraglutide detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator.

Key changes to the updated RMP

EU-RMP version 2, edition 19, dated 9 December 2013 and ASA version 1.0, dated 30 June 2014 has been superseded by:

- EU-RMP version 8, edition 20, date 11 February 2015 and ASA version 3.0, dated 19 February 2015

The new ongoing safety concerns are shown in Table 12.

Table 12: Updated ongoing safety concerns.

Updated ongoing safety concerns	
Important identified risks	Hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only) Gastrointestinal adverse events Altered renal function Allergic reaction Acute gallstone disease Pancreatitis
Important potential risks	Hyperglycaemia due to discontinuation of insulin Medullary thyroid cancer Neoplasm (including breast cancer) Pancreatic cancer Cardiovascular disorders Immunogenicity – anti-liraglutide antibody formation Immunogenicity – immune complex disorders
Missing information	Children and adolescents < 18 years Pregnant and lactating women Patients with severe hepatic impairment Patients with severe renal impairment Patients with congestive heart failure NYHA III-IV Patients with a history of major depression or other severe psychiatric disorders Concomitant use of other weight lowering products Off-label use

NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus

RMP evaluator comment

The evaluator has no objection to the above changes and recommends to the Delegate that the updated version is implemented.

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

- The EU-RMP version 8, edition 20, date 11 February 2015 with ASA version 3.0, dated 19 February 2015, to be revised to the satisfaction of the TGA, must be implemented (see outstanding issues above).

VI. Overall conclusion and risk/benefit assessment

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

Quality

There were no objections to registration from the biological-chemistry evaluator.

- The manufacturing process is identical to that of the currently approved Victoza up until assembly.
- The composition of liraglutide 6.0 mg/ml remains unchanged from that of the currently approved Victoza.
- The primary packaging material is a 3 ml glass cartridge which is identical to that of the currently approved Victoza. However, liraglutide 6.0 mg/ml, 3 ml cartridge for use in weight management is assembled in a prefilled pen injector PDS290. This pen injector is different to that of the currently approved Victoza.
- Biopharmaceutic data were not required for this product because the route of administration is the same as that for the currently approved Victoza.

Nonclinical

There were no nonclinical objections to the registration of Saxenda.

Clinical

The clinical evaluator considered that the risk-benefit profile was unfavourable (see clinical evaluation report) because:

- Population group need to be taking a reduced calorie diet and on an exercise plan to achieve benefits seen in the trial.
- If they do this and take Saxenda, then some of them will lose 5-10% of body weight, but many will not.
- And all will be exposed to the risk of toxicity, which is predominantly symptomatic (for example, gastrointestinal side effects) but can also be serious (hypoglycaemia, immunogenicity, pancreatitis).
- Long term data is lacking: side effects are possible for all users but also rebound weight gain is likely.

Pharmacokinetic and pharmacodynamic studies

The pharmacokinetic properties of liraglutide 3.0 mg in obese or overweight people are similar to those for liraglutide 1.8 mg in healthy volunteers and T2DM patients. Exposure is mainly influenced by sex (lower in men) and body weight. Exposure may be low in very obese men; and high in obese women of lower weight (<60 kg).

Liraglutide reduces weight mainly through reduced appetite (mechanism not entirely understood) and therefore less food intake. Liraglutide also has beneficial effects on fasting plasma glucose, postprandial glucose, and glucagon levels. Increased heart rate is a class effect of GLP-1 analogues.

In the Victoza (liraglutide 1.8 mg) QTc trial, no QTc interval prolongation was observed. This was confirmed for Saxenda by an analysis of ECGs from a subset of patients in the Phase III program.

Efficacy

There was one Phase II dosing finding study (1807) and four Phase III trials (1839, 1922, 3970, 1923). The program was developed in consultation with EMA.

Inclusion criteria

As per the 2007 EMA guideline[13] adopted by the TGA, the participants recruited into the trials had a degree of obesity associated with an increased health risk; and, in particular, an increased risk of mortality. This was operationalised as BMI >30 or >27 in patients with significant comorbidities such as, hypertension, hyperlipidaemia, diabetes, cardiovascular disease. This was retained for the proposed indication.

Patients with obesity due to endocrine disorders (for example, Cushings syndrome) or treatment with drugs that might cause weight gain (for example, insulin, psychotropic drugs) or eating disorders were excluded from the trials.

Inclusion criteria by study

These are shown in Table 13.

Table 13: Inclusion criteria.

Phase	Study	n	Inclusion criteria
Phase II	1807	564	BMI: 30-40 kg/m2; T2DM excluded
Phase III	1839	3731	BMI≥30 or BMI≥27 with co-morbidities, overt T2DM excluded; stratified by pre-diabetes
Phase III	1922	846	T2DM & BMI≥27 (1.8 mg arm; in addition to 3.0 mg and placebo arms)
Phase III	1923	422	BMI≥30 or BMI≥27 with dyslipidaemia &/or hypertension; overt T2DM excluded Prior 5+% weight loss with a 1200 kCal diet
Phase III	3970	359	BMI≥30; T2DM excluded; moderate-severe obstructive sleep apnoea

Intervention

The 3.0 mg dose was used in all the Phase III trials. Dose titration was done in all the trials. That is, Saxenda was initiated at 0.6 mg per day for one week, and increased at weekly intervals until a dose of 3.0 mg was reached.

Various doses up to 3.0 mg were used in the Phase II study (1807). The Phase III study in T2DM patients (1922) included a 1.8 mg arm.

[13] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

Comparator

The EMA agreed that placebo comparator was acceptable, given that there is no accepted, standard pharmacological approach to weight loss. That is, Saxenda was an add-on to baseline exercise and diet; and the comparator was "add on" placebo.

Duration

All the studies had data to 52 weeks, except Study 3970 (patients with obstructive sleep apnoea), which was only of 32 weeks duration. For the Phase II study (1807), the primary analysis was at 20 weeks, but there were also analyses at 52 and 104 weeks.

Baseline data

Pooling data across all 5 studies:

- Men: 29%
- BMI <30: 5%
- 65+ years: 7%
- 75+ years: 0.4%

Comparison of patient populations included in the clinical development programs for Saxenda (weight loss) versus Victoza (T2D)

On average, the participants in the Saxenda development program were younger (47 years versus 55 years), heavier (mean weight 106 kg versus range 80-100 kg), and had a lower rate of cardiovascular events.

Missing data

Only 70% of participants completed the Phase III trials: liraglutide: 72%; placebo: 66%. This is typical of trials for weight loss products.

More participants on liraglutide 3.0 mg discontinued due to adverse events (for example, gastrointestinal upset) than placebo (~11% versus 4%). Fewer participants in the liraglutide group, compared to placebo, withdrew due to "ineffective therapy" (~1% versus 3%).

However, as is usually the case in trials with a high percentage of withdrawals, the commonest categories in the subject disposition table were: "withdrawn consent" (that is, unspecified) and "other loss to follow-up". It is probably reasonable to assume that many of these were due to ineffective therapy or adverse events (for example, gastrointestinal upset), but this information was not captured; for the obvious reason that the withdrawals/losses to follow-up were no longer participating in the study and did not want any further contact with the researchers. Participants, who withdrew were asked to come in for a visit at the end of the study (typically at Week 56), but only one-quarter accepted this invitation.

Various methods are available to impute missing data. Historically, last observation carried forward (LOCF) is probably the most commonly used method.

In a single group of patients with depression, LOCF is probably conservative (that is, tends to under-estimate the improvement over time) because in most patients, depression will resolve. However, when comparing two groups, it can be difficult to know what effect LOCF has on the comparative treatment effect. The under-estimation could be relatively greater in the placebo group than the treatment group and this might lead to over-estimation of the comparative treatment effect.

In a single group of patients wanting to lose weight, LOCF probably does not result in a conservative estimate of weight loss over time. This is because patients tend to regain weight over time (unlike depression, which tends to improve over time).

The sponsor submitted a modified baseline observation carried forward (BOCF) imputation, in which patients, who gained weight, before being lost to follow-up, had their final results imputed using LOCF. The sponsor also provided an unmodified BOCF imputation.

As briefly outlined above, although the likely direction of the effect of these different imputation methods can be predicted in a single group, it can be difficult to predict the direction of their effects in a comparative analysis across two groups.

In the results given below, the standard LOCF results are presented by default, with completers and unmodified BOCF results provided as a sensitivity analysis.

Selected results for the two studies that compared doses

Phase II Study 1807 (BMI 30-40, T2DM excluded)

These are shown in Tables 14-15.

Table 14: 20 weeks, ITT, last observation carried forward (LOCF).

	Placebo	Liraglutide mg				Orlistat
		1.2	1.8	2.4	3.0	
n	98	94	90	92	92	95
Change in body wt (kg)	-2.8	-4.8	-5.5	-6.3	-7.2	-4.1
5% responders	29.6	52.1	53.3	60.9	76.1	44.2
10% responders	2.0	7.4	18.9	22.8	28.3	9.5

Table 15: 52 weeks, ITT, last observation carried forward (LOCF).

	Placebo	Liraglutide mg				Orlistat
		1.2	1.8	2.4	3.0	
n	98	94	90	92	92	95
Change in body wt (kg)	-2.7	-4.6	-6.2	-7.0	-8.9	-4.7
5% responders	27.6	45.7	53.3	53.3	75.0	45.3
10% responders	10.2	18.1	26.7	29.3	37.0	15.8

Phase III Study 1922 (T2DM, BMI>27)

This is shown in Table 16.

Table 16: 56 weeks, ITT, last observation carried forward (LOCF).

	Placebo	Liraglutide mg	Liraglutide mg
		1.8	3.0
n	211	204	412
Change in body wt (kg)	-1.96	-4.6	-5.9
5% responders	12.7	35.0	49.9
10% responders	3.8	13.3	22.1

Results for weight loss

This is shown in Table 17.

Table 17: Placebo-subtracted, percentage weight loss, LOCF.

Phase	Study	n	Point estimate (95% CI)
Phase II	1807	564	-6.08 (-7.84, -4.33)
Phase III	1839	3731	-5.39 (-5.82, -4.95)
Phase III	1922	846	-3.95 (-4.82, -3.08)
Phase III	1923	422	-6.06 (-7.50, -4.62)
Phase III	3970	359	-4.15 (-5.21, -3.09)
Phase III, 56 week studies			-5.24 (-5.61, -4.86)
Pooled			-5.18 (-5.53, -4.83)

Using LOCF to impute missing data, pooled average weight loss was 7.5% (7.8 kg) with liraglutide 3.0 mg versus 2.3% (2.5 kg) with placebo. The placebo subtracted weight loss (LOCF) was 5.2% (see last row of above table).

The completer's analysis gave a placebo subtracted weight loss of 5.6%.

Baseline observation carried forward: 4.5%.

The results were consistent across studies with the exception of Study 1922, where there was less weight loss, but this was expected because it was in patients with T2DM.

Weight loss was consistent across subgroups, although there was less weight loss for men (-3.6%) compared with women (-5.8%).

In the pooled 56 week studies, 31% of patients on liraglutide achieved a 10% weight loss, compared with 8% for placebo. For completers, it was 38% versus 13%.

More details for the individual studies and weight loss results, including results reported as 5% and 10% responders, are given in the Clinical Evaluation Report (section 7).

Numerous **secondary endpoints** were analysed (for example, HbA1c, fasting plasma glucose, systolic blood pressure). These were generally consistent with the results for weight loss. Details are given in the clinical evaluation report.

Study 3970, reported on the AHI, had an average baseline value of 49.2 events/hour, which reflects a population with severe disease. The improvement over 32 weeks was greater for liraglutide than placebo (-12.2 versus -6.1 events/hour). This is related to weight loss, as expected. Interpretation of these results is difficult because there is no established/agreed minimal clinically important difference (MCID). There were also positive changes in sleep related patient reported outcomes; although interpretation of the clinical relevance of these results is difficult.

Effect of treatment discontinuation

Study 1839: after 56 weeks, participants with pre-diabetes at screening who completed on liraglutide were re-randomised to either:

- liraglutide (that is, liraglutide/liraglutide), 351 participants,
- placebo (that is, liraglutide/placebo), 304 participants.

Follow-up was for a further 3 months.

Results were:

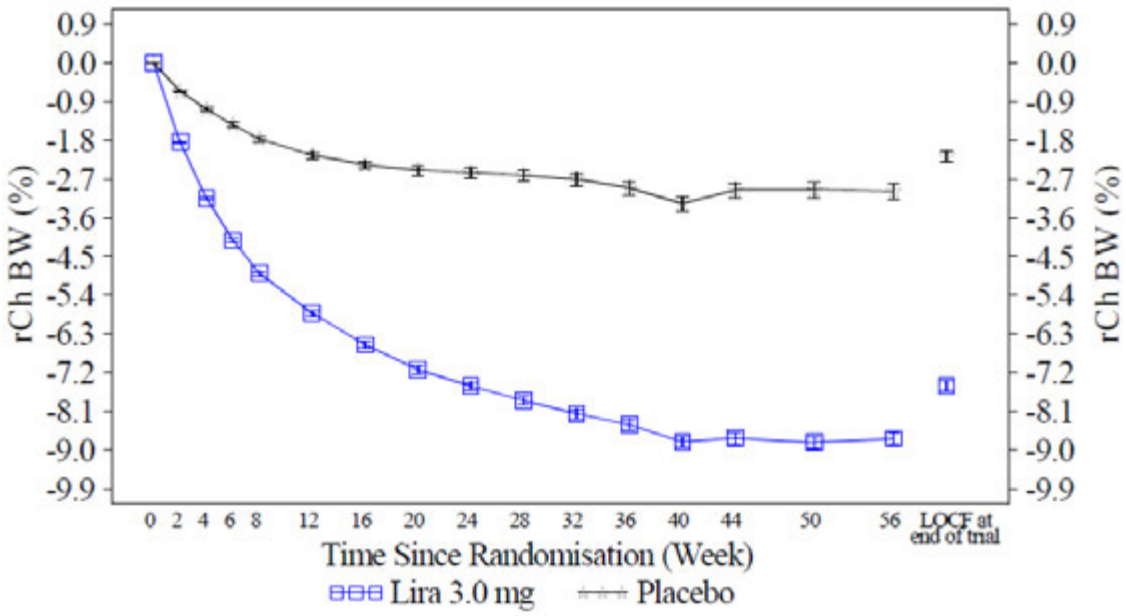
- liraglutide/liraglutide: re-gained 0.7% of body weight (0.6 kg)
- liraglutide/placebo: re-gained 2.9% of body weight (2.6 kg)

Although the liraglutide/placebo group re-gained 2.9% of body weight, their overall weight loss from the beginning of the study was still greater than for those participants originally randomised to placebo (6.8%, 6.7 kg versus 3.1%, 3.3 kg).

Continuing weight loss on liraglutide

The available data show that, for the average/typical patient who continues on liraglutide, weight loss continues to 40 weeks; after which, for the typical patient, small increases in weight occur (Figure 2).

Figure 2. Pooled studies, body weight percentage change from baseline liraglutide (n = 3301) versus placebo (n = 1890).



Information in PI about stopping

The sponsor conducted various analyses of data from the two largest Phase III studies (1839, 1922) in an attempt to predict non response. Positive predictive and negative predictive values of about 75% were obtained using criteria of 3% weight loss at Week 12 or Week 16 or 4% weight loss at Week 16. After negotiation with the EMA, the sponsor agreed to include the following in the SmPC: "Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg dose if patients have not lost at least 5% of their initial body weight." This is included in the SmPC.

The FDA PI does not have a similar statement. Both the EMA SmPC and the FDA PI have information under posology that the prescriber should consider discontinuing treatment if dose escalation is not tolerated.

Safety

The analysis of safety is based on the pooled analysis of the one Phase II study and the four Phase III studies. Data from Victoza in T2DM (1.8 mg) was used as supporting information. In general the adverse event data for Saxenda is consistent with that for Victoza.

Numbers were as follows:

- Exposure to liraglutide for weight loss: 3872 patients
- Exposure to liraglutide, 3.0 mg, for weight loss for at least 12 months: 2341 patients.

The most commonly reported adverse events were gastrointestinal disorders, which is similar to that of Victoza. Nausea occurred in 39% of the liraglutide (3 mg) group versus 14% in the placebo group. Many patients experience nausea in the first weeks of treatment during dose titration. The efficacy of dose titration to reduce GI AEs and improve tolerability was not assessed. That is, dose titration was used in all experimental groups, and there was no comparison to a group who did not have dose titration. Vomiting, constipation and diarrhoea were also more common with Saxenda.

Asthenic conditions like fatigue occur early and with increased incidence with liraglutide (8% versus 5%).

Decreased appetite occurred in line with the mechanism of action of liraglutide (10% versus 2%).

Hypoglycaemia

High levels of GLP-1 have been implicated in hypoglycaemia in fasting patients after glucose administration (reactive hypoglycaemia) and after Roux-en-Y Gastric Bypass surgery.

For patients without T2DM, no severe hypoglycaemia was reported. Any (non severe) hypoglycaemia reported as an adverse event was low: liraglutide, 3 mg (1.6%), placebo (1.1%).

For patients with T2DM, severe hypoglycaemia was reported for 1% of patients in the liraglutide 3.0 mg group (3 patients) and 1% of patients in the placebo group (2 patients) and occurred only in patients taking concomitant sulphonylurea.

Pulse rate

GLP-1 analogues are known to increase pulse rate. The mechanism has not been established, but is possibly via GLP-1R in the cardiac pacemaker.

Based on the pool of the 5 trials (1 Phase II + 4 Phase III), the mean resting pulse rate increased after the start of treatment in the liraglutide 3 mg group and peaked at 6 weeks

(mean change from baseline: 4.5 bpm; placebo: 1.1 bpm). The effect declined over time, but was still 2.8 bpm higher than placebo at the end of the trials.

The effect on pulse rate is of similar size for the 1.8 mg dose and the 3.0 mg dose.

MACE

The pre-specified MACE (cardiovascular death, non fatal stroke, myocardial infarction) analysis for the weight loss trials gave a pooled hazard ratio of 0.40 (95% CI: 0.15, 1.05). This was based on 17 events. The pooled analysis for the diabetes trials gave a similar result.

QTc studies

In the Victoza (liraglutide 1.8 mg) QTc trial, no QTc interval prolongation was observed. This was confirmed for Saxenda by an analysis of ECGs from a subset of patients in the Phase III program.

