Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for lixisenatide

Proprietary Product Names: Lyxumia / Lyxumia Treatment initiation pack / Lixisenatide Sanofi / Lixisenatide Sanofi Treatment initiation pack / Lixisenatide Winthrop / Lixisenatide Winthrop Treatment initiation pack

Sponsor: Sanofi-Aventis Australia Pty Ltd

August 2013

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 Ageing, 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 <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (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, in that it will provide 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

I. Introduction to product submission

Submission details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	20 March 2013
Active ingredient:	Lixisenatide
Product Names:	Lyxumia / Lyxumia Treatment initiation pack / Lixisenatide Sanofi / Lixisenatide Sanofi Treatment initiation pack / Lixisenatide Winthrop / Lixisenatide Winthrop Treatment initiation pack.
Sponsor's Name and Address:	Sanofi-Aventis Australia Pty Ltd 12-24 Talavera Road Macquarie Park NSW 2113
Dose form:	Solution for injection
Strengths:	10 µg (0.05 mg/mL) and 20 µg (0.1 mg/mL)
Containers:	Pre-filled injector pen
Pack sizes:	Each pack contains 1, 2 or 6 prefilled injector pens; Treatment initiation packs contain 1 x 0.05 mg/mL prefilled injector pen and 1 x 0.1 mg/mL prefilled injector pen.
Approved Therapeutic use:	For the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with metformin, metformin and sulphonylurea, basal insulin and metformin, basal insulin and sulphonylurea when these, together with diet and exercise, do not provide adequate glycaemic control (see sections *Clinical trials* and *Precautions* (Risk of Hypoglycaemia)) for available data on the different combinations.
Route of administration:	Subcutaneous injection
Dosage (abbreviated):	The product is administered once daily within the hour prior to the first meal of the day or the evening meal. The starting dose is 10 µg once daily for 14 days. Then, the dose should be increased to 20 µg once daily, which is the maintenance dose. When added to existing metformin therapy, the current metformin dose can be continued unchanged. When added to a combination of a basal insulin and a sulphonylurea, a reduction in the dose of the basal insulin or the sulphonylurea may be considered according to individual response to reduce the risk of hypoglycaemia (see Precautions).

ARTG Numbers:	192716, 192717, 192718, 192719, 192720, 192722, 192723, 192724

Product background

Lixisenatide is a stable agonist at receptors for glucagon-like peptide 1 (GLP-1), a gut derived incretin hormone that stimulates insulin release and suppresses glucagon secretion, inhibits gastric emptying and reduces appetite and food intake.

This AusPAR describes the application by Sanofi-Aventis Australia Pty Ltd (the sponsor) to register lixisenatide for the treatment of adults with type 2 diabetes mellitus (T2DM) to achieve glycaemic control in patients not adequately controlled on oral antidiabetics and/or basal insulin:

In combination with the following oral antidiabetics:

- metformin,
- a sulphonylurea, or
- a combination of metformin and a sulphonylurea,

In combination with a basal insulin:

- alone,
- in combination with metformin, or
- in combination with a sulphonylurea

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods on 10 April 2013.

The international regulatory status for lixisenatide at the time this application was considered by TGA is shown in Table 1.

Table 1. Lixisenatide international regulatory status at January 2013

Country	Submission Date	Status (pending; approved; deferred; withdrawn; rejected)
EU	28 October 2011	Pending (CHMP Positive Opinion adopted on 15 November 2012)
Ukraine	10 November 2011	Pending
Mexico	28 November 2011	Approved (19 December 2012) for "Treatment for patients with type 2 diabetes non well controlled with oral antidiabetic drug products (as metphormine, sulfonylurea or both) and/or with basal insulin (alone, in combination with metphormine or with a sulfonylurea)."
Brazil	29 November 2011	Pending
Canada	29 November 2011	Pending
Australia	7 December 2011	Pending
South Africa	9 December 2011	Pending
Switzerland	16 December 2011	Pending
Taiwan	30 March 2012	Pending
India	23 April 2012	Pending
Russian Federation	28 April 2012	Rejected - New submission being prepared*
Japan	11 June 2012	Pending
USA	20 December 2012	Pending

* Dossier was submitted in Russian Federation in April 2012 and recently in late November 2012, the company was informed that the dossier has been rejected by the health agency. The list of deficiencies that the company has been provided with includes a series of pharmaceutical questions as well as some labeling requests for modification. There was no question directly related to the assessment of Benefit/Risk ratio.

Of note, the company did not have an opportunity to respond to these deficiencies during the review process; Indeed, as per the local review process, the application was reviewed by the health agency and the rejection letter was then issued. The company is currently working on these deficiencies and intends to submit a new application in near future.

Product Information

The approved Product Information (PI) for Lyxumia current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

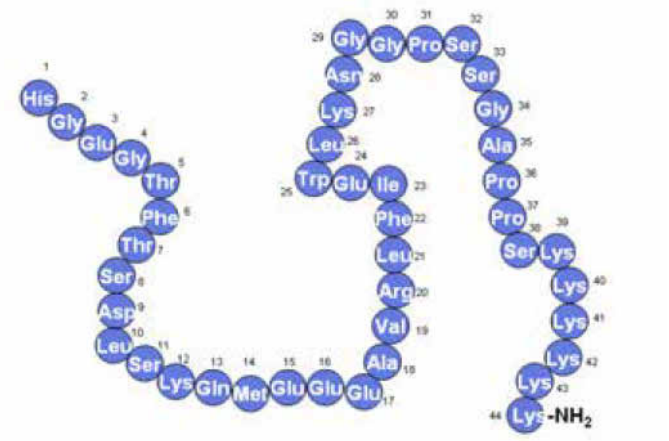
Lixisenatide (structure shown in Figure 1) is a synthetically produced polypeptide that is a potent and selective GLP-1 receptor agonist. It is structurally similar to GLP-1 as well as exenatide, which is registered in Australia under the tradename Byetta (by Eli Lilly) as an adjunct therapy to improve glycaemic control in patients with T2DM. Both lixisenatide and exenatide are incretin mimics that exhibit several of the antihyperglycaemic actions of GLP-1.

The proposed 0.05 mg/mL and 0.1 mg/mL solutions for injection will be marketed as multi-dose 3 mL cartridges that are irreversibly integrated into fixed dose disposable pen injectors which deliver 14 x 0.2 mL daily doses. This corresponds to 10 µg of the drug substance for the 0.05 mg/mL product and 20 µg of the drug substance for the 0.1 mg/mL drug product.

Drug substance (active ingredient)

The drug substance has the following structure:

Figure 1. Structure of lixisenatide



Lixisenatide is an amorphous, hygroscopic, white to off-white powder that is slightly soluble (1-10 mg/mL) in aqueous systems over the pH range 2-9. It is manufactured using solid phase peptide synthesis from L-amino acids as described in the Sanofi-Aventis Deutschland GmbH Drug Master File (DMF). The DMF has been assessed and found to be acceptable.

The method of manufacture leads to a large number of impurities. Acceptable toxicological justification was provided for the proposed impurity limits.

The assay limits and method has been accepted and is considered stability indicating.

Adequate specifications and limits are also included in the drug substance specification to control residual solvents, acetate content, water content, microbial content, bacterial endotoxins and chiral purity. Acceptable method and validation details were provided.

Data were provided showing that the drug substance is stable for up to 18 months when stored at -20°C (protected from light) and on this basis the company has proposed a retest period of 30 months.

Drug product

The drug products, which are manufactured at the same site as used to make the drug substance, are formulated as simple buffered solutions with a stabilising agent and an antimicrobial preservative. The manufacturing process uses conventional methods. Sterility and endotoxin aspects of the product's manufacture have been considered and found to be acceptable. The pen injector device has also been assessed by the TGA and found to be suitable for its intended purpose.

The key determinants of the product's quality, aside from sterility, are its assay and degradation product limits. The drug product specification includes limits for specific degradants at levels that have been toxicologically justified. Appropriate limits are also included for unspecified degradants and total impurities. The assay limits are 96.0-105.0% of the label claim at release and 90.0-105.0% of the label claim at expiry, which are typical limits for this kind of product.

The assay and degradants are measured using a very similar high performance liquid chromatography (HPLC) technique to that used for the control of assay and degradation products in the drug substance and each of the nominated degradants are resolved using this method. This approach has been accepted by the TGA on the basis that the errors caused by inclusion of impurities will not significantly affect the assay result.

Stability data were presented to support the proposed shelf-life for the unopened product of 24 months (protect from light) when stored between 2°C and 8°C. Data were also supplied to support the in-use shelf life of 14 days when the product is stored below 30°C.

Biopharmaceutics

The submission included two bioavailability studies (DDR6864 and BEQ11094) as well as a justification for not providing a study to determine the absolute bioavailability of lixisenatide.

The studies revealed that, after subcutaneous (SC) administration of lixisenatide in patients with T2DM, the rate of absorption was rapid (time to maximum plasma concentration (Tmax) 1-3.5 h) and not influenced by the dose administered. As a peptide, lixisenatide is eliminated through glomerular filtration, followed by tubular reabsorption and subsequent metabolic degradation resulting in smaller peptides and amino acids, which are reintroduced in the protein metabolism. After multiple dose administration in patients with T2DM, mean apparent half-life generally ranged from 1.5 to 4.5 h and the mean apparent clearance ranged from 20 to 67 L/h at steady state.