Pancreatitis

There has been concern about an increased risk of pancreatitis with incretin-based therapies, including liraglutide.

In a 2014 paper in the *New England Journal of Medicine*,[14] the EMA and FDA stated that both agencies agreed that the hypothesis that there is a casual association between incretin based therapies and pancreatitis or pancreatic cancer is not supported by the available data. Both agencies are continuing to investigate this safety signal.

In the weight loss program, adjudicated events of acute pancreatitis were greater for liraglutide than placebo: 7 events versus 1 event; 0.2 events per 100 person-years versus <0.1 events per 100 person-years.

The only comparison to T2DM was for non adjudicated events and these can be subject to inconsistent reporting. Setting this methodological problem aside, the rate of pancreatitis was higher in the weight loss trials than for T2D: 0.6 events per 100 person-years versus 0.2 events per 100 person-years. This could be related to the increased dose used in the weight-loss program (3 mg versus 1.8 mg) or the different diseases. The sponsor has made the point that obesity is associated with an increased risk of pancreatitis.

Acute gallstone disease

This was higher for liraglutide 3 mg (2.3%) versus placebo (0.9%). Although the risk was related to weight loss (increased risk with increased weight loss), the increased risk was observed across all weight loss categories, suggesting other factors might also be involved.

There have been no previous safety concerns about gallstone disease from clinical trials or post marketing data for T2DM (Victoza, 1.8 mg). Hypothesised mechanisms include an increased risk of gallstone formation, induced by weight loss (perhaps leading to an increased risk of pancreatitis), or decreased gallbladder emptying.

Renal failure

This is mentioned in the Victoza PI as a risk and will also be mentioned in the Saxenda PI. It is probably related to dehydration caused by GI AE.

Neoplasms

Breast cancer occurred more frequently in women treated with liraglutide 3.0 mg versus placebo (0.4 events per 100 person-years versus 0.1 events per 100 person-years). Breast cancer was too infrequent in the clinical trials to make any definitive conclusions about

[14] Egan AG, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med* 370: 794-7.

the possible effect (or possibly long term effect of) liraglutide treatment on breast cancer risk. Human breast cancers do not express the GLP-1R.

In the weight management trials, there were no reports of exocrine pancreatic cancer.

In the clinical development program for T2DM, liraglutide was shown to cause dose-dependent and treatment duration dependent medullary thyroid tumours in rodents. Medullary thyroid cancers are an extremely rare form of human cancer. Several post approval commitments (case series registry, pharmaco-epidemiological studies) are underway for Victoza, as mandated by EMA and FDA. There is no evidence, so far, that the rodent findings are generalizable to humans. One medullary thyroid cancer was diagnosed in the placebo group during the development program for weight loss (Saxenda).

Immunological events

Anaphylactic reactions are described as rare in both the approved Victoza and proposed Saxenda PIs. This is supported by the available data.

Injection site reactions

These were more frequent with Saxenda (14%) than placebo (11%); but more frequent than in the T2DM development program: Victoza (2%), placebo (2%).

Older patients

Numbers of patients 75 years or older in the clinical development program are limited. The proposed text in the PI is: "No dose adjustment is required based on age. Therapeutic experience with patients 75 years or older is limited."

Safety beyond 12 months of treatment

There is little data available and the data that are available (extension to the dose-finding trial 1807) have several limitations:

- There was no placebo group
- Treatment with liraglutide and orlistat were open label
- Only 47 patients completed the second year of treatment with 3.0 mg of liraglutide

Lack of long term safety data is not listed as "missing information" in the "summary of safety concerns", however, the concerns are captured under "important potential risks".

Risk management plan

FDA Risk Evaluation and Mitigation Strategy (REMS)

The FDA has implemented a Risk Evaluation and Mitigation Strategy (REMS) to notify healthcare practitioners about the potential risk of medullary thyroid cancer and acute pancreatitis with Saxenda.

The content of the FDA communication to healthcare providers is as follows:

- *Potential Risk of Medullary Thyroid Carcinoma*

  Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.

- *Risk of Acute Pancreatitis*

> *Based on spontaneous postmarketing reports, acute pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with liraglutide.*
>
> *In clinical trials studying Saxenda, there were more cases of pancreatitis in patients treated with Saxenda than in patients treated with placebo.*

The FDA PI for Saxenda and Victoza also carries a boxed warning:

> *WARNING: RISK OF THYROID C-CELL TUMORS*
>
> *Liraglutide causes thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Saxenda causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, as the human relevance of liraglutide-induced rodent thyroid C-cell tumors has not been determined.*
>
> *Saxenda is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the risk of MTC and the symptoms of thyroid tumors.*

There is no boxed warning on the EU SmPC for either Victoza or Saxenda. There is no boxed warning on the Australian PI for Victoza.

Post marketing studies

The pharmacovigilance program underway for Victoza is also applicable to Saxenda, although the indication and doses differ. The main planned studies are:

- LEADER (Victoza, T2D, 1.8 mg): randomised international safety study, mainly concerned with cardiovascular endpoints, but also reporting on cancers, pancreatitis, and anti liraglutide antibodies. (due to report 30 March 2016).
- Follow-up of 1839 (Saxenda, 3.0 mg, BMI>30 or BMI>27 with co-morbidities, overt T2D excluded) for data on breast neoplasms (due to report August 2015).
- Non randomised safety surveillance studies in UK and US (seems to be only planned for Victoza).
- Medullary thyroid cancer case series registry (seems to be only planned for Victoza).

Conditions of registration

- Implement the EU-RMP version 8, edition 20, date 11 February 2015 with ASA version 3.0, dated 19 February 2015, to be revised to the satisfaction of the TGA.
- Advise the TGA of any studies relevant to Saxenda as soon as they become available.

Risk-benefit analysis

Delegate's considerations

Obesity is an important health problem. Pharmacological treatments for obesity have a mixed track record.

Obstacles to the uptake of Saxenda include:

- it requires subcutaneous injection
- it causes nausea (and other gastrointestinal upset) in many patients.

Efficacy

- The average placebo subtracted weight loss with Saxenda, after 12 months, was between 4.5% and 5.6%, depending on how missing values were imputed. This level of weight loss is likely to have beneficial effects on morbidity and mortality. This is average weight loss. Particular individuals might achieve better (or worse) results. The EMA has included a stopping recommendation in the SmPC, which might facilitate better efficacy in patients who continue; and protect other patients from long-term use of a therapy that does not have efficacy for them.
- The large amount of missing data (30%) seen in the clinical development program is typical of studies of pharmaceutical agents for weight loss. Nevertheless, it is a major shortcoming of the clinical development program and complicates interpretation of the results. In particular, the average placebo subtracted treatment effect for the ITT population cannot be known with any certainty.
- For study participants who remained on Saxenda, weight loss peaked at about 40 weeks; after which, small increases in weight occurred.
- Some weight is re-gained when Saxenda is stopped. It is possible that all the weight could re-gained over time; that is, a return to baseline.
- As expected, average placebo adjusted weight loss in T2DM patients (Study 1922) was lower than the overall pooled estimate (4.0% versus 5.2%). Within the T2D group, weight loss was greater with the 3.0 mg dose than the 1.8 mg dose. Also, parameters of glycaemic control were better. However, there are no data on whether patients, for whom T2DM is major consideration, should be moved to the higher dose.

Safety

- The safety profile of Saxenda (3.0 mg) is similar to that of Victoza (1.8 mg). The higher dose used for weight loss seems to have little effect on the rate of AEs, except for GI events, which are more frequent with the 3.0 mg dose. Nausea occurred in most patients during dose titration and is probably the most common reason for discontinuation.
- Increased pulse rate is a class effect of GLP-1 analogues. In the Saxenda development program, the placebo subtracted increase in pulse rate peaked at 3.4 bpm at 6 weeks and then declined; however it was still 2.8 bpm higher than placebo at 56 weeks. There was no suggestion of dose response. There is limited information on the long term (>12 months) effect of this increase in pulse rate and therefore some uncertainty remains around this issue. The pre-specified MACE (cardiovascular death, non fatal stroke, myocardial infarction) analysis for the weight loss trials gave a pooled hazard ratio of 0.40 (95% CI: 0.15, 1.05) provides some reassurance, although this was based on only 17 events. The pooled analysis for the diabetes trials gave a similar result. Because the increase in pulse rate is not dose dependent, data from the large post marketing safety studies of liraglutide 1.8 mg (Victoza) LEADER should be informative.
- There is a lack of long term safety data and the current data are insufficient to assess whether uncommon events, such as neoplasms, pancreatitis and MACE occur more frequently with the 3.0 mg dose versus the 1.8 mg dose. Also, the precise risks of these uncommon adverse events, with long term use, have not been characterised for either dose.

Summary of issues

Efficacy

- The sponsor submitted one Phase II study and four Phase III studies. About 30% of the participants did not complete these studies, but this is typical of weight loss studies. This missing data complicates the interpretation of the results. The sponsor has provided estimates of the placebo subtracted weight loss for the ITT population of between 4.5% and 5.6%, depending on how the missing data are dealt with. The EMA and FDA have accepted the placebo subtracted weight loss as being "clinically relevant".
- The EMA SmPC has a recommendation in the Indication about stopping, in attempt to predict non response:

  Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg dose if patients have not lost at least 5% of their initial body weight.

- For study participants who remained on Saxenda, weight loss peaked at about 40 weeks; after which, small increases in weight occurred.
- In the submitted studies, some weight was re-gained when Saxenda was stopped. It is possible that all the weight could re-gained over time; that is, a return to baseline.

Safety

- Adverse events for liraglutide 3.0 mg for weight loss are similar to those for liraglutide 1.8 mg for T2DM; although there was more nausea (and other gastrointestinal symptoms).
- Unsurprisingly, interpretation of the available pre-market data (one Phase II and four Phase III studies) for uncommon AEs such as neoplasms, pancreatitis, and cardiac events, was limited because of follow-up for most patients in the studies was for 12 months (the data for the subgroup with 24 month follow-up had some limitations). Also, the sample size was based on the efficacy endpoint of weight loss, not on adverse events. As for most new products, there were limited data about the risk associated with long term use. The EMA and FDA were satisfied that there were no signals from the current data that would prohibit registration.
- Increased pulse rate is a class effect of GLP-1 analogues. For liraglutide, it does not seem to be dose dependent (that is, there is a similar increase with both the 3.0 mg and 1.8 mg doses). The results of LEADER trial (1.8 mg, T2DM) are due in 2016.

Proposed action

The Delegate has no reason to say, at this time, that Saxenda should not be approved for registration.

Question for sponsor

Please clarify the post marketing studies (underway or planned) for Victoza and Saxenda and how they will reduce uncertainties around the safety of liraglutide for weight loss; and, in particular, the long term safety.

Request for ACPM advice

- Have the efficacy and safety of Saxenda for the proposed indication of weight management in adult patients been satisfactorily established by the data submitted by the sponsor?

Response from sponsor

Summary

Novo Nordisk believes that the benefit-risk balance of liraglutide 3.0 mg is positive and in favour of approval of liraglutide 3.0 mg for weight management. Below, a summary of the discussion in the subsequent sections is provided.

- The proposed indication has been updated to include a stopping rule recommending treatment discontinuation if a patient has not lost ≥5% of initial body weight following 12 weeks of treatment with liraglutide 3.0 mg/day.
- Among early responders, that is, subjects continuing treatment following stopping rule assessment:
  - 86% of the subjects lost ≥5% of the baseline body weight.
  - 51% of the subjects lost ≥10% of the baseline body weight.
  - mean weight loss was 11.2% in those completing one year of treatment.
- According to the NHMRC Clinical Practice Guidelines,[15] a 5% weight loss is associated with significant health benefits including improvements in obesity related co-morbidities.
- Obesity is a chronic, relapsing condition requiring ongoing management.[16] Liraglutide 3.0 mg is a valuable treatment for weight management and should be continued as long as there is a clinical benefit, including prevention of weight regain.[17]
- Treatment with liraglutide 3.0 mg is associated with significant improvement in the following obesity related co-morbidities and parameters:
  - Glycaemia (HbA_{1c} reduction, reversal of pre-diabetes, delayed progression to T2DM).
  - Cardiovascular risk markers (reductions in blood pressure, waist circumference, lipids) o Severity of obstructive sleep apnoea (reductions in AHI).
  - Health related quality of life (improvements in physical function and mental health).
- The efficacy and safety of liraglutide for weight management is well-documented; the exposure to liraglutide 3.0 mg in the weight management programme is in accordance

[15] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Canberra: 2013.

[16] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013; Ferguson C, et al. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention, 14 Aug 2012; European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007; European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical: Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocr Pract.* 17 (Suppl 2): 1-53 (2011); Jensen MD, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 129(25 Supplement 2): S102-40 (2013); Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Developing products for weight management. Draft Guidance. Feb 2007.

[17] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013.

with the requirements in the TGA adopted ICH-E1 guidance[18] and the TGA adopted 2007 EMA regulatory guideline.[19]

- In the completed Phase II and III trials 3384 subjects were exposed to liraglutide 3.0 mg (2974 patient years of exposure); of these >2300 subjects were exposed for ≥1 year.
- In the extension to Studies 1839, 903 and 694 subjects have been exposed to liraglutide 3.0 mg for ≥2 years and 3 years, respectively.

For the identified safety concerns, the PI includes appropriate precautions. In addition, relevant pharmacovigilance activities are in place to provide further insight into the safety profile.

The clinical relevance of the effect of liraglutide 3.0 mg on body weight and obesity related parameters

In the TGA adopted guideline on clinical evaluation of medicinal products used in weight control, two alternative primary efficacy endpoints are defined:[20]

- Mean weight loss: ≥10% of baseline weight, which is also ≥5% greater than that associated with placebo.
- Categorical weight loss: Proportions of responders (>10% weight loss at the end of a 12- month period) in the various treatment arms.

The efficacy of liraglutide 3.0 mg has been demonstrated in five phase 2 and 3 trials with durations of up to 56 weeks. Liraglutide 3.0 mg was consistently superior to placebo on all mean and categorical weight related endpoints in each of the five trials and in the pooled analyses (Table 18). Importantly, the proportion of subjects who achieved >10% weight loss at end of treatment was statistically significantly greater with liraglutide 3.0 mg than with placebo (Table 18); thus, the categorical primary efficacy endpoint stipulated in the TGA adopted 2007 EMA guideline[21] was met. In further support of the clinically relevant effect of liraglutide 3.0 mg on body weight, liraglutide 3.0 mg was superior to orlistat (trial 1807), the only medicine currently approved for long term weight management in Australia.

[18] International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. E1: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of nonlife-threatening conditions. 27 Oct 1994.
[19] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[20] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[21] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

Table 18: Mean (%) and categorical (% of subjects) weight loss in the liraglutide 3.0 mg for weight management programme – end-of-treatment.

	Mean weight loss (%)			≥5% weight loss (% subjects)			>10% weight loss (% subjects)		
	Lira 3.0 mg	Placebo	ETD	Lira 3.0 mg	Placebo	OR	Lira 3.0 mg	Placebo	OR
1839	-7.99	-2.60	-5.39*	63.5	26.6	4.80*	32.8	10.1	4.34*
1922	-5.93	-1.98	-3.95*	49.8	13.5	6.39*	22.9	4.2	6.81*
3970	-5.73	-1.58	-4.15*	46.4	18.1	3.92*	22.4	1.5	18.96*
1923$	-6.26	-0.20	-6.06*	50.7	21.3	3.81*	27.4	6.8	5.14*
1807	-9.18	-3.09	-6.08*	78.1	29.7	8.47*	35.9	9.7	5.21*
Pooled LOCF	-7.49	-2.30	-5.18*	60.3	24.1	4.80*	30.5	8.4	4.78*
Pooled completers	-8.73	-3.10	-5.64*	70.4	32.3	5.00*	38.2	12.7	4.24*

* p <0.0001
For the individual trial and in the pooled analysis, missing data were imputed using the last observation carried forward (LOCF). Mean body weight loss (%) and the estimated treatment difference (ETD) between liraglutide 3.0 mg (lira 3.0 mg) and placebo were estimated by an ANCOVA model; categorical weight loss and the treatment odds ratio (OR) were estimated by a logistical regression analysis. End-of-treatment was 56 weeks for trials 1839, 1922 and 1923, 32 weeks for trial 3970 and 52 weeks for trial 1807.
$ Weight loss achieved in trial 1923 followed a preceding weight loss of ≥5% induced by a low caloric diet during run-in.

While the estimated placebo adjusted mean weight loss with liraglutide 3.0 mg was ≥5% in most trials and in the pooled analyses, Novo Nordisk acknowledges that a baseline-adjusted weight loss of ≥10% was not reached; that is, the weight loss did not meet the mean weight loss primary endpoint (see above) stipulated in the TGA adopted 2007 EMA guideline.[22] Notably, however, the recent Australian NHMRC[23] and RACGP[24] clinical guidelines, guidelines from other scientific societies[25] and the FDA[26] and the 2014 EMA[27] draft guidelines all acknowledge that a modest 5-10% weight loss is associated with significant health benefits, including improvements in obesity related co-morbidities such as pre-diabetes, T2DM, hypertension, hyperlipidaemia and CV disease. Specifically, the Australian NHMRC guideline[28] acknowledges that a modest weight loss provides a range of health benefits:

- *"Adults who are overweight or obese can be strongly advised that modest weight loss reduces cardiovascular risk factors.*
- *Adults with prediabetes or diabetes can be strongly advised that the health benefits of modest weight loss include prevention, delayed progression or improved control of type 2 diabetes.*

[22] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[23] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013.
[24] Grima M, Dixon JB. Obesity--recommendations for management in general practice and beyond. *Aust Fam Physician* 42: 532-541 (2013).
[25] Jensen MD, et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 129(25 Supplement 2): S102-40 (2013); Yumuk V, et al. An EASO position statement on multidisciplinary obesity management in adults. *Obes. Facts* 7: 96-101 (2014).
[26] Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Developing products for weight management. Draft Guidance. Feb 2007.
[27] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[28] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013.