The same test method, a ligand binding assay designated DOH0498, was used for the determination of lixisenatide in Studies BDR6864 and BEQ11094. However, due to problems with this method, the results from the bioavailability studies are considered as suggestive rather than definitive.

Study BDR6864 compared a dose of 10 µg of lixisenatide given via SC administration in the thigh, upper arm and abdomen. The results suggest equivalence between arm and abdomen but that the maximum concentration (Cmax), though not the area under the plasma concentration-time curve (AUC), is lower for the thigh.

Study BEQ11094 compared the bioavailability of the two proposed product strengths given as a 10 µg dose of lixisenatide. The results suggest equivalence of the two strengths after dose normalisation.

Advisory committee considerations

Details of the submission were considered at the 144th meeting of Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) in May 2012. The PSC endorsed all of the questions raised by the TGA in relation to the pharmaceutical and biopharmaceutical aspects of the submission.

Quality summary and conclusions

All issues raised in relation to pharmaceutical and biopharmaceutical aspects were resolved.

The PSC raised concerns about lixisenatide antibodies. The PSC noted that there was no clear indication or statement in the draft PI regarding the percentage of patients that developed antibodies or the timeframe in which the antibodies developed. The PSC considered that if binding to the antibody is non-reversible, a target mediated clearance of the protein will occur as the antibodies develop and this will result in a significant drop in efficacy. This was drawn to the attention of the Delegate.

III. Nonclinical findings

Introduction

The general quality of the submitted nonclinical data was high. Pivotal studies examining repeat dose toxicity, genotoxicity, carcinogenicity and reproductive toxicity were conducted under good laboratory practice (GLP) conditions. Safety related studies not performed under GLP were nevertheless adequately documented.

Pharmacology

Primary pharmacology

Glucagon like peptide 1 is a hormone that is released by enteroendocrine cells in the distal small bowel and colon within minutes of ingesting a meal. It acts to regulate plasma glucose concentrations by stimulating glucose-dependent insulin release and insulin synthesis, suppressing glucagon secretion, inhibiting gastric emptying and reducing appetite and food intake.[1]

Lixisenatide was shown to bind to human GLP-1 receptors *in vitro* with nanomolar affinity (inhibition constant (K_i) = 1.33 nM in radioligand binding experiments), having almost four-times greater affinity than human GLP-1. Glucagon like peptide 1 receptor agonist activity was demonstrated *in vitro* in isolated perfused pancreas from normoglycaemic rats, with lixisenatide and GLP-1 both enhancing glucose-stimulated insulin secretion. Similarly, glucose-stimulated insulin secretion was enhanced in isolated perfused pancreas obtained from obese Zucker Diabetic Fatty rats that had been pre-treated with lixisenatide, but not from pre-treated lean rats. The rat GLP-1 receptor is 90% homologous to the human receptor.[2]

Anti-diabetic activity was demonstrated *in vivo*, including in a number of rodent models of diabetes. Improved oral glucose tolerance was seen after a single dose of lixisenatide (administered 15–30 min prior to glucose challenge) in diabetic db/db mice (half maximal effective concentration (EC_{50}) = 1.24 µg/kg IP), insulin-resistant obese Zucker rats (statistically significant at ≥5 µg/kg SC) and normoglycaemic dogs (≥0.15 µg/kg SC). Plasma glucose excursions were still significantly reduced when db/db mice were injected into the peritoneum (IP) with lixisenatide (486 µg/kg) up to 12 h prior to glucose challenge (and a non-significant reduction [38%] was still apparent at 18 h post-dose). Baseline plasma glucose concentrations in normoglycaemic dogs were unaffected by treatment, and the suppression of plasma glucose excursions in the species was associated with reduced insulin and C-peptide levels; suppression of glucose-induced glucagon secretion was also shown. Inhibition of gastric emptying was demonstrated in mice.

In studies involving repeated treatment, lixisenatide reduced water consumption, fasting blood glucose levels, and glycosylated haemoglobin (HbA_{1c}), improved glucose tolerance, and increased pancreatic β-cell volume and messenger ribonucleic acid (mRNA) levels in diabetic mice (at 4.9–486 µg/kg IP twice daily (BID) for 6–13 weeks). By comparison, untreated diabetic mice showed a progressive impairment of the response to oral glucose challenge over the course of the study. In obese diabetic rats on a high-fat diet, SC infusion of lixisenatide (48.6 µg/kg/day via osmotic minipumps) was associated with reduction in

[1] Drucker D.J. and Nauck M.A. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet* 2006;368:1696–1705.
[2] Drucker D.J. Glucagon-like peptides. *Diabetes* 1998;47:159–169.

elevated basal plasma glucose concentration, reduced HbA_{1C} and improved glucose tolerance after 5.5 weeks of treatment. Plasma insulin levels were increased, suggestive of improved pancreatic β-cell function.

Lixisenatide is proposed to be used in combination with metformin, a sulfonylurea and/or a basal insulin (as dual or triple combinations). Lixisenatide did not modify the reduction in serum glucose induced by insulin glargine in dogs.

Secondary pharmacodynamics and safety pharmacology

Radioligand binding studies to screen for secondary activity (91 different receptors and ion channels) support lixisenatide having a high degree of specificity for the GLP-1 receptor. Affinity was greatest for the N-type Ca^{2+} channel (half maximal inhibitory concentration (IC_{50}) for displacement of radioligand, 40–100 nM; ≥30 times weaker compared with the K_i at the GLP-1 receptor). In functional experiments (cultured rat dorsal root ganglion cells), inhibitory activity at the N-type Ca^{2+} channel was very weak (IC_{50} approximately 10 μM; approximately 70000-times the clinical Cmax at the maximum recommended human dose).

Other secondary pharmacodynamic studies demonstrated cardioprotective effects for lixisenatide in the isolated Langendorff–perfused rat heart model of ischaemia/reperfusion injury, significantly reducing the infarct area at a concentration of 0.3 nM. Similar effects were observed with GLP-1(7–36)amide and liraglutide (an existing registered GLP-1 receptor agonist) at the same concentration. The mechanism for the cardioprotective effect of GLP-1 receptor agonists may be through activation of anti-apoptotic signalling pathways such as phosphoinositide 3-kinase and mitogen-activated protein kinases.[3] Lixisenatide also had anti-atherosclerotic and serum cholesterol lowering activity in male apolipoprotein E (ApoE) knockout mice following SC infusion for 16 weeks (133–164 μg/kg/day), which is in keeping with similar findings for exenatide (another existing registered GLP-1 receptor agonist[4]). Although these effects are not directly related to the primary indication being sought, they are relevant to the overall risk profile for individuals with type 2 diabetes.

Specialised safety pharmacology studies covered the central nervous system (CNS) and cardiovascular and respiratory systems. No neurological effects were observed in mice following SC administration of lixisenatide at doses up to 2000 μg/kg. With intravenous (IV) administration in rats, CNS function was unaffected at 0.1 μg/kg, while higher doses were associated with reduced body tone (≥1 μg/kg), apathy, decreased locomotor activity, abnormal dispersion within the home cage, impairment of righting reflex (≥10 μg/kg), and decreased spatial locomotion, grip strength and pain response (≥50 μg/kg). One animal dosed at 50 μg/kg exhibited clonic convulsions 5 min post-dose. Based on a plasma volume of 4.2 mL/100 g for male Wistar rats[5], the dose in rats without CNS effect corresponds to a plasma concentration approximately 3.4-times higher than the clinical Cmax at the maximum recommended human dose (0.704 ng/mL; Study ACT6011), while those doses with effect were approximately 34–1690-times higher than the peak level anticipated in patients. The sponsor tissue distribution studies indicated that lixisenatide did not cross the blood-brain barrier to any appreciable extent in the species (see *Pharmacokinetics* below for further discussion). However, Hunter and Hölscher[6] were able

[3] Bose A.K., Mocanu M.M., Carr R.D., Brand C.L. and Yellon D.M. Glucagon-like peptide 1 can directly protect the heart against ischemia/reperfusion injury. *Diabetes* 2005;54:146–151.
[4] Arakawa M., Mita T., Azuma K., Ebato C., Goto H., Nomiyama T., Fujitani Y., Hirose T., Kawamori R. and Watada H. Inhibition of monocyte adhesion to endothelial cells and attenuation of atherosclerotic lesion by a glucagon-like peptide-1 receptor agonist, exendin-4. *Diabetes* 2010; 59: 1030–1037.
[5] Lee H.B. and Blaufox M.D. Blood volume in the rat. *J. Nucl. Med.* 1985;26:72–76.
[6] Hunter K. and Hölscher C. Drugs developed to treat diabetes, liraglutide and lixisenatide, cross the blood brain barrier and enhance neurogenesis. *BMC Neurosci.* 2012;13(33): 1–6.

to detect transfer of lixisenatide across the blood-brain barrier in mice following IP administration at doses ≥2.5 nmol/kg (approximately 12 µg/kg), with repeat daily dosing associated with an increase in neuronal proliferation and cyclic adenosine monophosphate (cAMP) formation. The effects observed in the CNS safety pharmacology study in rats may have been mediated either centrally or peripherally.