- *Adults with kidney disease or sleep apnoea can be advised that improvements in these conditions are associated with a 5% weight loss.*
- *Adults with musculoskeletal problems, gastro-oesophageal reflux or urinary incontinence can be advised that weight loss of 5% or more may improve symptoms.*
- *Adults who are overweight or obese can be advised that quality of life, self-esteem and depression may improve, even with small amounts of weight loss."*

Accordingly, in addition to weight loss, liraglutide 3.0 mg treatment was associated with statistically significant and clinically relevant improvements in several of these obesity related co-morbidities and validated risk parameters for CV disease[29] versus placebo:

- Improvements in glycaemia (that is, reductions in HbA1c) across sub-populations with prediabetes (-0.34% versus -0.1%) and T2D (-1.3% versus -0.4%).
- More subjects with pre-diabetes at baseline had reversal of their pre-diabetes (69.2% versus 32.7%) and fewer progressed to T2D (0.2% versus 1.1%) after 1 year.
- Improvements in cardiometabolic parameters in the pooled analyses; systolic blood pressure (-3.74 versus -0.81 mmHg), diastolic blood pressure (-2.02 versus -1.18 mmHg), waist circumference (-7.6 versus -3.6 cm), BMI (-2.8 versus -0.9 kg/m^2) and the lipid profile.
- Reduced severity of obstructive sleep apnoea as assessed by change in the AHI (-12.2 versus -6.1 episodes/hour).
- Improvements in health related quality of life, indicating favourable effects on physical function and mental health.

The beneficial effects of liraglutide 3.0 mg on body weight and secondary parameters were seen across a broad range of subpopulations. Thus, no subpopulations could be identified that would not benefit from treatment with liraglutide 3.0 mg.

To ensure that only patients who are most likely to benefit from liraglutide 3.0 mg will receive long term treatment, the proposed indication has been updated to include a stopping rule. When evaluating the weight loss effect according to the updated indication (that is, in early responders with ≥5% weight loss after 12 weeks on liraglutide 3.0 mg; 65% of the subjects were early responders), enhanced weight loss was observed vs. the overall population in the weight management trials. Also, the improvements in the secondary obesity related parameters were enhanced in early responders versus the overall population (not shown).

Table 19: Weight loss at 1 year: early responders versus overall population.

	Early responders	Overall population
≥5% Weight Loss	86.2%	60.3%
≥10% Weight loss	51.2%	30.5%
Mean weight loss in subjects completing 1 year of treatment	11.2%	8.7%

[29] Jellinger PS, et al. American Association of Clinical Endocrinologists' Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis: executive summary. *Endocr Pract.* 18: 269-293 (2012); Gordon DJ, et al. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation* 79: 8-15 (1989); Stone NJ, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 63(25 Pt B): 2889-2934 (2014); De-Koning L, et al. Waist circumference and waist-to-hip ratio as predictors of cardiovascular events: Meta-regression analysis of prospective studies. *Eur Heart J.* 28: 850-856 (2007); Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. *Nature* 444: 881-887 (2006); Zhu S, et al. Waist circumference and obesity associated risk factors among whites in the third National Health and Nutrition Examination Survey: clinical action thresholds. *Am J Clin Nutr.* 76: 743-749 (2002).

In conclusion, across all subpopulations, treatment with liraglutide 3.0 mg versus placebo resulted in significant weight loss, with more subjects achieving a weight loss of > 10%. In addition, significant improvements were seen in important obesity related co-morbidities versus placebo. Novo Nordisk believes that, based on the regulatory guidelines and on the current recommendations issued by scientific societies, the clinical relevance of these benefits achieved with liraglutide 3.0 mg treatment is adequately established. Importantly, these benefits are substantially enhanced by applying the proposed stopping rule. For early non responders, discontinuation of treatment will limit exposure to liraglutide 3.0 mg.

Duration of treatment

The prevalence of overweight and obesity in Australia is among the highest in the developed world, affecting more than 60% of adults and 25% of children and adolescents; for adults this number is predicted to increase to close to 80% by 2025.[30] The risk of morbidity and mortality due to CV disease, hypertension, dyslipidaemia, T2DM,[31] sleep apnoea[32] and certain types of cancers[33] increases with the severity of obesity. The consequences of overweight and obesity are widely recognised as one of Australia's leading health concerns.[34]

Scientific evidence suggests that weight gain and obesity lead to hormonal, metabolic and neurochemical adaptations that affect the regulation of the energy balance, promoting maintenance of the increased weight and making weight loss difficult.[35] Moreover, during weight loss, the body compensates by reducing energy expenditure and increasing the production of hormones that stimulate appetite.[36] These combined compensatory effects favour weight regain and explain why few people are able to maintain their weight loss with lifestyle interventions alone. Accordingly, multiple scientific societies and health authorities have recognised obesity as a chronic disease that usually requires long-term management to induce and maintain weight loss.[37] Thus, in this respect, management of

[30] Grima M, Dixon JB. Obesity--recommendations for management in general practice and beyond. *Aust Fam Physician* 42: 532-541 (2013).
[31] Guh DP, et al. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health* 9: 88 (2009); Must A, et al. The disease burden associated with overweight and obesity. *JAMA* 282: 1523-1529 (1999).
[32] Li C, et al. Prevalence of self-reported clinically diagnosed sleep apnea according to obesity status in men and women: National Health and Nutrition Examination Survey, 2005-2006. *Prev Med* 51: 18-23 (2010).
[33] Bhaskaran K, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. *Lancet* 384: 755-765 (2014); Eheman C, et al. Annual Report to the Nation on the status of cancer, 1975-2008, featuring cancers associated with excess weight and lack of sufficient physical activity. *Cancer* 118: 2338-2366 (2012).
[34] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013.
[35] Ferguson C, et al. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention. 14 Aug 2012; Thaler JP, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 122: 153-162 (2012).
[36] Thaler JP, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest.* 122: 153-162 (2012); Sumithran P, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med.* 365: 1597-1604 (2011); Reinehr T, Roth CL. The gut sensor as regulator of body weight. *Endocrine* 49: 35-50 (2015).
[37] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013; Ferguson C, et al. Obesity Drug Outcome Measures. A Consensus Report of Considerations Regarding Pharmacologic Intervention, 14 Aug 2012; European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007; European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical: Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan. *Endocr Pract.* 17 (Suppl 2): 1-53 (2011); Jensen MD,

obesity does not differ from treatment of other chronic diseases such as hypertension and T2DM.

Across the trials in the weight management programme, treatment with liraglutide 3.0 mg resulted in a fast and clinically relevant weight loss, which appeared to plateau after approximately 40 weeks of treatment and after which the achieved weight loss was maintained (Figure 2). Weight loss with liraglutide 3.0 mg was achieved and maintained only as long as subjects remained on treatment. This phenomenon was also observed with orlistat[38] (the only medicine approved for long-term weight management in Australia) leading to recommendations in the NHMRC clinical practice guideline[39] that:

> *therapy should be continued for as long as there are clinical benefits (e.g., prevention of significant weight regain).*

Furthermore, it is acknowledged in the TGA adopted 2007 EMA regulatory guideline[40] that:

> *drug effect can be continuing despite a reduction in the rate of weight loss and may even be manifest as a failure to regain weight lost.*

In conclusion, obesity is a chronic condition that requires long term treatment to prevent obesity related morbidity and mortality. Data from the weight management programme substantiate that liraglutide 3.0 mg is a valuable treatment option for weight management. The proposed stopping rule will ensure that only patients most likely to benefit from treatment will receive long term treatment. To ensure that continued treatment with liraglutide 3.0 mg is clinically indicated, the following recommendation is proposed for inclusion in the PI: "The need for continued treatment should be re-evaluated annually".

Safety profile, including long-term safety

The safety profile of liraglutide 3.0 mg is well-documented. In the completed phase 2 and 3 trials 3384 subjects were exposed to liraglutide 3.0 mg (2974 PYE; included in the submission), of these more than 2300 subjects were exposed for ≥1 year. From the interim data from the extension to trial 1839[41] (1839-ext), 903 and 694 subjects were exposed to liraglutide 3.0 mg for ≥2 years and 3 years, respectively. Thus, a substantial number of subjects have been exposed to long term treatment with liraglutide 3.0 mg. This exposure is beyond the requirements for drugs intended for long term treatment of non life threatening conditions as stipulated in the ICH E1 guidance[42] and in the TGA adopted 2007 EMA guideline.[43] Reassuringly, the safety profile of liraglutide 3.0 mg in obese and

et al. 2013 AHA/ACC/TOS Guideline for the Management of Overweight and Obesity in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *J Am Coll Cardiol.* 129(25 Supplement 2): S102-40 (2013); Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Developing products for weight management. Draft Guidance. Feb 2007.

[38] Davidson MH, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. *JAMA* 281: 235-242 (1999).

[39] Australian Government, National Health and Medical Research Council Department of Health. Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia, Canberra: 2013.

[40] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

[41] Comprising subjects with pre-diabetes at randomisation in the main treatment period, cut-off date 1 October 2014. Data were included as part of the Section 31 response.

[42] International Conference on Harmonisation. ICH Harmonised Tripartite Guideline. E1: The extent of population exposure to assess clinical safety for drugs intended for long-term treatment of nonlife-threatening conditions. 27 Oct 1994.

[43] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

overweight individuals was similar to that established for Victoza (liraglutide for T2DM at doses up to 1.8 mg) in completed clinical trials and through post-marketing surveillance. In the post marketing setting with Victoza, events of altered renal function have been reported. This is described as an identified risk in the RMP and continuously monitored and reported in the liraglutide PSURs. Importantly, these events are rare; in the latest PSUR the reporting rate was 0.07 events per 1000 PYE[44] (corresponding to 258 case reports, where of approximately one third were co-reported with the preferred term dehydration or GI events that might lead to dehydration).[45] No safety signal for acute renal impairment was observed with liraglutide 3.0 mg in the weight management programme.

The weight management programme was sufficiently large to identify events of cholecystitis, cholelithiasis, pancreatitis and increase in resting pulse as risks associated with liraglutide 3.0 mg treatment. These safety concerns, as well as altered renal function, can all be managed effectively in routine clinical practice, based on the warnings and guidance for prescribers proposed for inclusion in the PI. Furthermore, to specifically address the risk of acute gall stone disease, a mechanistic study is planned to assess the possible effects of liraglutide 3.0 mg on gallbladder emptying. As part of the liraglutide 3.0 mg EU post-marketing requirements, the proposed protocol has been submitted to the EMA for review in May 2015. Finally, trial 1839-ext has now been completed (last patient last visit first quarter of 2015) providing a total exposure to liraglutide 3.0 mg of 3161.3 PYE, with 787 subjects exposed to liraglutide 3.0 mg for 3 years. This provides further assurance of long term efficacy and safety of liraglutide 3.0 mg; no updates to current safety information are required based on this data. The trial report will be provided to the TGA, upon completion of analysis, in the first half of 2016.

As is common for many clinical development programmes, the weight management development programme was not designed to fully explore the incidence rates of rare events including MACE and neoplasms (that is, malignant breast neoplasms and benign colon neoplasms) where a potential association can be established only after long term exposure. However, the currently available data do not support any such association.

In the evaluation of these specific rare event types, the extensive amount of safety data[46] with Victoza are considered applicable for liraglutide 3.0 mg. In terms of pharmacology, liraglutide, like native GLP-1 and other approved GLP-1R agonists, is selective for the GLP-1R, of which there are no known subtypes.[47] In terms of clinical evidence, there was no dose and/or exposure relationship for increase in pulse (that is, a signal that potentially could lead to an increased risk of MACE) or the specific neoplasm types. This supports the applicability of safety data with Victoza for the weight management population regarding these events. This was also acknowledged by the EMA and the FDA in their final assessment of liraglutide 3.0 mg. There is no evidence available supporting an association between MACE or neoplasms and treatment with Victoza. Reassuringly, also a signal for these events is not evident from the emerging number of approved GLP-1R agonists (Byetta, Bydureon and Lyxumia in Australia). The latter includes recent data from the large Lyxumia CV outcomes trial (CVOT) ELIXA that were presented at the American Diabetes Association conference in Boston (Session 3-CT-SY28, 8 June 2015).

The safety concerns will all be addressed by routine and additional pharmacovigilance activities as outlined in the RMP for liraglutide. Among the additional PV activities, the

[44] Post-marketing exposure estimated to 4 million PYE as of 30 December 2014, based on total volume sold assuming an average daily dose of 1.2 mg.
[45] Events were identified with the standardized MedDRA query (SMQ) Acute renal failure (narrow scope), preferred terms for GI events and dehydration: 'dehydration', 'dyspepsia', 'diarrhoea', 'nausea' and 'vomiting'.
[46] Based on data from both the comprehensive clinical trial programme and the extensive post-marketing experience. The latter estimated to 4 million PYE as of 30-Dec-2014, based on total volume sold assuming an average daily dose of 1.2 mg.
[47] Bjerre Knudsen L, et al. Glucagon-like Peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 151: 1473-86 (2010).

large Victoza CVOT, LEADER and the prospective Optum Research Database Study in the US can be highlighted.

LEADER has enrolled more than 9000 subjects at high risk of cardiovascular disease, who are followed for 3½ to 5 years. In addition to MACEs, the effect of liraglutide on a number of efficacy and safety outcomes, including neoplasms and pancreatitis, is being investigated. The trial population is relevant for the evaluation of the adverse events of interest for liraglutide 3.0 mg, as this population is inherently more susceptible to CV disease, pancreatitis, and breast and colorectal cancer as a consequence of T2DM[48] and higher age compared to the weight management population. In addition, all subjects had a diagnosis of CV disease or CV risk factors at randomisation, and thus represent the most sensitive scenario for detecting a causal relation between liraglutide and CV disease. Furthermore, the BMI of the subjects at randomisation was 32.5 ± 6.3 kg/m^2 with more than 7500 subjects with BMI >27 kg/m^2 (80% of all subjects) and more than 5500 subjects with BMI >30 kg/m^2 (59% of all subjects); thus, the BMI range substantially overlaps with that in the weight management programme. Finally, based on the simulated exposure range in a population with similar demographics as in the LEADER trial the overlap in exposure between the LEADER trial population and the obese population is expected to be approximately 50%. The CV outcomes, as well as all events of pancreatitis and neoplasms, are being adjudicated by an independent, external, blinded event adjudication committee. Subgroup analyses in the patients who are obese will be performed.

To address the specific concern regarding MACE, Novo Nordisk does not believe that conducting a specific cardiovascular outcome trial (CVOT) for liraglutide 3.0 mg is warranted. The only identified potential adverse CV signal, increase in pulse, has, as discussed above, been shown to be similar across all clinically relevant doses and drug exposures of liraglutide (that is, no dose or exposure response at doses ≥1.2 mg) and any potential adverse CV effect of liraglutide treatment is therefore, expected to occur also at the doses applied in the LEADER trial. In addition, in accordance with regulatory recommendations,[49] the studied population in a liraglutide 3.0 mg CVOT would consist of obese subjects but would have to be enriched with respect to CV risk to obtain event rates and an absolute number of events to yield acceptable confidence intervals within a realistic timeframe; that is, a population very similar to that in the LEADER trial. An independent, external data monitoring committee (DMC) evaluates unblinded safety data from the LEADER trial on an ongoing basis; no concerns have been raised. At its latest meeting (29 May 2015), the DMC recommended that the trial should continue according to protocol. The report for the LEADER trial will be finalised and provided to the TGA in the final quarter of 2016, that is, within approximately 1 year after the launch of Saxenda in Australia (planned to be 2 months after an approval of liraglutide 3.0 mg). Thus, the results of the LEADER trial will become available before any Australian patients are exposed to long term treatment with liraglutide 3.0 mg.

[48] Giovannucci E, et al. Diabetes and cancer: a consensus report. *CA Cancer J Clin.* 60: 207-221 (2010); Noel R, et al. Increased risk of acute pancreatitis observed in patients with type 2 diabetes. 24th International Conference on Pharmacoepidemiology and Therapeutic Risk Management. Copenhagen, Denmark. International Society for Pharmacoepidemiology: 2008; Girman CJ, et al. Patients with type 2 diabetes mellitus have higher risk for acute pancreatitis compared with those without diabetes. *Diabetes Obes Metab.* 12: 766-771 (2010); Lai SW, et al. Risk of acute pancreatitis in type 2 diabetes and risk reduction on anti-diabetic drugs: a population-based cohort study in Taiwan. *Am J Gastroenterol.* 106: 1697-1704 (2011); Munsell MF, et al. Body mass index and breast cancer risk according to postmenopausal estrogen-progestin use and hormone receptor status. *Epidemiol Rev.* 36: 114-136 (2014); National Cancer Institute. Fact Sheet: Obesity and cancer risk, 1 Mar 2012; Sadr-Azodi O, et al. Abdominal and total adiposity and the risk of acute pancreatitis: a population-based prospective cohort study. *Am J Gastroenterol.* 108: 133-139 (2013).

[49] Food and Drug Administration, "Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes", Dec 2008; Food and Drug Administration. Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting, March 28-29, 2012 (17 May 2012).

The Optum Research Database Study is a prospective cohort study using an extensive insurance claims database in the US. In the latest interim report for the Optum Research Database Study (submitted to the FDA on 25 March 2015) more than 35,000 Victoza initiators had been identified from 01 February 2010 through 31 March 2014; no safety concerns regarding CV disease, pancreatitis or malignant neoplasms had emerged with Victoza. Also this study population (that is, patients with T2DM) overlap to a great extent with the weight management population. The final study report will be provided to the TGA in the first half of 2016.

In conclusion, the safety profile of liraglutide 3.0 mg is well described. The identified risks of acute gallstone disease, pancreatitis and renal impairment and the potential CV risk associated with the increase in pulse are addressed by specific warnings and guidance to prescribers in the proposed PI. Additional long term safety will become available by completion of trial 1839-ext which will be supplemented by relevant data from the LEADER trial and the Optum Research Database Study. LEADER data will become available in the final quarter of 2016, that is, before Australian patients have been exposed to long term treatment with liraglutide 3.0 mg. The pharmacovigilance activities will provide additional information concerning rare AEs.

Benefit/risk conclusion

The wide range of clinically relevant benefits with liraglutide 3.0 mg treatment (that is, weight loss and improvements in important obesity related co-morbidities) is further enhanced by implementing the stopping rule. In view of the enhanced benefits, the identified risks of acute gallstone disease, pancreatitis and renal impairment and the potential risk associated with the increase in resting pulse, which are mitigated by specific guidance in the PI, are considered manageable. Based on the totality of the data, there is no signal for an increased CV risk with liraglutide 3.0 mg and it is unlikely that liraglutide 3.0 mg treatment is associated with malignant breast neoplasms or benign colon neoplasms. Liraglutide treatment addresses a significant unmet medical need, especially in view of the large medical, psychosocial and economic consequences of obesity, both for the individual and for society. Thus, Novo Nordisk considers the benefit-risk balance to be positive and in favour of approval of liraglutide 3.0 mg for weight management. FDA, EMA and Health Canada also agreed with this risk/benefit assessment and have approved liraglutide 3.0 mg for weight management.

ACPM considerations: first round

The Advisory Committee on Prescription Medicines (ACPM), taking into account the submitted evidence of pharmaceutical efficacy, safety and quality, considered Saxenda solution for injection containing 6 mg/mL of liraglutide (rys) to have an overall negative benefit-risk profile for the proposed indication.

In making this recommendation, the ACPM:

- Was not clear whether the efficacy findings met the relevant EMA guideline on the clinical evaluation of medicinal products used in weight control,[50] which was adopted by the TGA;
- Noted that long term use may be required to maintain weight loss;
- Was not clear whether safety with long term use at the proposed dose of 3 mg/day had been established.

[50] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Have the efficacy and safety of Saxenda for the proposed indication of weight management in adult patients been satisfactorily established by the data submitted by the sponsor?

The ACPM considered the efficacy and safety of Saxenda for the proposed indication has not been established satisfactorily by the data submitted by the sponsor.

Delegate's request for further advice

Weight reductions reported from the clinical development program and the regulatory guideline adopted by the TGA

In the TGA adopted guideline,[51] the relevant section is:

> *Weight loss is the primary endpoint. Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.*

A draft EMA guideline[52] (not yet adopted) contains similar information, although it specifies a 5-10% (non placebo subtracted) weight loss, rather than the 10% in the currently adopted guideline. Both guidelines recommend at least a 5% placebo subtracted weight loss:

> *Baseline weight is the subject's weight at randomisation. Weight loss should be documented both as absolute weight loss (kg) and percentage weight loss relative to baseline body weight. Demonstration of a clinically significant degree of weight loss of at least 5- 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs.*
>
> *Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.*
>
> *Proportions of responders with ≥ 5% weight loss should be documented as a secondary endpoint.*
>
> *Further, the predictive value of weight loss after e.g. 3 months treatment with respect to long term effects should be documented in order to identify a population with expected long term benefit.*

The FDA guidance contains similar information:

> *c. Efficacy benchmarks*

[51] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[52] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014.

In general, a product can be considered effective for weight management if after 1 year of treatment either of the following occurs:

- *The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant*
- *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant .*

Improvements in blood pressure, lipids, glycemia, or other areas commensurate with the degree of weight lost are expected in patients treated with an effective weight-management product. Therefore, changes in common weight-related comorbidites should be factored into the efficacy assessment of investigational weight-management products.

Interpretation of the results from the clinical development program is complicated by the missing data (~30%); however, this is not unusual in weight loss trials. Pooled results for placebo subtracted weight loss (roughly 12 months) for different methods of dealing with the missing data were:

- LOCF: 5.2%
- Completers: 5.6%
- Baseline observation carried forward (modified): 4.5%

The sponsor argued in the Section 31 response that the alternative criterion from the guideline could be used: proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12 month period. In the pooled 56 week studies, 31% of patients on liraglutide achieved a 10% weight loss, compared with 8% for placebo (LOCF). For completers, it was 38% versus 13%.

Regardless of the method of dealing with missing data, it seems unlikely that the criterion in the currently adopted EMA guideline[53] of at least 10% (non placebo subtracted) weight loss from baseline (averaged across trial participants) was achieved (the results for LOCF were -9.18% to -5.73%, depending on the trial). However, it is reasonable to argue that the criterion of 5% placebo subtracted weight loss (at 12 months, averaged across trial participants) was achieved.

Also, the draft EMA guideline[54] specifies a (non placebo subtracted) clinically significant degree of weight loss of 5-10%, which was met by all the trials.

Clinical importance of 5% placebo subtracted weight loss

Sustained weight loss of 3% might result in improvement in cardiovascular risk, however, weight loss of 5% is generally considered clinically important.[55] That is, 5% weight loss is

[53] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[54] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014.
[55] Moyer V, et al. Screening for and Management of Obesity in Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med.* 157: 373-378 (2012); Carvajal R, et al. Managing obesity in primary care practice: a narrative review. *Ann NY Acad Sci.* 1281: 191-206 (2013).

likely to result in reductions in morbidity and mortality. This fits with the EMA guideline (5% placebo subtracted), adopted by the TGA.[56]

Comparison of amount of weight loss with Saxenda versus other non surgical interventions available in Australia

In efficacy trials, intensive lifestyle interventions (diet and exercise) can produce average weight loss of 7-10% of initial body weight at 12 months. However, results from these intensive efficacy trials are far better than those attained in everyday clinical practice, where clinically meaningful weight loss is usually not achieved with diet and exercise; specifically, the mean weight loss is typically <3% at 12 months.[57] The weight loss in the control arms (diet and exercise) of the Saxenda trials was between 0.2% and 3.1%.

Orlistat (Xenical, available over the counter in Australia; 120 mg capsules) produces a mean, placebo subtracted weight loss of about 3%.[58]

Phentermine (S4) only has an indication for short term use for weight loss.

There are no other medicines, registered in Australia, with an indication for weight loss.

Obesity is a chronic disease and long term use is probably required to maintain weight loss.

The sponsor has made the point that:

> *the weight loss achieved with liraglutide 3.0 mg began around week 2 and continued until week 40-44 where after the weight loss achieved was maintained.*

However, this does not get at the issue of how long patients should expect to be on this product for weight loss.

This issue was also raised by the EMA (page 85, EPAR):[59]

> *It is not clear if and how long the benefits will persist after treatment discontinuation; in fact, it is likely that weight would return to baseline. In trial 1839, subjects treated with liraglutide who had completed 1 year of treatment were re-randomised to 3-months treatment with liraglutide or placebo. Subjects who switched from liraglutide to placebo gained a mean 2.91% (2.63 kg) of body weight compared to 0.69% (0.61 kg) in those who continued on liraglutide (treatment difference: -2.18% [-2.60; -1.75], p<0.0001). However, weight change in subjects who switched from liraglutide to placebo (-6.77% [-6.73 kg]) still remained greater than patients initially randomised to placebo (plus diet and exercise) (-3.11% [-3.29 kg]).*

On page 88 of the EPAR, the EMA makes the point that:

> *The prospect of lifelong treatment for weight management may concern potential users.*

Other medicines to mitigate risk factors for cardiovascular disease (e.g., anti-hypertensives, statins, anti diabetes medicines) are used long term.

[56] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.
[57] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 311: 74-86 (2014).
[58] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 311: 74-86 (2014).
[59] European Medicines Agency, European Public Assessment Report (EPAR) for Saxenda.

Uncertainty about safety with long term use

The sponsor made the point that as of the July 2013 cut off used in the dossier, 2300 patients had been exposed to liraglutide 3.0 mg for at least 12 months.

In the Section 31 response, the sponsor provided more data for the extension to trial 1839 (cut off date October 2014):

- 900 patients had been exposed to liraglutide 3.0 mg for at least 24 months.
- 700 patients had been exposed to liraglutide 3.0 mg for at least 36 months.

The sponsor pointed out that exposure to the 1.8 mg dose for T2DM was 3.9 million PYE as of Dec 2014; and has listed the ongoing and planned post-marketing studies.

As a "rough rule of thumb", the "rule of three" suggests that unsuspected/unknown adverse events, more common than 1-in-900/3 = 1-in-300, are unlikely (95% confidence) to be detected with a 2-years of follow-up among 900 patients.[60] For 3 years of use, the corresponding figure is 1-in-700/3 = 1-in-233. In other words, heuristically, the long term data submitted by the sponsor do not rule out uncommon (including as yet un-identified) adverse events (for example, more uncommon than 1-in-300 after 2 years of use) once a large population of patients is exposed to the product, post-authorisation.

The EMA's summary (EPAR) included a similar conclusion. For example, page 77:

> *With the day 120 and 180 responses, additional interim data from the extension of trial 1839 have been added, which confirm the safety profile established during the main trials. In total, in trial 1839 and its double blind, placebo controlled extension up to 1-Oct-2014, 903 subjects were exposed to liraglutide 3.0 mg for ≥2 years and 694 patients were exposed for 3 years. Important event rates of MACE, gall bladder events and pancreatitis did not increase over time; however the number of events was too low for more robust conclusions.*

And on page 78:

> *The general AE profile is in line with the experience with Victoza. However, current data are insufficient to assess if uncommon events (pancreatitis, neoplasms) occur more frequently with Saxenda's higher dose (3.0 mg) compared to the dose in T2DM (1.8 mg).*

Also, page 88:

> *There is limited information about long-term (>1 year) safety. Dose-responsiveness for rare events cannot be excluded based on current data. This implies that other uncertain risks such malignancies cannot be judged accurately with use of the T2DM data. Such events are of relevance because they are associated with severe morbidity and mortality (see discussion of the RMP). Some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (breast cancer and benign colon neoplasms), which could be a chance finding but needs follow-up in the RMP, similar to GLP-1 analogues in general.*

Nevertheless, on page 89, the EMA concludes:

> *The overall B/R of Saxenda is positive, provided that the Applicant commits to perform a number of post authorisation measures.*

And later on that same page:

[60] Hanley JA, Lippman-Hand A. If nothing goes wrong, is everything all right? interpreting zero numerators. *JAMA* 249: 1743-1745 (1983); Eypasch E, et al. Probability of adverse events that have not yet occurred: a statistical reminder. *BMJ* 311: 619-620 (1995).

> *According to the Applicant, the ongoing post-authorisation commitments for Victoza (liraglutide 1.2 and 1.8 mg for T2DM) will provide information regarding the long-term safety of Saxenda pertaining to the concerns raised by the CHMP (risks associated with increase in pulse, pancreatitis, malignant breast and benign colon neoplasms).*

Post marketing case reports of acute renal injury with liraglutide

There have been case reports of renal impairment, acute renal failure, and worsening chronic renal failure with liraglutide (Victoza), when used in patients with T2DM, as have also been reported for other GPL-1 agonists. Sometimes haemodialysis was required. Some of the case reports were in patients without any underlying renal disease.

(Unlike exenatide, which is primarily excreted by the kidneys, liraglutide undergoes generalised proteolysis, without excretion by kidneys.)

The following is from the FDA PI:

> *A majority of reported events occurred in patients who had experienced nausea, vomiting or diarrhoea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function was reversed in many of the reported cases with supportive treatment and discontinuation of the potentially causative agents, including liraglutide.*

In the Australian PI for Victoza, acute renal failure, renal impairment and dehydration are listed in the Adverse Effects section as uncommon – incidence: 0.001 to 0.010. The reader of the PI is referred to the Precautions section, which has a statement that dehydration, including renal impairment and renal failure been reported; and that patients treated with Victoza should be warned about the potential risk of dehydration in relation to gastrointestinal side effects.

A similar subsection is proposed for the Precautions section of the Saxenda PI:

> *Signs and symptoms of dehydration, including renal impairment and acute renal failure have been reported in patients treated with GLP-1 receptor agonists. Patients treated with Saxenda should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.*

Discussion

The data show that Saxenda meets the criterion in the current 2007 EMA guideline (adopted by the TGA) of 5% placebo subtracted (average) weight loss at 12 months. Saxenda does not meet the criterion of 10% non placebo subtracted (average) weight loss at 12 months. However, this criterion is not in the new (draft) 2014 EMA guidelines (which in all probability be adopted by the TGA); and is not in the FDA 2007 guidance (still draft).

In short, at this point in time, and pending further ACPM advice, my view is that the clinical development program has satisfactorily established efficacy for Saxenda.

This means that any decision to reject the application for registration would be because the evidence submitted by the sponsor has not satisfactorily establish safety; or put another way, that the benefit-risk balance is not favourable.

In this context, there is an argument that obesity/overweight is a lifestyle problem, not a medical problem; and that adjunct pharmaceutical treatments should be used with caution, if at all. In short, some would argue that, for a weight loss medicine, any material adverse drug reactions are unacceptable.

However, the following is from a recent systematic review of drug treatments for weight loss:[61]

> *Regardless of initial weight loss success [with diet and exercise], longer-term weight maintenance is difficult. With continued lifestyle treatment, weight regain can be ameliorated but not eliminated. The need for constant vigilance to sustain behaviour changes in the face of biologic and environmental pressures to regain weight emphasises the challenges faced by even the most motivated patients who have achieved weight loss. Thus, there is a need for adjunctive therapies that can help patients who are not able to lose or sustain sufficient weight loss to improve health with lifestyle interventions alone.*

The currently available data suggest that, besides gastrointestinal events (more frequent with the 3.0 mg dose), the safety profile of Saxenda (3.0 mg) is similar to that of Victoza (1.8 mg).

Nausea occurred in most patients during dose titration and is probably the most common reason for discontinuation. It is unclear whether the higher rates of gastrointestinal adverse events will increase the risk of dehydration and acute renal injury.

Based on the currently available evidence, the effects on pulse rate do not seem to be dose dependent. There are no specific signals coming out of the clinical development program for major cardiovascular events (the point estimate suggests a protective effect, but the confidence intervals are wide, reflecting the small number of cardiovascular events seen in the clinical development program).

As per the EMA evaluation, dose responsiveness for rare events (for example, pancreatitis, certain malignancies, renal injury) cannot be excluded based on current data. That is, the risk of rare adverse events cannot be judged accurately with use of the T2DM data. However, the EMA concluded that:

> *The overall benefit-risk of Saxenda is positive, provided that the Applicant commits to perform a number of post authorisation measures.*

The Australian RMP includes the same measures as the EU RMP: statements in the PI (as per the Victoza PI: pancreatitis, dehydration/acute renal injury, increased pulse rate) and post marketing studies (to be conducted in EU and US).

Regulatory framework

Section 25 (evaluation and registration of therapeutic goods) of the *Therapeutic Goods Act 1989* provides that if an application is made for registration of therapeutic goods in relation to a person in accordance with Section 23, the Secretary must evaluate the goods for registration having regard to the criteria set out in paragraphs 25(1)(d) to (k).

At issue is whether efficacy and safety of liraglutide have been satisfactorily established, pursuant to Section 25(1)(d) of the Act, for the purpose for which it is to be used.

More specifically, if the ACPM accepts that efficacy has been satisfactorily established (according to the EMA guidelines, adopted by the TGA), then at issue is whether safety has been satisfactorily established for the proposed indication (purpose for which it is to be used); that is, weight management: BMI 30 mg/kg^2 or greater; BMI 27 mg/kg^2 or greater with at least one comorbidity.

The risk of off label use is mitigated by the registered indications and because the product is a prescription (S4) medicine.

[61] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 311: 74-86 (2014).

The sponsor's plan (accepted by the EMA) is to mitigate known risks through statements to inform prescribers and patients in the PI; and better characterise rare adverse drug reactions and identify any currently unknown adverse drug reactions through spontaneous AE reporting and post authorisation safety studies.

Further information from sponsor

Please outline how the post authorisation LEADER study of Victoza (1.8 mg) for T2D will be generally applicable to Saxenda (3.0 mg) for obesity/overweight.

Please also provide information as discussed with the TGA at the meeting of 2 July 2015.

The ACPM also be provided with:

- Information from Delegate for sponsor after first ACPM meeting, 12 June 2015
- Minutes from meeting between TGA and sponsor, 2 July 2015
- Advice from external experts

ACPM considerations: second round

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, concluded that Saxenda solution for injection, containing 6 mg/mL of liraglutide has an overall negative benefit-risk profile for the proposed indication.

In making this recommendation, the ACPM advised that:

- There was significant uncertainty with the clinical meaningfulness of efficacy in relation to the potential toxicity of Saxenda solution for injection containing 6 mg/mL of liraglutide at this time.
- Saxenda did not meet the clinically significant degree of weight loss of at least 10% of baseline weight which is required by the current TGA adopted EMA guideline recommending the "demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo".[62] This was not met in the clinical studies.
- Questioned the clinical importance of 5% placebo subtracted weight loss; it was the opinion of the Committee that literature and the expert clinical opinion provided was divided on this issue.
- There was considerable uncertainty with regard to safety of the higher dose of liraglutide proposed, particularly with regard to potential long-term and widespread use.
- There was no hard evidence that Saxenda reduced morbidity and mortality associated with cardiovascular risk factors.
- Mature data set to be provided when available.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

- Have the efficacy and safety of Saxenda for the proposed indication of weight management in adult patients been satisfactorily established by the data submitted by the sponsor?

[62] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

The ACPM advised that Saxenda had marginal benefit based on proxies used to demonstrated outcomes. Therefore, Saxenda had an unfavourable and uncertain benefit-risk profile for the indication of weight loss.

ACSOM advice

The submission was considered by the TGA's Advisory Committee on the Safety of Medicines (ACSOM), who provided advice.

Background

The proposed indication for liraglutide is as an adjunct to a reduced-calorie [sic] diet and increased physical activity for chronic weight management in adult patients with an initial BMI of 30 kg/m^2 or greater (obese), or 27 kg/m^2 or greater (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and T2DM), hypertension, dyslipidaemia, or obstructive sleep apnoea. Also under consideration is that, if the medicine is approved, the indication would also specify that treatment with liraglutide should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.

Obesity and being overweight are complex chronic problems that are significant to the individual and to the community. In 2011-12, 35.3% of Australian adults were overweight and a further 27.5% were obese. Between 1995 and 2012 the average adult man's weight increased by 3.6 kg, while the average adult woman's weight increased by 4.0 kg.[63] In the community being overweight and obese vary according to gender, geographic location and socioeconomic group. Being overweight and obese are significant contributors to the burden of disease in the Australian community.[64]

Liraglutide is a GLP-1R agonist. GLP-1 is a regulator of appetite and energy intake, which may be acting by increasing feelings of fullness and lowering feelings of hunger, perhaps through delayed gastric emptying. GLP-1 also stimulates insulin secretion and lowers inappropriately high glucagon secretion. GLP-1 receptors are present in several areas of the brain involved in appetite regulation, as well as in the intestine.