In cardiovascular pharmacology studies, lixisenatide (50–500 µg/kg IV) increased mean arterial blood pressure in conscious rats, which is consistent with previously reported actions of GLP-1 agonists in this species.[7, 8] The effect may be mediated by CNS as well as peripheral GLP-1 receptor activation[9], but a significantly more prominent role for the latter would be expected given the limited CNS exposure. No cardiovascular or respiratory effects were observed in dogs at doses up to 10 µg/kg IV (approximately 15 times the maximum recommended human dose on a µg/m^2 body surface area basis).
Weak inhibition of the human ether-a-go-go potassium (hERG K^+) channel was shown for lixisenatide, but with the IC_{50} > 30 µg/mL (a concentration more than 40000-times higher than the clinical Cmax), no clinical significance is attached to the finding. Lixisenatide had no effect on resting membrane potential or action potential parameters in isolated rabbit Purkinje fibres at 0.57 µg/mL (>800 times the clinical Cmax). ECG abnormalities were not observed in the repeat-dose toxicity studies with lixisenatide in dogs.

Pharmacokinetics

Lixisenatide was rapidly absorbed following SC administration in all species, with plasma Cmax typically occurring between 0.25–1 h in mice and rats, 1–2.7 h in rabbits, 2 h in dogs and pigs and 1–2 h in humans. Bioavailability by the SC route was 15–50% in mice, approximately 3% in rats, 90% in rabbits and dogs, and 70% in pigs. Terminal elimination half-lives after SC administration were shorter in mice and rats (0.5–1 h) compared with the larger species (1–4.5 h in rabbits, 3–6 h in dogs, 2.7 h in pigs and 3–5 h in humans).

In the early phases of repeat-dose toxicity studies involving twice daily SC administration, plasma AUC was approximately dose-proportional in mice, less than dose-proportional in rats, and less than dose-proportional at lower doses in dogs, but approximately dose-proportional at higher doses. Anti-lixisenatide antibodies developed with continued treatment in the laboratory animal species, complicating the interpretation of the toxicokinetic data. In the 6 month rat study, almost no antibody formation was seen up to day 7, but most animals were antibody-positive by day 28. Only total plasma lixisenatide concentrations (that is, both bound and unbound to anti-lixisenatide antibodies) were quantified in the studies. Antibody development was associated with a marked increase in plasma AUC for total lixisenatide, and severely impacted the dose dependence and proportionality of exposure. The increase in exposure is consistent with markedly reduced clearance of lixisenatide from plasma when bound to anti-lixisenatide antibodies. The bound form should be excluded from glomerular filtration, and may also be protected from metabolic degradation by peptidases. Anti-lixisenatide antibodies also commonly developed in humans, and, as in the laboratory animal species, this was associated with significantly increased exposure to total lixisenatide.

The neutralising potential of anti-lixisenatide antibodies was only investigated in one species and in one study (rat carcinogenicity). Using an *in vitro* functional assay (GLP-1 receptor mediated formation of cyclic AMP) and pooled plasma toxicokinetic samples, it

[7] Barragán J.M., Rodríguez R.E., et al., Interactions of exendin-(9-39) with the effects of glucagon-like peptide-1-(7-36) amide and of exendin-4 on arterial blood pressure and heart rate in rats. *Regul. Pept.* 1009;67:63–68.
[8] Barragán J.M., Rodríguez R.E. and Blázquez E. Changes in arterial blood pressure and heart rate induced by glucagon-like peptide-1-(7-36) amide in rats. *Am. J. Physiol.* 1994;266**:**E459–466.
[9] Barragán J.M., Eng J., Rodríguez R. and Blázquez E. Neural contribution to the effect of glucagon-like peptide-1-(7-36) amide on arterial blood pressure in rats. *Am. J. Physiol.* 1999;277**:** 784–791.

was shown that while biological activity was not abolished in antibody-positive samples, changes in plasma AUC were not associated with parallel changes in the concentration of biologically active drug. As examples, the plasma AUC for total lixisenatide was more than doubled in high-dose males between days 86 and 359, while the biologically active concentration was largely unchanged (<8% increase); in females over the same period, bioactivity was halved while AUC remained unchanged in the mid-dose group, and a 133% increase in AUC in the high-dose group was associated with an increase in bioactivity less than half that size. These findings indicate some neutralising capacity for anti-lixisenatide antibodies. A dose-relationship was seen for bioactivity on day 4 and day 359, but not on day 86. Neutralising potential of anti-lixisenatide antibodies in humans is suggested by apparent equivalent efficacy in antibody positive and negative subjects (as change in HbA_{1c}, and according to the Clinical Overview) despite increased total lixisenatide exposure.

Lixisenatide showed low to moderate plasma protein binding in rats (62%) and dogs (49%), similar to that in humans (55%). Tissue distribution studies using radiolabelled lixisenatide in rats showed rapid and wide distribution of radioactivity following IV and SC administration. Fifteen minutes after SC administration (the Tmax in blood), the highest concentrations of radioactivity were found at the injection site, followed by the pancreas, renal tissue (cortex), pineal body, salivary gland, stomach and lung. The kidneys, adrenals, thyroid, pituitary, salivary glands and lung showed the highest concentrations of radioactivity after IV dosing. Radioactivity levels in the testis, brain and spinal cord were close to background at all time points. Enzyme linked immunosorbant assay (ELISA) measurements in brain tissue indicated drug levels that corresponded to the amount of plasma in the brain.

In vitro studies showed extensive metabolism of lixisenatide following incubation with human liver and kidney S9 fractions (a metabolic activation system), with 28 metabolites generated. The rate of metabolism in kidney S9 fractions from laboratory animal species (mouse, rat, rabbit and dog) was similar to that for humans; degradation was also similar in liver S9 fractions of non-rodents compared with humans, while greater stability was evident in mouse and rat liver S9 fractions. Phenylalanine and alanine residues were the main sites for metabolic cleavage.

Pharmacokinetic drug interactions

Negligible or only weak inhibition was seen with lixisenatide against cytochrome P450 (CYP) CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A in experiments with human liver microsomes. The most potent activity was at 2C19 (32% inhibition at 20 μM; a concentration >137,000-times higher than the clinical Cmax at the maximum recommended human dose). Lixisenatide did not induce CYP1A, 2B6, 2C9 or 3A/3A4 in primary cultures of human hepatocytes, and was shown not to inhibit the human OCT2 (kidney) or OATP1B1 (liver) transporters expressed in Chinese hamster ovary (CHO) cells (≤37 nM or 180 ng/mL; 255-times the clinical Cmax). No *in vivo* drug-interaction studies were conducted in animals.

Toxicology

Acute toxicity

Single-dose toxicity studies were conducted by the SC and IV routes in mice (≤500 μg/kg), rats (≤5000 μg/kg) and dogs (≤200 μg/kg SC and ≤100 μg/kg IV), and revealed no mortality or other notable findings apart from effects on body weight in rats (inhibition of body weight gain or small loss of body weight). The highest doses tested in the respective species are >100, >2000 and approximately 150–300-times higher than the maximum recommended human dose on a $\mu g/m^2$ body surface area basis (for a 50 kg subject).

Repeat dose toxicity

Repeat dose toxicity studies of up to 13 weeks duration in mice, 26 weeks in rats and 52 weeks in dogs were conducted. All studies involved SC administration (the clinical route), except for a 4 week IV study in rats. Lixisenatide was administered BID (second injection, approximately 8 h after the first) to promote exposure. The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with ICH[10] guidelines.

Relative exposure

Cross-species exposure comparisons should ideally be based on systemic exposure to biologically active drug. The reported plasma AUC values for total lixisenatide measured after the development of antibodies are not considered to be a reliable indicator of this given that the biologically active fraction (comprising at least drug not bound to antibodies) is unknown and likely highly variable across species (being dependent on the nature and extent of the antibody response). Accordingly, and as a conservative measure, exposure ratios are calculated below based on animal plasma AUC values obtained no more than 14 days after the initiation of treatment. The human reference value used is that for antibody-positive subjects as it represents a worst case scenario for clinical exposure (8.6-fold increase in exposure compared with antibody-negative subjects).

Table 2. Relative exposure in selected repeat-dose toxicity and carcinogenicity studies [SC administration]

Species	Study duration	Dose (µg/kg/day)	$AUC_{0-24\,h}$ (ng.h/mL)	Exposure ratio*
Mouse (CD-1)	13 weeks	33.2	24.7	3.4
		331.2	322	44
		1656	1812	250
		3313	2618	361
	2 years *[carcinogenicity]*	80	48[a]	7
		400	211[a]	29
		2000	951[a]	131
Rat (SD)	13 weeks	8.2	3.8	0.5
		33.2	20.5	2.8
		331.2	138	19
		1656	320	44
		3313	429	59
	6 months *[pivotal]*	10	11.1	1.5
		200	132	19
		4000	2298	353
	2 years *[carcinogenicity]*	80	68	9
		400	255	35

[10] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)

Species	Study duration	Dose (µg/kg/day)	$AUC_{0-24\ h}$ (ng.h/mL)	Exposure ratio*
		2000	843	116
Dog (Beagle)	13 weeks	40	225	31
		600 / 200†	1399 / 466	64–193
		2000 / 800 / 500†	4711 / 1875 / 1166	161–650
	12 months *[pivotal]*	4	19.0	2.6
		400	932[b]	129
		2000	4711[b]	650
	8 months *[juvenile animals]*	10	27.2	3.8
		40	127	18
		400	1010	139
		200#	478	66
Human (diabetic patients)	ACT6011 (antibody-positive subjects)	[20 µg/day]	7.25	–

* = animal:human plasma AUC over 0 to 24 h ($AUC_{0-24\ h}$); [a] = estimated based on day 14 data in Study 2033-1952;[b] = estimated based on day 1 data in Study 2003-1926; † = dose reduction during the course of the study (on day 29 at the mid-dose level, and on days 15 & 29 at the high-dose level); # = once daily (QD) administration (BID administration otherwise)

Major effects

The major findings in the repeat-dose toxicity studies were effects on body weight and food consumption, and microscopic changes in liver, testis, epididymis and subcutaneous injection sites. In addition, the parotid gland displayed (non-neoplastic) changes in the 2 year mouse carcinogenicity study.