Liraglutide was first registered in Australia in 2010 under the trade name Victoza with an approved dosage of 1.2 mg to 1.8 mg/day, as an adjunct to diet and exercise for treatment of adults with T2DM to achieve glycaemic control, in dual combination with metformin or a sulfonylurea or in triple combination with metformin and a sulfonylurea. An RMP was not required at the time of approval of liraglutide for this indication.

Under the trade name Saxenda, liraglutide is newly approved in both the US (December 2014) and EU (March 2015) for a similar weight management indication as that sought in Australia. The US FDA required the implementation of a REMS to manage the specific risks of medullary thyroid carcinoma and acute pancreatitis. No additional risk minimisation measures were required in Europe.

Gastrointestinal reactions are the most frequently reported adverse reactions during treatment with liraglutide: nausea (39.3%), diarrhoea (20.9%), constipation (19.4%) and vomiting (15.7%). In clinical trials, more participants on liraglutide 3 mg than on placebo discontinued treatment due to adverse events (approximately 10% versus 4%).

The committee noted the following summary of safety concerns for liraglutide for this indication:

[63] Australian Bureau of Statistics, 2013, *Profiles of Health, Australia, 2011-13,* cat no. 4338.0.
[64] Australian Institute of Health and Welfare, 2015.

- Important identified risks: hypoglycaemia in combination with other anti-glycaemic agents (T2DM patients only); gastrointestinal adverse events; altered renal function; allergic reaction; acute gallstone disease; pancreatitis
- Important potential risks: hyperglycaemia due to discontinuation of insulin; medullary thyroid cancer; neoplasm (including breast cancer); pancreatic cancer; cardiovascular disorders; immunogenicity (as anti liraglutide antibody formation and immune complex disorders)
- Important missing information: children and adolescents < 18 years; pregnant and lactating women; patients with severe hepatic impairment; patients with severe renal impairment; patients with congestive heart failure NYHA III-IV (New York Heart Association classification III-IV); patients with a history of major depression or other severe psychiatric disorders; concomitant use of other weight lowering products; off-label use.

Compared to lifestyle interventions, the role of medicines in weight loss is unclear and currently internationally there are very few effective and safe agents available. The committee noted that weight loss is a complex area for analysis and interpretation of results, including what result is significant to the patient and what result is clinically relevant. The committee also noted the positive decisions on liraglutide of other regulators (FDA, EMA) and the negative view of liraglutide of the ACPM.

In addition to the information presented in the agenda papers, the committee referred to a paper by Wadden et al.[65] and a US FDA briefing document.[66]

The committee provided advice on specific questions asked by the TGA relating to the RMP.

Advice

- Long term treatment with liraglutide may be required to maintain weight loss. Noting that safety in long term use is not currently included as an RMP safety concern, can the committee comment upon the adequacy of the pharmacovigilance plan to characterise long term safety? If not considered adequate can the committee advise which pharmacovigilance activities would be appropriate to investigate long term safety?

Approximately 2500 patients have been exposed to liraglutide for one year for weight management, and 175 patients have been exposed for two years. The committee was informed that trial extensions have produced data on three years of use of liraglutide. This was a very limited population on which to determine safety information, given the potential wide usage of the medicine. AEs or complications with a small absolute risk have the potential to affect substantial numbers of people in this situation.

Clinical trials show that, for the average/typical patient, weight loss reaches a maximum after about 40 weeks of treatment, after which small increases in weight can occur. Additional weight gain occurs following discontinuation of the medicine.

Given that the overall safety of a given medicine reflects a balance of safety and efficacy, the ACSOM expressed concerns that the demonstrated efficacy of liraglutide is marginal at best, especially given the need for long term therapy and the potential for even lower efficacy outside the trial setting. The mean estimated placebo subtracted weight loss for the intention to treat population was between 4.5% and 5.6%, depending on how the missing data are dealt with. In the pooled 56 week studies, 31% of patients on liraglutide achieved a 10% weight loss, compared with 8% of patients on placebo. For completers, it

[65] Wadden TA, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 37:1443-51 (2013).
[66] FDA Briefing Document, NDA 206321, Liraglutide Injection 3 mg, Endocrinologic and Metabolic Drugs Advisory Committee Meeting, September 11, 2014.

was 38% versus 13%. It is equivocal as to whether these outcomes meet the EMA guidelines for clinically significant weight loss, which include

> *Demonstration of a clinically significant degree of weight loss of at least 10% of baseline, which is also at least 5% greater than that associated with placebo.*

Thus, a key concern is that without the advice and support to entrench lifestyle modifications available to clinical trial participants, a durable weight loss may require long term use of liraglutide at the higher (3 mg) dose, and there are limited longer term data (safety and efficacy) at this dose. The committee therefore advised that the pharmacovigilance plan currently does not adequately characterise the long term safety of liraglutide. However, the committee noted that this may be addressed by several studies, including international randomised clinical trials, which are currently in place to examine longer term effects of liraglutide in weight management. These studies will be reporting in 2015 and 2016.

To support the pharmacovigilance plan to characterise long term safety, the committee also suggested that a large scale data linkage study would be useful.

- Based on the available evidence can the committee comment on the adequacy of the pharmacovigilance plan to investigate the important potential risk of breast cancer? If not considered adequate can the committee advise which additional pharmacovigilance activities would be appropriate to further investigate this risk?

There was a three fold observed numerical imbalance in subgroup analysis of the incidence of confirmed breast neoplasm in patients treated with liraglutide for weight management compared to placebo (that is, lifestyle modifications).

The committee noted that overweight and obese patients have an increased risk of certain cancers. A member commented that it has been suggested that breast cancer diagnosis becomes easier and more accurate in patients with reduced BMI (that is, there is a detection bias related to greater weight loss), however, the modest degree of average weight loss in the active treatment group may not be sufficient to explain this.

The committee noted that the LEADER study (1.8 mg dose in patients with T2DM) is a randomised international double blind placebo controlled safety study, mainly concerned with cardiovascular endpoints, but also reporting on cancers, pancreatitis, and anti liraglutide antibodies. It will collect information on baseline cancer risk and potential confounders for all identified cases of breast cancer, including prior history of breast cancer, family history of breast cancer, BRCA1/BRCA2 status, and age at menopause. The final study report is due in March 2016, by which time the study will have followed subjects for at least 3.5 years and up to 5 years.

The committee advised that the LEADER study appeared to lack statistical power for detecting changes in the incidence of breast cancer: the baseline rate of breast cancer is lower than for the cardiovascular events being monitored, and half of the study population are men, who have a far lower prevalence of breast cancer. Further, the dose in LEADER is 1.8 mg, so if the risk of breast cancer is dose dependent then the results from LEADER could be misleading. The LEADER study will answer a number of questions regarding clinical endpoints and other safety concerns, but the committee questioned its power to investigate the risk of breast cancer.

- Given the possible widespread use of this product, does the committee consider that routine risk minimisation activities are sufficient based on the safety profile? If not considered sufficient can the committee advise which risk minimisation activities might be appropriate to improve the safe use of this product in Australia?

Given the prevalence, and rising prevalence, of adults who meet the criteria for prescribing liraglutide, this medicine could be used in a large proportion of the population.

In addition to routine risk minimisation activities, risk minimisation for liraglutide for weight management should require that it be prescribed in the context of a comprehensive weight management strategy including modification of diet and behaviour. The committee advised that prescribing should occur in a setting or multidisciplinary team where services exist to provide a comprehensive weight management strategy as well as management of GI adverse effects (for example, dietician advice on dietary adjustments to reduce GI problems).

As an additional risk minimisation activity, the committee supported a stopping rule/de-prescribing criteria for liraglutide, for example, that use of liraglutide should be discontinued after 12 weeks at a dosage of 3 mg/day if there has been insufficient (<5%) loss of initial body weight. A stopping rule will ensure discontinuation of treatment in patients without a clinically relevant weight loss. This will limit patient exposure to the identified and potential risks associated with liraglutide 3 mg treatment.

The committee noted that NHMRC Clinical Practice Guidelines[67] advise that a 5% weight loss is associated with significant health benefits including improvements in obesity-related co-morbidities. In addition to dysglycaemia (pre-diabetes and T2DM), hypertension, dyslipidaemia and obstructive sleep apnoea, as named in the proposed indication, co-morbidities of obesity and overweight also include gastro-oesophageal reflux disease, polycystic ovary syndrome, infertility, osteoarthritis and depression.

Given the apparent marginal efficacy of the medication and the limited safety data beyond one year of use of liraglutide, the committee was uncertain whether there was a basis for prescribing beyond one year. Moreover, regain of lost weight would serve to negate earlier benefits and overall reduce the benefit-risk balance.

- Can the committee comment on whether the safety of the product will be enhanced by restricting access, for instance, to a particular prescriber group?

The committee noted that endocrinologists are already experienced with initiating prescribing of liraglutide and managing the adverse events of nausea and vomiting in patients with T2DM.

Any prescriber familiar with the management of insulin dependent diabetic patients should be able to safely prescribe liraglutide. Such experience includes patient education on self-administration of injections, injection pens, product storage and disposal of sharps.

No specific risks were identified by the committee that could be mitigated by restricting prescribing to any particular prescriber group.

- Can the committee comment on whether the safety of the product will be enhanced by a mandatory educational program (that is, a prescriber certification program) for general practitioners?

The committee advised that mandatory education of general practitioners would be expected to support safe prescribing of liraglutide, including addressing its risks and benefits and its appropriate place in overall patient management.

Currently there are limited data beyond two years and this point needs to be made clear to all prescribers.

The committee noted the sponsor's intention that the prescriber would register with the patient familiarisation program and the patient support program prior to the provision of samples to the prescriber.

[67] National Health and Medical Research Council (2013) Clinical practice guidelines for the management of overweight and obesity in adults, adolescents and children in Australia. Melbourne: National Health and Medical Research Council.

- Should 'acute renal injury' be added to the list of 'important identified safety concerns' (noting that 'altered renal function' is already on the list)?

GI AEs of liraglutide treatment may lead to dehydration, renal impairment and acute renal failure.

The committee advised that 'acute renal injury' and 'altered renal function' would not generally be taken to be interchangeable terms. It is important that both of these safety concerns be recognised by prescribers. Both terms should appear in the list of important identified safety concerns in the RMP.

Other issues

There was general discussion on the mixed benefits of other medicines and surgical therapies indicated for obesity and overweight.[68]

Inotropic agents that increase the heart rate pose risks of cardiovascular adverse events, including fatalities, especially in populations already at risk of cardiovascular events, such as people with T2DM. Liraglutide has been shown to increase pulse rate, with Wadden et al.[69] reporting that pulse rate rose above randomisation values in liraglutide treated participants early in treatment (at 6 weeks), returning towards pre-treatment levels after longer treatment duration (at 44 weeks). In comparison, weight loss by diet and exercise is expected to reduce heart rate. This cardiac effect of liraglutide adds to concerns on the overall safety when balanced against efficacy that could be described as marginal. The sponsor could be requested to provide additional details regarding the safety concern on pulse rate.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Saxenda liraglutide (rys) 6 mg/mL solution for injection prefilled pen indicated for:

> *Saxenda is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of*
>
> - *≥30 kg/m² (obese) or*
> - *≥27 kg/m² to <30 kg/m² (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea*
>
> *Treatment with Saxenda should be discontinued after 12 weeks on the 3.0 mg/day dose if a patient has not lost at least 5% of their initial body weight.*
>
> *Long term use should be informed by the following:*
>
> - *Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (>12 months) might not have been identified in the clinical development program [refer CLINICAL TRIALS].*
> - *Long term efficacy data are limited. The treatment effect has only been documented for 1 year [refer CLINICAL TRIALS].*

[68] For example, sibutramine (Reductil), an orally administered centrally-acting serotonin-norepinephrine reuptake inhibitor structurally related to amphetamines, was cancelled as a prescription medicine after a major study showed a higher rate of cardiovascular events in obese and overweight patients using sibutramine than in patients managing their weight through exercise and diet alone.

[69] Wadden TA, et al. Weight maintenance and additional weight loss with liraglutide after low-calorie-diet-induced weight loss: the SCALE Maintenance randomized study. *Int J Obes (Lond)* 37:1443-51 (2013).

Specific conditions of registration applying to these goods

- The liraglutide, in T2DM and weight management, EU-RMP (edition 22, version 1.0, dated 18 June 2015), revised as specified by the ASA (version 5.0, dated 21 December 2015) and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

Reasoning for outcome

Background

Overseas regulatory status

- The TGA's major international regulatory partners (EMA, FDA, Health Canada) have registered liraglutide for weight loss.
- EMA, FDA, Health Canada have all registered Saxenda subject to active (in addition to routine/passive) pharmacovigilance
- In Australia, the post marking pharmacovigilance will consist of routine/passive pharmacovigilance (which includes the reporting of suspected adverse reactions and regular submission of Periodic Benefit Risk Evaluation Reports) and a commitment to active pharmacovigilance: multiple international studies, some randomised.
- The EMA has not required any additional risk minimisation measures (that is, in the EU risk minimisation is routine: statements in PI, registration as a prescription only medicine; not over the counter).
- The FDA has a REMS for Saxenda to inform healthcare providers of:
  - the potential risk of medullary thyroid cancer
  - the risk of acute pancreatitis.

  This is similar to the FDA's REMS for Victoza (1.8 mg) for T2DM.
- The potential risk of medullary thyroid cancer was identified in nonclinical animal studies (rodents are particularly susceptible to this form of cancer). It is an uncommon form of thyroid cancer in humans and there have been no signals in any of the liraglutide clinical studies or post market. For Victoza, the EMA and TGA have warnings in the SmPC/PI, but no additional risk minimisation measures.
- Similarly, for Victoza, the TGA and EMA have a precaution about pancreatitis in the PI/SmPC and have it listed as an important identified safety concern in the "summary of safety concerns" in the RMP. In a recent commentary,[70] regulators from the FDA and EMA stated that assertions of a causal association between incretin based medicines and pancreatitis (or pancreatic cancer) are inconsistent with the current data. The FDA and EMA have not reached a final conclusion, but the current data provide reassurance.
- Unlike the EMA, for the weight loss medicine Saxenda, the TGA has decided to include a warning about the risk of pancreatitis, not just in the PI, but in prescriber/pharmacist/patient educational materials (additional risk minimisation measure).

[70] Egan AG, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med* 370: 794-7.

Clinical need

Diet and exercise typically produce, on average, a 3% loss of weight over 12 months. This is the average; a select few patients achieve spectacular results, for most patients the 12-months results are disappointing; also, if initial weight loss is achieved, it is often not maintained.

System wide, public health interventions to encourage healthy eating and exercise (for example, safe walking tracks, food labelling, media campaigns) may be an effective way of reducing the prevalence of obesity in the population; however, they may be more effective in preventing people from becoming overweight/obese (primary prevention) than reducing weight in people who are already overweight/obese (secondary prevention).

In Australia, orlistat is the only weight loss medicine registered for long term use. Phentermine was grandfathered for short term (3 month) use.

Weight loss medicines have a troublesome history.

Efficacy

The large, pre-market, clinical development program demonstrated that Saxenda produced an average weight loss of 5% at 12 months, on top of the effect of diet and exercise (~3%). The pivotal Phase III studies met regulatory guidelines for design of weight loss trials. They also met the regulatory criterion for the minimal clinically important difference at 12 months.

Safety

Safety data from the Saxenda clinical development program was largely as expected, based on data from Victoza for T2DM.

- Nausea/vomiting on starting treatment is common.
- Heart rate is increased, but the clinical importance of this is currently unknown (the Phase IV, post marketing study LEADER will be informative).
- The risk of pancreatitis might be increased.
- There is a rare risk of renal injury/impairment, sometimes requiring haemodialysis and probably related to nausea/vomiting and subsequent dehydration.

There was an imbalance of breast cancer cases in the Saxenda clinical development program. However, the numbers were small (as would be expected in pre-market studies), making interpretation difficult. Also, most breast-cancer cases were quite advanced at diagnosis (Stage II, nodal involvement) suggesting that they were present, but undiagnosed at baseline, given the short interval between randomisation and diagnosis. The sponsor also put forward an argument that the greater weight-loss in the liraglutide group might have led to increased detection. In any case, the imbalance of breast cancer cases is listed in the Precautions section of the PI and will be followed-up via active pharmacovigilance. All three of the TGA's major regulatory partners (EMA, FDA, Health Canada) have taken this approach. In addition, the TGA will include information about the imbalance of breast-cancer cases in education for prescribers/dispensers/patients. There has been no potential signal for breast cancer for Victoza.

Study NN2211-3880 was a post approval safety commitment for Saxenda in the EU. It used the Clinical Practice Research Datalink (CPRD) primary case database in the United Kingdom. Reassurance comes from a 17 June 2015 report from the UK's Medicines and Healthcare Products Regulatory Agency (MHRA) which has concluded that the results of NN2211-3880 did not show any association between liraglutide use and breast cancer.

Advice received

- Three independent external Australian clinical experts in the management of overweight/obesity were commissioned by the TGA to examine the data. All three advised that the benefit-risk balance was positive. None of the independent experts had any conflicts of interest to declare.
- The clinical evaluator considered that the risk-benefit profile was not positive (see clinical evaluation report) because:
  - Population group (that is, those adults in whom it is indicated) need to be taking a reduced calorie diet and on an exercise plan to achieve benefits seen in the trial.
  - If they do this and use Saxenda, then some of them will lose 5-10% of body weight, but many will not.
  - And all will be exposed to the risk of toxicity, which is predominantly symptomatic (for example, GI side effects) but can also be serious (hypoglycaemia, immunogeneticity, pancreatitis). EMA/FDA/Health Canada determined that these risk could be mitigated (by, for example, statements in the PI) and that the benefit-risk ratio was positive.
  - Long term data is lacking: side effects are possible for all users but also rebound weight gain is likely.
- The ACPM advised the benefit-risk balance was not positive because of concerns about widespread use, in conjunction with uncertainties about long-term efficacy and safety. The ACPM also advised that the efficacy criteria for a weight-loss medicine, as specified in EMA/FDA guidelines, had not been met. The Delegate discussed this advice (which was surprising given Saxenda had been approved by the EMA/FDA/Health Canada) with senior medical officers at the TGA. It was determined that the efficacy criteria had been met.
- The ACSOM advised on several aspects of registration of Saxenda:
  - The LEADER post marketing trial is not powered for the breast cancer endpoint and is for the 1.8 mg dose; so that it may underestimate any potential breast-cancer risk, if that risk is dose dependent.
  - The NHMRC Clinical Practice Guidelines advise that a 5% weight loss is associated with significant health benefits including improvements in obesity related co-morbidities. (In addition to dysglycaemia (pre-diabetes and T2DM), hypertension, dyslipidaemia and obstructive sleep apnoea, as named in the proposed indication, co-morbidities of obesity and overweight also include gastro-oesophageal reflux disease, polycystic ovary syndrome, infertility, osteoarthritis and depression).
  - Prescribing should occur in a setting or multidisciplinary team where services exist to provide a comprehensive weight management strategy as well as management of GI adverse effects (for example, dietician advice on dietary adjustments to reduce gastrointestinal problems).
  - No specific risks were identified by the committee that could be mitigated by restricting prescribing to any particular prescriber group.
  - Education of general practitioners would be expected to support safe prescribing of liraglutide, including addressing its risks and benefits and its appropriate place in overall patient management.
  - 'Acute renal injury' and 'altered renal function' would not generally be taken to be interchangeable terms. It is important that both of these safety concerns be recognised by prescribers. Both terms should appear in the list of important identified safety concerns in the RMP.

The sponsor also provided reports (supporting registration of Saxenda) from two Australian experts in the management of obesity (who are also members of the sponsor's advisory board). The sponsor understood that the Delegate would read this advice, but that the obvious conflict of interest would be taken in account. The sponsor also obtained reports (supporting registration of Saxenda) from the Australian and New Zealand Obesity Society and the Australian Diabetes Society.

Reasoning

- After consulting with senior medical officers within the TGA, the Delegate did not agree with the advice of the ACPM or of the clinical evaluator that the 12 month efficacy of Saxenda had not been established.
- However, the Delegate agreed with the advice of ACPM and the clinical evaluator that the long-term efficacy and safety had not been fully characterised.
- The Delegate also agreed with the ACPM that these concerns associated with uncertainties about long term efficacy and safety would be amplified if there was widespread use before safety was more fully characterised.
- A senior medical officer at the TGA advised on risk mitigation of these two concerns.

Long term efficacy and safety not fully characterised

It is almost invariably the case that, for a medicine indicated for treatment of a chronic condition, long-term (>12 months, say) efficacy and safety is not fully characterised at the time of registration. This is not to say that nothing is known; or that regulatory guidelines for registration have not been met (EMA and FDA have specific guidelines on weight loss products); or that a good scientific prediction cannot be made based on the available data; or that the benefit-risk balance is not positive, based on the available data. It means that further studies are needed, post launch, to further characterise the benefits and risks of the medicine, to ensure that the benefit-risk ratio remains positive, throughout the medicine's life cycle. Also, in the case of Saxenda, Victoza has been on the market for several years for T2D; so long term data are available; with the important caveat that this is for a lower dose (1.8 mg versus 3.0 mg). The main areas of uncertainty and the risk mitigation measures adopted by the TGA in response to the ACPM concerns are listed below.

- An as yet unidentified rare adverse reaction (unknown unknown)

  The Indications include the following statement:

  – Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (>12 months) might not have been identified in the clinical development program [refer CLINICAL TRIALS].

  – Educational materials for prescribers/dispensers/patients also include this information.

- Limited efficacy data beyond 12 months

  The Indications include the following statement:

  – Long term efficacy data are limited. The treatment effect has only been documented for 1 year.

  – Educational materials for prescribers/dispensers/patients also include this information.

- Effect of Saxenda on CV events has not been fully characterised.

In the pivotal Phase III studies, there were fewer cardiovascular events in the Saxenda group than the placebo group (see Appendix for details). Favourable (but not statistically significant) trends for cardiovascular disease in Phase III trials (that are not powered for this endpoint and who enrolled low-risk patients: middle aged women without heart disease) do not necessarily provide convincing evidence of cardiovascular safety. This uncertainty has been mitigated in the following ways:

The PI contains the following boxed warning: Saxenda increases heart rate. The clinical significance of the increase in heart rate with Saxenda is unclear. The effects of Saxenda on cardiovascular morbidity and mortality have not been established. [See PRECAUTIONS] (This warning could be removed or altered, depending on the results of the phase-4 study, LEADER.)

Precautions section of the PI contains a subsection on "Cardiovascular events", which provides warnings about the limitations of the currently available data on patients with cardiac or cerebrovascular disease (see PI).

Educational materials for prescribers/dispensers/patients include words to the effect of: Based on the currently available data, the effect of Saxenda on the future risk of heart disease and stroke has not been established (see PI for boxed warning).

- The educational materials also highlights the potential for rare cases of severe nausea/vomiting leading to severe dehydration and renal injury. Risk mitigation is to inform patients of this rare problem and to advise them to cease Saxenda (and seek medical advice) if nausea, vomiting and diarrhoea are persistent or moderate/severe.
- The educational materials also inform prescribers/ dispensers/patients of the uncertainties around breast cancer, as outlined above. The sponsor is aware of ACSOM advice on the breast cancer endpoint in LEADER; and previous similar advice from the pre market area. The sponsor should be aware that any non-reassuring result for breast cancer cases in LEADER, even if not statistically significant, could require regulatory action.

Widespread use

The TGA considered whether the 'Dosing and Administration' section of the PI should include a statement saying that prescribing of Saxenda should be limited to specialist endocrinologists. This was not because the TGA was concerned that other medical practitioners, including general practitioners, could not safely prescribe Saxenda. Rather, it was considered as a possible mechanism to ensure gradual uptake of the product, in the face of uncertainties about long term efficacy and safety; for product that might be used long term (although the currently available data were sufficient to demonstrate a positive benefit-risk balance). Such a statement in the 'Dosing and Administration' section of the PI could be potentially removed when additional pharmacovigilance studies report.

The TGA also noted that the positive risk-benefit balance, based on the currently available data, was only for those patients who met the criteria in the Indications. The benefit-risk balance for patients, who did not meet the BMI criteria in the Indications, but who wanted to "lose a couple of kilos" was unknown.

The sponsor argued that uptake would be gradual because of:

- high cost ($1000/month) and the sponsor was not seeking Pharmaceutical Benefits Scheme (PBS) subsidy
- route of administration (SC injection)

Also, uptake in the US (launched Q1 2015) had been gradual.

The TGA accepted these arguments and did not require a statement in the 'Dosing and Administration' section of the PI. The TGA noted that the FDA PI, EMA SmPC, and the

Health Canada PM did not contain such a statement in the Dosing and Administration section of the PI. The advice from ACSOM was also noted.

Summary of reasoning

- Quality/presentation was acceptable.
- 12-month efficacy, as specified for registration of weight loss products in EMA/FDA regulatory guidelines, was satisfactorily established.
- No new safety concerns were identified in the clinical development program for Saxenda (liraglutide 3 mg) for weight loss that had not already been identified for Victoza (liraglutide 1.8 mg) for T2DM. The one exception to this was an imbalance of breast cancer cases, based on small numbers (as would be expected in pre market data). This is listed in the 'Precautions' section of the PI and will be followed-up via active pharmacovigilance. All three of the TGA's major regulatory partners (EMA, FDA, Health Canada) have taken this approach. In addition, the TGA has required the sponsor to include information on breast cancer in educational materials. There has been no potential signal for breast cancer for Victoza (either pre- or post-market). A post approval study based on linked data in the UK (NN2211-3880) did not show any association with breast cancer. The sponsor is aware that a non reassuring result from LEADER (despite a lack of statistical significance) could require regulatory action.
- Only about 10% of patients in the clinical development program for Saxenda had a diagnosis of pre-existing cardiovascular disease. This data limitation is being addressed through active pharmacovigilance (for example, LEADER), statements in the PI (including a boxed warning) and prescriber/pharmacist/patient education.
- Other known concerns with liraglutide (that is, also identified for Victoza) are being mitigated through statements in the PI and prescriber/pharmacist/patient education (for example, pancreatitis, dehydration, renal injury/impairment).
- Limited data on long-term efficacy and safety is being addressed through statements included in the Indications and prescriber/pharmacist/patient education.
- In short, the sponsor has adequately addressed the ACPM's concerns. The TGA PI is stronger than the FDA PI, EMA SmPC, and HC PM. Prescriber/pharmacist/patient education is more extensive in Australia than the REMS in the US. There are no additional risk minimisation measures (for example, education) in the EU or Canada.
- The sponsor has made a commitment to an extensive active pharmacovigilance program via studies in the EU and US. As is the case with any medicine, a new safety concern could be identified post market (a current "unknown unknown"); or the active pharmacovigilance studies (for example, LEADER) might not provide reassurance about a known concern. In that case, the TGA would take appropriate regulatory action in collaboration with its regulatory partners (EMA/FDA).

Documentation from the Delegate, used in post ACPM discussions with sponsor

Preamble

The TGA acknowledges that overweight/obesity is an important public health problem. It is linked to many serious diseases: acute coronary syndrome, stroke, T2DM, osteoarthritis, sleep apnoea, and certain types of cancer (for example, oesophagus, breast, colon, endometrium, pancreas, ovary, non-Hodgkin's lymphoma). It contributes to hundreds of hospitalisations and deaths in Australia each year.

The sponsor obtained statements from:

- President of the Australian and New Zealand Obesity Society (ANZOS) who stated the need for:

  …multipronged and complementary treatments involving both behavioural and medical interventions.

- President of the Australian Diabetes Society:

  It is evident that lifestyle modifications (diet and exercise) have limited effect on reducing and maintaining weight loss and that further modifications are required. An integrated model of care for obesity is necessary that can include diet and exercise in conjunction with pharmacotherapy and motivational interventions to elicit weight loss, but more importantly to effectively maintain the weight loss that is achieved … The Australian Diabetes Society considers that a medication that can elicit and more importantly maintain this weight loss is critical in the integrated model of care for obesity.

Efficacy

In the Delegate's view, concerns about efficacy are not strong reasons for rejection. Briefly:

- The regulatory guidelines for efficacy were met (Table 20);
- Weight loss is obviously a surrogate endpoint. However, it is accepted as a valid endpoint for pre-marketing Phase III studies of weight control medicines by the TGA's major regulatory international partners (EMA, FDA, Health Canada). Also, medicines are commonly registered on surrogate endpoints (for example, HbA1c, blood cholesterol);
- A diet and exercise subtracted (that is, placebo subtracted) weight loss of 5% is considered a suitable benchmark in regulatory guidelines;
- 12 month follow up is the length of follow up stipulated in EMA guidelines, adopted by TGA (and also in the FDA guidelines).

Table 20: Regulatory guidelines for efficacy.

Guideline	Met?
Current EMA 5% diet and exercise/placebo subtracted	yes
Current EMA 10% from baseline non diet and exercise/placebo subtracted	yes[1]
Current EMA guideline Responders: 10% weight loss at 12 months no specific threshold in guideline 31% versus 9% RR >3.0, RD = 22%, NNT = 5	yes
Draft EMA 5% diet and exercise/placebo subtracted	yes
Current FDA 5% diet and exercise/placebo subtracted	yes
Current FDA Responders: 5% weight loss at 12 months	yes

1. Met if the early responder stopping rule of at least 5% weight loss at 3 months is applied

This is not to say, that Saxenda is a cure for obesity, which is a chronic disease that is difficult to manage. Saxenda is effective in some (that is, not all) patients. Even in those patients, in whom Saxenda is initially effective, the long term efficacy is uncertain, given the majority of patients in the clinical development program were followed for 12 months; the extension of 1839 includes 700+ patients, currently followed for 3 years.

Comparison of ACPM's reasoning with that of EMA and FDA

ACPM did not identify any new technical issues, with the design or analysis of the pre-marketing trials, which were not also identified by EMA and FDA (for example, missing data is a well known problem with weight loss trials). Also, the ACPM did not identify any AEs, which were not identified by the EMA or FDA.

However, the judgements of TGA's major regulatory partners (EMA, FDA, Health Canada) about the benefit-risk balance of Saxenda are different from the ACPM's advice. Specifically, TGA's major regulatory partners judged that the benefit-risk balance was positive. In contrast, the ACPM has advised that:

> *There was significant uncertainty of the clinical meaningfulness of efficacy in relation to the potential toxicity … at this time.*

The ACPM advice is also different from the advice the TGA has received from three independent Australian endocrinologists. In short, whether to register Saxenda does not hinge on clarification of contested technical advice about the evidence (for example, design of the trials or analysis of data).

FDA reasoning

The FDA approved Saxenda in December 2014. The FDA advisory panel voted 14 to 1 in favour. The one opposing vote was related to concerns about an imbalance in breast cancer in the pre-marketing studies.

The panel noted the unmet need for effective treatments for obesity (that is, treatment options are limited). The FDA's statistician conducted a series of sensitivity analyses around missing data and concluded that the placebo subtracted weight loss might be around 4.6%, which is below the threshold of 5% in the FDA guidelines. This did not concern the panel.

Panellists were concerned about:

- limited efficacy data beyond one year
- uncertainty around safety
  - gall bladder disease
  - pancreatitis
  - breast cancer
  - thyroid cancer
  - increased pulse rate
  - acute renal injury (probably related to dehydration associated with nausea and vomiting; but, this might not explain all cases)

The panellists considered that the uncertainty around safety could be addressed in post-marketing studies. The panellists agreed that the LEADER study (1.8 mg, patients with T2D) was sufficient to characterise the cardiovascular safety of the 3.0 mg dose, in terms of identifying signals that would need to be followed. LEADER is due to report in 2016 and will also provide data on neoplasms.

The FDA has implemented a Risk Evaluation and Mitigation Strategy (REMS), which highlights the risk of medullary thyroid cancer and acute pancreatitis.

The FDA PI includes a boxed warning about thyroid cancer.

EMA reasoning

The EMA considered that the benefit-risk balance was positive, EPAR (page 89):

> *The overall B/R of Saxenda is positive, provided that the Applicant commits to perform a number of post authorisation measures.*

Efficacy, EPAR (page 87):

> *According to the weight reduction guideline (CPMP/EWP/281/96 - 2007) an important goal of treatment of obesity is to prevent associated morbidity and mortality. The over-all effect on* ***weight loss*** *by Saxenda is considered clinically relevant. After treatment with liraglutide 3.0 mg, weight loss was 7.5% with liraglutide 3.0 mg vs. 2.3% with placebo, a placebo-subtracted weight loss of 5.2%, with narrow confidence intervals. 10%-Responders were 30.5% for liraglutide 3.0 mg v 8.4% for placebo. This is also in accordance with the requirement of the guideline. Saxenda is at least as efficacious as Victoza for glucose regulation. This may be important for patients with treatment targets related to both diabetes and weight loss. The other* ***secondary endpoints*** *related to cardiovascular risk that were included in the testing hierarchy all tested statistically significant.*

Uncertainty about long-term efficacy, EPAR (page 85):

*It is not clear if and how long the benefits will **persist** after treatment discontinuation; in fact, it is likely that weight would return to baseline. In trial 1839, subjects treated with liraglutide who had completed 1 year of treatment were re-randomised to 3-months treatment with liraglutide or placebo. Subjects who switched from liraglutide to placebo gained a mean 2.91% (2.63 kg) of body weight compared to 0.69% (0.61 kg) in those who continued on liraglutide (treatment difference: -2.18% [-2.60; -1.75], p<0.0001). However, weight change in subjects who switched from liraglutide to placebo (-6.77% [-6.73 kg]) still remained greater than patients initially randomised to placebo (plus diet and exercise) (-3.11% [-3.29 kg]).*

Unfavourable effects, EPAR (page 85, and subsequent):

*The **general AE** profile is in line with the experience with Victoza.*

The most commonly reported AEs with liraglutide 3.0 mg were gastrointestinal disorders like nausea (liraglutide: 65.4 v placebo 20.9 events/100 PYE), diarrhoea (34.7 v 14.9), constipation (26.3 v 11.5), vomiting (26.4 v 5.6). Most patients experience such events already in the first weeks of treatment, during dose titration. Other patients express decreased appetite (12.0 v 2.9), which is in line with the pharmacology of liraglutide. Also asthenic conditions like fatigue (9.6 v 6.1) occur more frequently with liraglutide.

*The consistent finding that GLP-1 analogues increase the pulse rate has caused concern with respect to **cardiovascular safety**. There are data, that GLP-1 receptors are present in the cardiac pacemaker suggesting a direct effect of liraglutide on the heart. In the large trials from the weight management programme, the maximum increase in pulse rate was 4.5 bpm for liraglutide (compared to placebo 1.1 bpm, treatment effect 3.4 bpm) after 6 weeks and slightly declined thereafter. The effect persists until end-of-trial and is then 2.5 bpm above placebo. There is no indication of a dose response. In the PD trials, the difference in pulse rate was 6-9 bpm during the night. In response to FDA regulations, the Applicant has provided an extensive cardiovascular meta-analysis to assess the risk of **MACE** (CV death or non-fatal stroke or myocardial infarction). The pre-specified MACE meta-analysis returned a hazard ratio for the weight management pool of 0.40 [95% CI: 0.15; 1.05] for total liraglutide vs. total comparator (primary analysis, 8 v 9 events).*

*In the weight management pool, the proportion of subjects reporting **acute gallstone disease** events was higher with liraglutide 3.0 mg (2.3%) than with placebo (0.9%) The imbalance was mainly driven by events of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. 0.1% , respectively, for liraglutide 3.0 mg vs. placebo).*

*Uncertainty of a possible link of the use of GLP-1 analogues and **acute pancreatitis** still exists. Adjudicated events of acute pancreatitis occurred in greater number with liraglutide compared to placebo: 7 (0.2% of subjects; 0.2 events per 100 PYE) with liraglutide 3.0 mg vs. 1 (<0.1% of subjects; <0.1 events per 100 PYE) with placebo during the main treatment periods. Events of acute pancreatitis were usually reason for hospitalisation, although most subjects recovered within 2 weeks. Non-adjudicated pancreatitis events were more frequent in this MAA dossier (0.6 events per 100 PYE) than in the T2DM MAA dossier (0.2 events per 100 PYE). In the T2DM trials, no adjudication was implemented; also, the methods of data-collection in this weight management dossier were different (more sensitive).*

***Renal failure** is addressed in the SmPC of Victoza as a risk, which is likely related to dehydration caused by gastro intestinal adverse events. In the weight management programme, rates were similar for liraglutide and placebo.*

> *… **psychiatric disorders** caused no concern in the weight management programme. Patients at risk for suicidality or with eating disorders were excluded from the trials.*
>
> *There is no evidence of an overall increased number of **malignancies** in the weight management program. However, the numbers of events were too low for sound statistical analysis and some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (breast).*
>
> *For the T2DM indication, a large cardiovascular safety study (**LEADER**) is on-going. Although the extrapolation of data from LEADER to Saxenda is not straightforward (different indication, different population, different dose), the trial is expected to provide additional valuable information. However, as the trial is on-going, data are not available to maintain the blind. The Data Monitoring Committee supervises the trial regularly and has recommended normal continuation of the trial. The final report of this trial is expected in 2016.*
>
> *There is limited information about **long-term (>1 year) safety**. Dose-responsiveness for **rare events** cannot be excluded based on current data. This implies that other uncertain risks such malignancies cannot be judged accurately with use of the T2D data.*

Regulatory background on other long-term weight-loss medicines

The track record of medicines for weight loss has been patchy. Examples of weight-loss medicines that have been withdrawn from major markets (not all were registered in Australia) include, fenfluramine, (valvulopathy), benfluorex (valvulopathy), rimonabant (anxiety, depression, suicide), and sibutramine (cardiovascular events). Sibutramine was on the market in Australia (and EU, US) for 10 years until the SCOUT trial reported an increase in cardiovascular events. Unsurprisingly, the interpretation of that study has been contested.