Body weight gain and food consumption

Significant inhibition of body weight gain (or transient body weight loss) and decreased food consumption were observed following SC treatment in every study in rats and dogs. These effects are consistent with lixisenatide's pharmacological activity to delay gastric emptying, and were reversible upon treatment withdrawal. Inhibition of body weight gain exceeded 10% (a criterion used to define a maximum tolerated dose) over the course of treatment at all dose levels in the pivotal studies in rats (up to 18% suppression in males and 28% in females) and dogs (up to 72% in males and 94% in females). Effects on body weight were more severe in dogs, and most prominent in the early phases of treatment. A dose escalation scheme was used in the pivotal (12-month) dog study to limit excessive body weight loss at the mid- and high-dose levels (over the first 1 and 3 months, respectively) for this reason. In contrast, mice treated with lixisenatide showed increased food consumption and body weight gain. The basis for this difference is unclear as lixisenatide was shown to delay gastric emptying in mice in the primary pharmacodynamic studies.

A no observed adverse effect level (NOEL) for reduced food consumption and decreased body weight gain was not established in either rats or dogs; systemic exposure at the lowest observed adverse effect level (LOEL) (4 µg/kg/day in both species) is subclinical in

rats and 2.6 times the anticipated maximum clinical exposure for dogs. Representing exaggerated pharmacology (rather than direct toxicity) and effects desirable in the context of treatment for type 2 diabetes, these findings are not considered adverse.

Liver

Increased vacuolation of hepatocytes was observed in female mice treated with lixisenatide at 3313 µg/kg/day for 13-weeks (relative exposure, approximately 360), consistent with glycogen accumulation (mediated by GLP-1 receptor activation[11]). Reduced hepatocyte vacuolation, indicative of glycogen depletion, was seen in the rat carcinogenicity study (≥80 µg/kg/day; relative exposure, ≥9) and in the 13 week repeat dose study in dogs (≥200 µg/kg/day; relative exposure, ≥64). This probably occurred secondary to the decreased food consumption and reduced body weight gain.

Chronic periportal inflammation was observed in a 5-day study in rats (≥140 µg/kg/day; relative exposure, 6.5; minimal to moderate in severity). Follow-up 5 day studies using animals of the same strain but from a different supplier or different strains of rats did not confirm the finding, and no treatment-related liver histopathological changes were found in the pivotal studies in rats (≤4000 µg/kg/day; estimated relative exposure, ≤353) or dogs (≤2000 µg/kg/day; estimated relative exposure, ≤650). Of note, the pivotal rat study employed animals from the same strain and supplier as in the 5-day study (but conducted 16 months later).

Parotid glands

Basophilic hypertrophic foci in the parotid glands were increased in incidence and severity at all dose levels in the mouse carcinogenicity study (≥80 µg/kg/day; relative exposure, ≥7). This is likely to have a pharmacological basis, occurring as a consequence of increased insulin release caused by GLP-1 receptor activation[12], with chronic insulin administration having been found to exert a hypertrophic effect on the parotid and submandibular salivary glands of healthy mice.[13]

No parotid gland changes were observed in rats (including in the carcinogenicity study) or dogs treated with lixisenatide.

Testis and epididymis

In dogs, treatment at ≥200 µg/kg/day for 13 weeks was associated with tubular dilation of the testes (minimal to mild; characterised by segmental to diffuse dilatation of the seminiferous tubular lumen with variable loss of germ cell layers and Sertoli cell vacuolation) and segmental sperm stasis (relative exposure, ≥64). In the 12 month dog study, seminiferous tubular atrophy, tubular vacuolation, spermatid stasis, hypospermatogenesis and tubule fibrosis were increased in incidence and/or severity at 400 or 2000 µg/kg/day; and moderate to severe oligospermia and aspermia (moderate to severe), and mild to moderate tubular dilation (initial segment and efferent ducts) and epithelial degeneration (comprising flattening of epithelium an loss of cilia in the initial segment) were seen in the epididymis at ≥400 µg/kg/day. Similar findings were observed in the testis (≥10 µg/kg/day) and epididymis (≥200 µg/kg/day) in an 8 month study in juvenile dogs. The use of a pair-fed control group in this study established that the effects are not attributable to decreases in food consumption and body weight gain. Reversibility

[11] López-Delgado M.I., Morales M., Villanueva-Peñacarrillo M.L., Malaisse W.J. and Valverde I. Effects of glucagon-like peptide 1 on the kinetics of glycogen synthase *a* in hepatocytes from normal and diabetic rats. *Endocrinology* 1998;139**:**2811–2817.
[12] Stoffers D.A., Kieffer T.J., Hussain M.A., Drucker D.J., Bonner-Weir S., Habener J.F. and Egan J.M. Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. *Diabetes* 2000;49:741–748.
[13] Wang P.L., Purushotham K.R. and Humphreys-Beher M.G. Effect of chronic insulin administration on mouse parotid and submandibular gland function. *Proc. Soc. Exp. Biol. Med.* 1994;205**:**353–361.

was demonstrated in the juvenile animal study and the 13-week study. The NOEL for toxicity to male reproductive tissues in the dog is 4 µg/kg/day (relative exposure, 2.6).