Another concern is that many people with normal BMI may want to use weight-loss medicines "off-label". Exposure of these people to possible adverse reactions would have a negative effect on the risk-benefit balance, at a population level. This risk is mitigated by the fact that Saxenda is a prescription only medicine.

A further concern is related to the fact that overweight/obesity is a common problem: Widespread use means that rare adverse events will occur in an important number of people, even if their frequency is only 1 per 10,000 PYE (say).

Until recently, only orlistat was available for long term weight loss in the EU and US. Since 2012, the FDA has registered 4 long term, weight loss medicines (including Saxenda) and the EMA has registered 2 (including Saxenda). This demonstrates that different regulators have made different judgements about the benefit-risk of particular weight loss medicines. Besides orlistat, only Saxenda has been approved by the FDA, EMA, and Health Canada (Table 21). Contrave (naltrexone/bupropion) has been approved by both FDA and EMA (Table 21).

The different benefit-risk thresholds of different regulators is illustrated by the different EMA/FDA decisions about locaserin and phentermine/topiramate.

Locaserin is approved in US, but not the EU. The EMA reported that it was unlikely to approve locaserin because of concerns about possible cancers, psychiatric disorders and heart valve problems (the sponsor withdrew the application in the EU).

The EMA has rejected phentermine/topiramate twice (2012 and 2013) because of:

> *…concerns about the medicine's long-term effects on the heart and blood vessels, particularly due to the effects of phentermine, which is known to increase the heart rate but whose long term effects are not clear. Secondly, there were concerns about the long-term psychiatric effects (depression and anxiety were reported in the*

studies) and cognitive effects (such as problems with memory and attention) related to the topiramate component of phentermine/topiramate. Topriamate is also known to be potentially harmful to the unborn baby if taken during pregnancy (concern about use in the first trimester before pregnancy is confirmed).

Phentermine/topiramate was submitted twice to the FDA before it was eventually approved.

Table 21: Regulatory guidelines for efficacy.

	Mechanism of action	TE*	AE	Registered			
				Australia	EU	US	Canada
Orlistat	Pancreatic lipase inhibitor	3%	flatus, faecal incontinence, oily spotting	Y	Y	Y	Y
Lorcaserin	Serotonin agonist (targets receptors in brain that generate a sense of satiety)	3%	headache, nausea Concerns about uncommon/rare adverse effects such serotonin associated valvulopathy and neuropsychiatric symptoms. Pre-market trials too small and too short to fully characterise safety.	N	N	Y	N
Liraglutide	Long acting GLP-1 agonist	5%	nausea, vomiting, increased pulse rate Concerns about uncommon/rare adverse effects such as neoplasms (breast, thyroid), pancreatitis, cardiovascular events. Pre-market trials too small and too short to fully characterise safety.	Under evaluation	Y	Y	Y
Naltrexone/ bupropion	Opioid receptor antagonist/ antidepressant	5%	Can increase pulse rate and blood pressure Has FDA warning for young adults on suicide ideation. Pre-market trials too small and too short to fully characterise safety.	N	Y	Y	N
Phentermine / topiramate	Noradrenaline sympathomimetic/ Anti-epileptic (mechanism of action not clear)	9%	Dry mouth, constipation, paraesthesia, depression, anxiety, increase in pulse rate. Pre-market trials too small and too short to fully characterise safety.	N	N	Y	N

* TE (Treatment effect): diet and exercise/placebo subtracted average percentage weight loss at 12 months.

Treatment effects in the above table might not be directly comparable because the study designs for the different medicines were different (for example, different inclusion/exclusion criteria, different intensity of background diet/exercise).

In efficacy trials, intensive lifestyle interventions (diet and exercise) can produce average weight loss of 7-10% of initial body weight at 12 months. However, results from these intensive efficacy trials are far better than those attained in everyday clinical practice, where clinically meaningful weight loss is usually not achieved with diet and exercise; specifically, the mean weight loss is typically <3% at 12 months.[71] The weight loss in the control arms (diet and exercise) of the Saxenda trials was between 3.1% and 0.2% (prior 5+% weight loss with calorie restriction).

Regulatory options to improve benefit-risk balance

Risk minimisation measures, Routine: Strengthen PI

A boxed warning could contain statements such as:

- Because this medicine might increase the risk of cardiovascular disease, TGA is requiring the sponsor to report during 2016 on a randomised trial designed to assess cardiovascular outcomes (LEADER).

A Note could be included in the Indication to the effect of long term use should be informed by the following:

- Long term safety data are limited. Adverse reactions that are uncommon (frequency < 1/100) and/or are associated with prolonged use (>12 months) might not have been identified in the clinical development program.
- Long term efficacy data are limited. The treatment effect has only been documented for 1 year.

The 'Precautions' and 'Adverse Events' sections of the PI should at least contain as much information as the Health Canada Product Monograph and the FDA PI.

Risk minimisation measures, Additional: education for prescribers, pharmacists, patients.

RMP

Safety concerns

Table 22 provides some comments, at this point in time, on the "important identified risks" and "important potential risks" for the "summary of safety concerns" in the EU RMP. More information on particular AEs is given in the Delegate's overviews.

[71] Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. *JAMA* 311: 74-86 (2014).

Table 22: Comments on the "important identified risks" and "important potential risks" for the "summary of safety concerns" in the EU RMP.

Important Identified Risk	Comment
Hypoglycaemia in combination with other anti-glycaemic agents (T2D patients only)	nil
Gastrointestinal adverse events	Dose dependent: more frequent with 3 mg for weight loss than with 1.8 mg for T2D. Prescriber education about gastrointestinal adverse events and acute renal injury, in addition to statements in the PI.
Altered renal function	Most cases probably related to dehydration associated with gastrointestinal adverse events. The following is from the FDA PI: Warnings and Precautions, Renal Impairment In patients treated with GLP-1 receptor agonists, including Saxenda, there have been reports of acute renal failure and worsening of chronic renal failure, sometimes requiring hemodialysis [see Adverse Reactions]. Some of these events were reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had experienced nausea, vomiting, or diarrhoea leading to volume depletion. Some of the reported events occurred in patients receiving one or more medications known to affect renal function or volume status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including liraglutide. Use caution when initiating or escalating doses of Saxenda in patients with renal impairment. Strengthen PI Prescriber/dispenser/patient education
Allergic reaction	nil
Acute gallstone disease	In the weight management pool, the proportion of subjects reporting acute gallstone disease events was higher with liraglutide 3.0 mg (2.3%) than with placebo (0.9%) The imbalance was mainly driven by events of cholelithiasis and cholecystitis ('cholelithiasis': 1.5% vs. 0.5%; 'cholecystitis acute': 0.4% vs. <0.1%; 'cholecystitis': 0.2% vs. <0.1%, respectively, for liraglutide 3.0 mg vs. placebo). (p68, EPAR) There were no prior safety concerns with respect to gallbladder events based on clinical trial or post-marketing pharmacovigilance data with liraglutide for T2DM (Victoza). An increased risk of gallstone formation, induced by weight loss, has been proposed as a potential mediator of the observed greater frequency of acute pancreatitis cases seen with GLP-1 based therapies. A recent publication showing reduced gallbladder emptying following acute administration of exenatide (a GLP-1 analogue) provides an alternative potential mechanism. (page 68, EPAR) The risk of acute gall stone disease is related to the weight loss that was achieved. Nevertheless, an increased incidence of gallbladder-related events was consistently observed across weight-loss categories, indicating that other

Important Identified Risk	Comment
	factors than weight loss may be involved. (page 68, EPAR) Strengthen PI
Pancreatitis	Adjudicated events of acute pancreatitis occurred in greater number with liraglutide compared to placebo: 7 (0.2% of subjects; 0.2 events per 100 PYE) with liraglutide 3.0 mg versus 1 (<0.1% of subjects; <0.1 events per 100 PYE) with placebo during the main treatment periods. The numbers within the weight management programme are too small to allow analysis of a possible dose-response. (page 67, EPAR) In a recent perspective,72 regulators from Europe and FDA have stated that both agencies agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data. The FDA and the EMA have not reached a final conclusion at this time regarding such a causal relationship. Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal. In accordance to this, a warning has been included in the SmPC and likewise, pancreatitis has been included in the RMP. (page 67, EPAR) Strengthen PI Prescriber/dispenser/patient education
Important Potential Risks	
Hyperglycaemia due to discontinuation of insulin	nil
Medullary thyroid cancer	Based on the available clinical data, the EMA concluded that the rodent findings for thyroid C-cell tumours do not translate to humans; although the FDA has a boxed warning; and a registry for MTC has been established in the US (more details of the FDA's REMS for thyroid tumours are given in the Delegate's overview of 4 May).
Pancreatic cancer	In the weight management trials, there were no reports of exocrine pancreas cancer. A single patient was diagnosed with multiple endocrine neoplasia Type 1 (MEN1) during treatment with liraglutide 3.0 mg, but had been under investigation for the disorder prior to trial enrolment (page 70, EPAR).73
Other neoplasm (including breast cancer)	In the clinical development program for weight loss, there was no imbalance for all neoplasms, combined. However, when subgroup analyses were done by individual types of cancer, imbalances were identified: breast cancer in women, benign colonic adenomas in men.74 Imbalances from subgroup analyses can be difficult to interpret because of the problem of multiple statistical comparisons: imbalances for a couple of cancer subtypes are expected due to chance alone. However a real effect cannot be excluded, based on the available data.

72 Egan AG, et al. Pancreatic safety of incretin-based drugs--FDA and EMA assessment. *N Engl J Med* 370: 794-7.
73 This subject was in the placebo group.
74 No imbalances were found for malignant colon adenomas.

Important Identified Risk	Comment
	EPAR, page 76: There is no evidence of an increased number of malignancies in the weight management program. However, the numbers of events were too low for sound statistical analysis and some types of neoplasms show a numerical disadvantage for liraglutide 3.0 mg (breast, colon). The Applicant commits to detailed follow-up of relevant cases. The data on breast cancer are succinctly summarized in the Adverse Reactions, Clinical Trials Experience section of the FDA PI In Saxenda clinical trials breast cancer confirmed by adjudication was reported in 14 (0.6%) of 2379 Saxenda treated women compared with 3 (0.2%) of 1300 placebo treated women, including invasive cancer (11 Saxenda and 2 placebo treated women) and ductal carcinoma in situ (3 Saxenda and 1 placebo treated woman). The majority of cancers were estrogen and progesterone receptor positive. There were too few cases to determine whether these cases were related to Saxenda. In addition, there are insufficient data to determine whether Saxenda has an effect on pre-existing breast neoplasia. [11 versus 2 cases is 4/1000 PYE versus 1/1000 PYE.] As the EPAR also points out, at present, whether this is a real signal or a chance occurrence, can be neither confirmed nor rejected. The following is from the EPAR (page 23): Liraglutide did not augment the proliferative effect of insulin detemir in an in vitro study in the breast cancer cell line MCF-7. No GLP-1 receptors were found on breast cancer cells (from breast carcinoma and several mammary cell lines). Artificial expression of the GLP-1 receptor in MCF-7 cells increased the proliferative capacity of this cell line. This is however considered not clinically relevant as GLP-1 receptors were not found on breast cancer cells. There are no specific additional pharmacovigilance activities for breast cancer; although it will be reported as part of the Victoza post-marketing studies (LEADER and the non-randomised database studies: NN2211-3380, NN2211-3784) and the Saxenda study 1839-ext. Although the Victoza studies are arguably generalisable to Saxenda for the outcome of cardiovascular disease (pulse rate is not dose dependent), the relevance of Victoza studies for the outcome of breast cancer is more tenuous. The sponsor has argued that a simulation study showed overlap between exposure of obese patients to liraglutide 3.0 mg and exposure of T2D patients to liraglutide 1.8 mg. 1839-ext (follow-up of ~700 patients on Saxenda for 3 years) might be too small to definitively address the issue of breast cancer. Colorectal Neoplasms: The following is from the FDA PI In Saxenda clinical trials, benign colorectal neoplasms (mostly colon adenomas) confirmed by adjudication were reported in 11 (0.33%) of 3291 Saxenda treated patients compared with 4 (0.2%) of 1843 placebo treated patients. Two positively adjudicated cases of malignant colorectal carcinoma were reported in Saxenda-treated patients (0.1%) and none in placebo-treated patients. The following is from the EPAR (p71): Colorectal carcinomas do not express the GLP-1 receptor and in the normal colon, only myenteric plexus cells express the receptor. Malignant colorectal neoplasms occurred at very low rate in weight management trials, with no imbalances between liraglutide

Important Identified Risk	Comment
	and placebo. More subjects treated with liraglutide 3.0 mg (11 with 11 events, 0.3%, 0.4 events per 100 PYE) than with placebo (4 subjects with 4 events, 0.2%, 0.3 events per 100 PYE) reported benign colorectal neoplasms, mainly colon adenomas in males aged above 50 years with a relevant medical history. The majority of the events were diagnosed during routine screening colonoscopy. Based on a lack of biological plausibility and no imbalances in completed trials with liraglutide in T2DM, the Applicant attributes the imbalance to chance. At present this can be neither confirmed nor rejected. Neoplasm is included in the RMP as an important potential risk. Strengthen PI Prescriber/dispenser/patient education
Cardiovascular disorders	Favourable (but not statistically significant) trends for cardiovascular disease in Phase III trials (that are not powered for this endpoint and who enrolled low risk patients: middle aged women without heart disease) do not necessarily provide convincing evidence of cardiovascular safety. Strengthen PI Prescriber/dispenser/patient education
Immunogenicity – anti-liraglutide antibody formation Immunogenicity – immune complex disorders	nil

Risk minimisation measures

The EU RMP contains "routine risk minimisation measures" (that is, statements in the PI/CMI). There are no "additional risk minimisation measures" (for example, Dear Health Care Provider (DHCP) letter, education) in the EU. Concerns around long-term and widespread use in Australia (as advised by ACPM) will be mitigated by strengthening the PI and by "additional risk minimisation measures" (for example, GP education, pharmacist education, prescribing only by certified GPs, dispensing only by certified pharmacists).

PhV

The EU RMP lists several post authorisation safety studies to better characterise the risk of adverse events. These are listed below.

- LEADER: Liraglutide Effect and Action in Diabetes. Evaluation of Cardiovascular Outcome Results. A long term evaluation.

This is a randomised, double blind, placebo controlled, multicentre, international trial (Table 23). Of the 138 study locations, one seems to be in Australia.

Table 23: LEADER study design.

LEADER study design	
Participants	T2DM 50+ years and cardiovascular, cerebrovascular or peripheral vascular disease or chronic renal or heart failure; or 60+ years and other specified risk factors for cardiovascular disease HbA1c: >7.0% Anti-diabetic medicine naïve or treated with oral anti-diabetic medicine(s) &/or NPH/long-acting insulin Exclusions: - T1DM - Use of GLP1-agonist or gliptin - Use of insulin other than NPH/long-acting
Intervention	Victoza (liraglutide 1.8 mg), as add-on to the patient's standard treatment for T2DM
Comparator	Placebo as add-on to the patient's standard treatment for T2DM
Outcome	Follow-up is for 3.5 to 5 years Primary: - Composite endpoint of cardiovascular death, non-fatal MI, non-fatal stroke Secondary: - Individual components of the primary composite endpoint - All-cause mortality - ACS, hospitalisation for heart failure The sponsor states that pancreatitis and neoplasms will also be assessed.

Recruitment has completed (9000+). Reporting is planned for the end of 2016 (originally planned for March 2016). There is always a risk with any RCT that reporting can be delayed due to unforseen problems. An obvious issue is that LEADER is assessing Victoza (1.8 mg in T2DM patients). The generalisability/relevance of LEADER to Saxenda (3.0 mg overweight/obesity) is discussed in the relevant sections on individual AEs.

The sponsor has provided the following information about LEADER in the pre ACPM response of 14 July (Table 24).

Table 24: Further LEADER study design information.

	LEADER Victoza liraglutide 1.8 mg n = 9340	Pre-marketing Saxenda liraglutide 3.0 mg n = 5813
Age (mean)	64 years	47 years
Men	64%	29%
Weight (mean)	92 kg	106 kg
BMI (mean)	33 kg/m2	38 kg/m2
Hypertension	90%	39%
Dyslipidaemia	77%	34%
Past CVD	81%	9%

1839-ext

This is an extension of one of the four Phase III pre-market trials, 1839 (BMI>30 or BMI>27 with co-morbidities, overt T2DM excluded; stratified by pre-diabetes). The last patient visit was at the beginning of 2015. It will provide efficacy and safety results for 787 patients who have taken Saxenda (liraglutide 3.0 mg) for 3 years. According to the sponsor it will report in the first half of 2016.

NN2211-3880

This (non-randomised) UK study is using routine electronic data from the Clinical Practice Research Datalink (CPRD). The intervention being studied is Victoza (1.8 mg for T2DM). Outcomes to be assessed include medullary thyroid cancer, other neoplasms, pancreatitis, and cardiovascular disease. It is due to report this year.

NN2211-3784

This (non-randomised) US study is using routine electronic data from the Optum research database. The intervention being studied is Victoza (1.8 mg for T2DM). Outcomes to be assessed include medullary thyroid cancer, other neoplasms, pancreatitis, and cardiovascular disease. It is due to report in the first half of 2016.

Appendix 1: Efficacy of Saxenda and regulatory guidelines for weight loss medicine

This attachment re-states the evidence for efficacy relative to regulatory guidelines in the context of the ACPM advice from the August 2015 meeting.[75]

Efficacy and the current EMA (and FDA) guidelines

The relevant section in the current EMA guideline,[76] which came into effect in 2008 and was adopted by the TGA, is:

[75] More details on efficacy are given in the Delegate's overviews of 4 May and 7 July 2015.
[76] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1)," 15 November 2007.

> *Weight loss is the primary endpoint. Demonstration of a clinically significant degree of weight loss of at least 10% of baseline weight, which is also at least 5% greater than that associated with placebo, is considered to be a valid primary efficacy criterion in clinical trials evaluating new anti-obesity drugs. Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.*

As discussed in the delegate's request for ACPM advice of 7 July 2015, the criterion of at least 10% 12 month weight loss from baseline (that is, non placebo subtracted) was not achieved (the results for LOCF were: -9.18% to -5.73%, depending on the trial). However, see later for the effect of the early responder stopping rule.

The criterion of 5% placebo subtracted 12-month weight loss **was** achieved. (The pooled estimates of the placebo subtracted weight loss were 4.5% to 5.6% depending on how missing values were dealt with).

A draft EMA guideline[77] (not yet adopted, consultation ended January 2015) specifies a 5-10% non placebo subtracted weight loss (that is, from baseline), rather than the 10% in the currently adopted guideline. Similar to the currently adopted guideline, it recommends at least a 5% placebo subtracted weight loss.

The criteria of both a non placebo subtracted weight loss of 10% **and** a placebo subtracted weight loss of 5% implies that standard care (that is, reduced calorie diet, increased physical activity) produces a 12 month weight loss of at least 5%. However, diet and exercise can be frustratingly ineffective over a 12 month period.[78] This is borne out by the data from the Saxenda clinical development program where the 12-month weight loss in the diet and exercise arms ranged from <1% (trial 1923; prior 5+% weight loss with 1200-1400 kCal diet) to ~3% (trial 1839; comorbidities, but not T2DM). Because diet and exercise produces only modest results over a 12 month period, the draft guidelines have been amended to specify 5%-10% non placebo subtracted weight loss (from baseline), rather than 10%.

As an alternative to (that is, "or"; not "and") average percentage weight loss, the current EMA guideline suggests:

> *Proportions of responders in the various treatment arms could be considered as an alternative primary efficacy criterion where response is more than 10% weight loss at the end of a 12-month period.*

No difference versus placebo is specified. In the pooled 56 week studies, 31% of patients on liraglutide achieved a 10% weight loss, compared with 8% for placebo (LOCF). This is a risk different of 22% or a number needed to treat at 12 months of about 5. (For completers, it was 38% versus 13%; giving a number needed to treat at 12 months of 4.)

The FDA guideline specifies a 5% placebo subtracted weight loss and does not mention weight loss from baseline (that is, does not mention non placebo subtracted weight loss). That is, Saxenda meets this FDA criterion.

An additional FDA criterion is:

> *The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active product group is at least 35 percent, is approximately double the proportion in the placebo treated group, and the difference between groups is statistically significant.*

[77] European Medicines Agency, Committee for Medicinal Products for Human Use (CHMP), "Draft guideline on clinical evaluation of medicinal products used in weight control (EMA/CHMP/311805/2014)," 26 June 2014.
[78] Douketis JD, et al. Systematic review of long-term weight loss studies in obese adults: clinical significance and applicability to clinical practice. *Int J Obes (Lond).* 29: 1153-67 (2005).

The percent of patients who lost 5+% of body weight in the active product groups of Saxenda clinical development program ranged from 46.4% to 78.1% (depending on the trial); for the placebo treated groups the range was 13.5% to 26.6%. Consequently, this FDA criterion was also met.

Effect of the early responder stopping rule on average percentage weight loss

As outlined in the sponsor's pre ACPM response, the effect of the stopping rule (5% weight loss at 12 weeks) is to increase the expected mean weight change from baseline (non placebo adjusted) to 11% at 12 months. A response of 10% is expected to be achieved by 50.1% of patients. That is, the effect of the stopping rule is that the 10% criterion (change from baseline; non placebo subtracted) in the current EMA guideline would be met. (86% of patients maintained the 5% weight loss at 12 months.)

Weight loss is a surrogate endpoint

Weight loss is of some value to patients in its own right (for example, improves self image and sense of wellbeing). However, broadly speaking, the main value of weight loss is that it reduces risk of morbidity and mortality, due to, inter alia, to a reduced risk of acute coronary syndrome, stroke, T2DM, osteoarthritis, sleep apnoea, and certain types of cancer (for example, oesophagus, breast, colon, endometrium, pancreas, non Hodgkin's lymphoma). That is, weight loss is a surrogate endpoint. Sometimes weight loss is justified on the basis of reduction in other surrogate endpoints that are themselves risk factors for acute coronary syndrome and stroke, such as hypertension and dyslipidaemia.[79]

The statement that weight loss is only a surrogate endpoint is not contentious. Relevant dot points from the ACPM minutes are:

- Questioned the clinical importance of 5% placebo subtracted weight loss; it was the opinion of the Committee that literature and the expert clinical opinion provided was divided on this issue.
- There was no hard evidence that Saxenda reduced morbidity and mortality associated with cardiovascular risk factors.

The Delegate takes these dot points to mean that the ACPM is questioning whether weight loss is a valid surrogate; and if it is, whether a 5% reduction is clinically relevant.

Benefit of an average 5% reduction in weight at a population level (in addition to any reduction due to diet and exercise)

Based on epidemiological data, shifting the entire weight distribution of a population, so that the average (mean) weight is reduced by 5%, would result in important reductions in cardiovascular disease, T2DM, cancer (and other medical conditions).

This is average, population level reasoning. Any medicine for weight loss will have different effects on different individual patients. Some patients will lose no weight; others might lose 10% or 20% of their baseline weight; but the net result could still be a 5% average weight reduction across the whole population of patients; and it is accepted that this would produce measureable benefits at a population level.

Benefit of a 5% reduction in weight for an individual patient

The following is from the August 2015 minutes:

[79] Wing RR, et al. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* 34: 1481-6 (2011); Moyer VA, et al. Screening for and management of obesity in adults: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med.* 157: 373-8 (2012); Carvajal R, Managing obesity in primary care practice: a narrative review. *Ann N Y Acad Sci.* 1281: 191-206 (2013).

> *The ACPM questioned the clinical relevance of 5% weight loss and noted that the literature was divided on this issue. The ACPM noted that the guidelines which recommend 5% weight loss as clinically relevant do so on the basis of improvements in cardiovascular risk profile i.e. reduced development of diabetes, reduced blood pressure (BP), improved lipid parameters and improved sleep apnoea. However, the ACPM considered that there were no data presented to support significant avoidance of mortality or morbidity outcomes, i.e. increment of improvement achieved in glycaemia, blood pressure, lipids and sleep apnoea, by a 5% weight loss.*
>
> *The ACPM considered it was unlikely that any increment of improvement in these cardiovascular risk parameters from a 5% weight loss would be sufficient to avoid, in the majority of patients, the necessity for pharmacotherapy. Therefore, patients would be using an additional lifelong medication, by injection, for no demonstrated benefit of outcome over that achieved by their cardiovascular medication. This would result in many patients would be exposed to increased toxicity for a prolonged period of time.*
>
> *The ACPM considered that in patients with "pre-diabetes" for whom 5% weight loss might prevent development of diabetes, if they developed diabetes, diet and exercise would be the most appropriate diabetes management options, not liraglutide (1.8 mg). Therefore, use of liraglutide 3 mg for weight loss in patients with "pre-diabetes" was considered to be inappropriate.*

Three independent Australian endocrinologists were specifically asked about the clinical meaningful of 5% weight loss.

Independent expert 1:

> *The overall conclusion of Bray and Ryan[80] is that a weight loss of 5 to 10% can significantly reduce the development of diabetes in those with pre diabetes and reduce blood pressure and risk factors for cardiovascular disease in higher risk patients, but that trial data indicate that weight loss of 10 to 15% or greater has more substantial, clinically significant benefits. Consistent with this, clinical trials conducted for regulatory purposes … commonly employ a criterion of weight loss from baseline of 5% to demonstrate efficacy, whereas goals set by clinicians for individual patients are more likely to suggest 10-20% with the aim of achieving a clinically meaningful outcome.*

Independent expert 2:

> *Is a 5% weight loss clinically significant? The answer is yes, for glycaemia, across the board; probably yes for blood pressure for individuals, and on a population basis yes; lipids/waist circumference/sleep apnoea yes. Not reported are mood changes, which I believe are likely to be of clinical benefit, in terms at least of morbidity.*

Independent expert 3:

> *In clinical practice, some patients who achieve 5% weight loss also have an associated dramatic improvement in metabolic and cardiovascular indicators (for example, hypertension, blood lipids, blood glucose, insulin sensitivity). Other patients do not, but 5% (average weight loss) is a reasonable regulatory hurdle. 10% weight loss is associated with unequivocal benefits, but averaged across all patients would be an unreasonable regulatory hurdle.*

Comment on weight loss is a surrogate; 5% is not clinically relevant

At a population level, the regulatory threshold (for example, EMA guidelines adopted by TGA, FDA guidelines) is a placebo subtracted, 5%, weight loss, averaged across all patients.

[80] Bray GA, Ryan DH. Update on obesity pharmacotherapy. *Ann N Y Acad Sci.* 1311: 1-13 (2014).

Based on current knowledge, it is therefore **not** reasonable to argue that the application to register Saxenda should be rejected because weight loss is a surrogate endpoint.

A 5% average population level weight reduction has been set as a regulatory threshold because the current consensus (admittedly not shared by all experts) is that this is clinically relevant. The EMA's CHMP concluded that the weight loss reported from the clinical development program for Saxenda is clinically relevant (see page 87 of the EPAR). Based on the currently available evidence, it is not reasonable to argue that the application to register Saxenda should be rejected because a placebo-subtracted population-level weight loss of 5% weight loss is not clinically relevant.

At an individual-patient level, the expert advice to the TGA is that 10% weight loss produces unequivocal benefits, but that 5% is probably also of benefit.

In their pre ACPM response, the sponsor has provided excerpts from the NHMRC Guidelines, which state that weight loss of only 5% can produce health benefits at the individual level (examples given include kidney disease, sleep apnoea, musculoskeletal problems, gastro oesophageal reflux, urinary incontinence, depression).

Appendix 2. Adverse event, cardiovascular disease

Pulse rate

GLP-1 analogues are known to increase pulse rate. The mechanism has not been established, but is possibly via GLP-1 receptors in the cardiac pacemaker.

Based on the pool of the 5 trials (1 Phase II + 4 Phase III), the mean resting pulse rate increased after the start of treatment in the liraglutide 3 mg group and peaked at 6 weeks (mean change from baseline: 4.5 bpm; placebo: 1.1 bpm). The effect declined over time, but was still 2.8 bpm higher than placebo at the end of the trials.

The effect on pulse rate is of similar size for the 1.8 mg dose and the 3.0 mg dose.

The EMA was reassured that the effect of liraglutide on pulse rate was not dose dependent. For example, the following is from page 65 of the EPAR:

> *According to the Applicant, there is no dose response for the effect on pulse. This is supported by data from trial 1922 in T2DM. The data from Trial 1807 are somewhat less convincing, but a dose response, if any, must be small.*

And, page 76:

> *The consistent finding that GLP-1 analogues increase the pulse rate has caused concern with respect to **cardiovascular safety**. There are data that GLP-1 receptors are present in the cardiac pacemaker suggesting a direct effect of liraglutide on the heart. The maximum increase in pulse rate is 4.5 bpm for liraglutide (compared to placebo 1.1 bpm, treatment effect 3.4 bpm) after 6 weeks and slightly declined thereafter. The effect persists until end-of-trial and is then 2.8 bpm above placebo. There is no indication of a dose response.*
>
> *The period of maximum effect on pulse rate is well covered by the safety database; however less information is available with respect to (very) long term effects of the increase in pulse. Because the effect on pulse is not strongly related to dose and seems to be a class effect, information from the large cardiovascular safety trials with liragutide (LEADER) and other GLP-1 analogues is relevant.*

Major adverse cardiac events (MACE)

The pre-specified MACE (cardiovascular death, non fatal stroke, myocardial infarction) analysis for the weight loss trials gave a pooled hazard ratio of 0.40 (95% CI: 0.15, 1.05). This was based on 17 events. The pooled analysis for the diabetes trials (Victoza) reported a similar result.

These results need to be seen in light of the entry criteria for the trials. Specifically, in relation to the outcome of MACE, patients with "clinically significant cardiovascular heart disease" in the last 6 months were excluded at the discretion of the investigator; as were patients with NYHA [New York Heart Association] Class III/IV heart failure.

Pooling data across all 5 trials (1 Phase II + 4 Phase III) the baseline characteristics were:

- Men: 29%
- Mean weight: 106 kg
- Mean BMI: 38 kg/m^2
- BMI<30 kg/m^2: 5%
- Mean age: 47 years
- 65+ years: 7%
- 75+ years: 0.4%
- History of cardiovascular disease: 9%
- Hypertension: 39%
- Dyslipidaemia: 34%

The increase in pulse rate raises concerns about an increase in MACEs, especially with long term use. Patients recruited to the clinical development program were largely middle aged women without heart disease. Consequently, there were only a few MACEs reported from the pre-market trials. The point estimate (Saxenda versus placebo) was 0.4, however the CI was wide; and given the types patients recruited to these trials, the possibility that Saxenda could increase the risk of MACEs when used in the real-world of everyday clinical practice remains a possibility (given the increase in pulse rate).

The sponsor made the following points:

- Cardiovascular safety data for Victoza (1.8 mg) from LEADER are applicable to Saxenda because the increase in pulse rate is not dose dependent. This was acknowledged by the EMA and FDA.
- All the patients in LEADER have a diagnosis of CV disease or had a CV risk factor, making them a sensitive cohort for detecting a causal association between liraglutide and CV disease.
- An independent external data monitoring committee has evaluated unblinded safety data from LEADER; and, to date, has not raised any concerns.
- The results from LEADER will be available in the final quarter of 2016. That is, if Saxenda is approved, no Australian patient will be exposed to more than 12 month of Saxenda before LEADER reports.
- A cardiovascular safety trial for Saxenda is not feasible: large sample size and long follow-up required.
- A simulation study showed overlap between exposure of obese patients to liraglutide 3.0 mg and exposure of T2DM patients to liraglutide 1.8 mg.

Attachment 3

Reasoning as to why the additional risk minimisation measure of prescriber (and dispenser and patient) education for Saxenda is needed

Risk minimisation measures (RMMs) are public health interventions designed to:

- Prevent adverse reactions associated with exposure to a medicine

- Reduce the number of adverse reactions associated with exposure to a medicine
- Reduce the severity of adverse reactions, should they occur
- Ensure the right patients are using the medicine, at the right dose, at the right time, prescribed by the right healthcare professional, and with the right information and right monitoring.

Other ways of describing the role of RMMs include:

- They aim to improve the benefit/risk balance of a medicine by reducing the burden of adverse reactions.
- They are a way of proactively managing/mitigating the risk of adverse reactions.
- They facilitate informed decision making about use of the medicine by the prescriber and the patient; thereby optimising use; improving the benefit/risk balance.
- They positively influence the actions of the prescriber, dispenser, and patients towards minimising the risks associated with a medicine.

Routine RMMs include:

- PI
- CMI
- Labelling
- Pack size and design
- Scheduling: S2/3, S4, S8

Additional RMMs include:

- Doctor education
- Pharmacist education
- Patient education
- Controlled access
- Other

Saxenda has been approved for marketing by EMA and FDA. The EMA has not required any additional RMMs. The FDA has required a REMS around medullary thyroid cancer and pancreatitis.

Medullary thyroid cancer

When Victoza (liraglutide 1.8 mg) was registered for T2DM in 2010, the EMA considered that medullary thyroid cancer was a vanishingly rare cancer in humans and that the higher risk reported from studies in rodents was because these animals are susceptible to this particular type of thyroid cancer (rare in humans). The EMA therefore considered that routine RMM (statements in PI) were appropriate; and the TGA also formed the same view. Because this type of thyroid cancer is so rare in humans, the EMA also considered that routine RMMs were appropriate for Saxenda (liraglutide 3.0 mg) (see for example EPAR for Saxenda, p82; the sponsor has also provided the more detailed EMA evaluation reports). A medullary thyroid cancer case series registry in the US is an additional PhV activity (MTC-22341).

Pancreatitis

For both Victoza and Saxenda, the EMA is applying routine RMM (statements in PI) for this safety concern (see for example EPAR, page 81; the sponsor has also provided detailed EMA evaluation reports). For Saxenda, the TGA noted the following:

- There was an imbalance of pancreatitis in the pre-marketing Saxenda studies, although the numbers were small and several of the cases were associated with gall-bladder disease.
- The size and duration of the clinical development program means that there is uncertainty around the risk of pancreatitis for the 3.0 mg dose of liraglutide (Saxenda).

The TGA therefore considered that prescribers should ensure patients are aware that the risk of pancreatitis has not been fully characterised, at this point in time.

Reasoning as to why the additional RMM of prescriber, dispenser, and patient education is needed for Saxenda

Doctor (and pharmacist and patient) education is required, to increase the probability that the patient will be fully informed as to the limitations associated with the use of Saxenda. Briefly, these are:

- Limited long term efficacy data, beyond 12 months.
- Limited long term safety data, beyond 12 months. We are awaiting the results from further studies to better characterise any possible risk of pancreatitis and breast cancer. Also, the effect of Saxenda on heart disease and stroke has not been established.

Fully informing patients of the limitations of Saxenda use will ensure that the right patients are using Saxenda for the right reasons and that they will be appropriately monitored.

Attachment 1. Product Information

The PI approved for Saxenda at the time this AusPAR was published is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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