No testicular effects were observed in mice (≤3313 µg/kg/day for 13 weeks; ≤2000 µg/kg/day in the 2 year carcinogenicity study; relative exposure, ≤131–361). In rats, testis changes (increased incidence/severity of seminiferous tubular atrophy and necrosis, spermatid stasis, mineralisation and chronic inflammation) were observed with treatment at 4000 µg/kg/day in the 6-month study (relative exposure, 353), but not at ≤2000 µg/kg/day in the carcinogenicity study (relative exposure, ≤116).

The greater sensitivity to testicular toxicity by lixisenatide in dogs *cf.* rats is paralleled by higher GLP-1 receptor expression in the male reproductive tract in the species: a comparative expression study showed 100- and 184-times higher expression in the testis and epididymides (whole tissues), respectively, in the dog compared with the rat. GLP-1 receptor expression was also shown to be higher in the dog compared with humans (10 times higher in testis and epididymides; 3.8 fold higher in the caput segment of the epididymis). It remains to be established, though, whether the testicular toxicity by lixisenatide is actually attributable to the drug's GLP-1 receptor agonist activity.

Sperm concentration was reported to be unaffected by treatment with lixisenatide in a 26 week clinical study.

Antibody formation

The formation of anti-lixisenatide antibodies was not associated with exacerbation of toxicity nor any adverse effects associated with antigen-antibody complex deposition (for example, glomerulonephritis). Despite exposure increasing (to total lixisenatide; bound and unbound), there was no apparent increase in pharmacological activity over time in the repeat dose toxicity studies. Some biologically active lixisenatide remained available in antibody-positive rats in the carcinogenicity study.

Subcutaneous injection sites

Refer to *Local tolerance* below. Local tolerance was also not seen to be affected by the development of anti-lixisenatide antibodies.

Genotoxicity

The standard battery of genotoxicity tests was performed with lixisenatide despite these types of studies not being considered to be applicable to peptides and proteins and therefore not needed (*Note for Guidance on Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*; CPMP/ICH/302/95). Lixisenatide was not mutagenic in the bacterial reverse mutation assay (conducted in a suitable set of *Salmonella typhimurium* and *Escherichia coli* strains), and showed no evidence of clastogenicity or aneugenicity in assays in human lymphocytes *in vitro*. No evidence of chromosomal damage was observed in the mouse micronucleus test at a dose up to 5000 µg/kg IV. All assays were appropriately conducted and validated with the exception of the *in vivo* clastogenicity assay. The highest dose tested produced no evidence of toxicity and was well below the Organisation for Economic Cooperation and Development (OECD) limit dose of 2000 mg/kg. The absence of a valid *in vivo* assay for chromosomal aberrations is not considered to be a significant deficiency given the drug's peptide status and negative results in the *in vitro* assays.

Carcinogenicity

The carcinogenic potential of lixisenatide by the SC route was investigated in 2 year studies in mice and rats. Dose selection was appropriate, with the high-dose levels producing estimated systemic exposure levels easily exceeding the 25 fold ratio

(rodent:human) recommended in the relevant guideline (*Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals*; CHMP/ICH/383/1995) in both species without impacting survival; significant inhibition of body weight gain was also evident in rats. Group sizes were appropriate, and dual control groups were used. Administration was twice daily (approximately 8 h apart).

In mice, an increased incidence of thyroid C-cell adenoma associated with increased focal C-cell hyperplasia was seen at ≥400 µg/kg/day in males and at 2000 µg/kg/day in females (relative exposure at the respective dose levels, 29 and 131). No treatment-related increase in tumour incidence occurred in the mouse at 80 µg/kg/day (relative exposure, 7). In rats, focal C-cell hyperplasia and thyroid C-cell adenomas were significantly increased in both sexes at all dose levels (≥80 µg/kg/day; relative exposure, ≥9); in addition, thyroid C-cell carcinomas were observed in both sexes at ≥400 µg/kg/day (relative exposure, ≥35).

Similar thyroid C-cell neoplastic and hyperplastic changes have also been observed in mice and rats treated with exenatide and liraglutide. The mechanism underlying these effects for the class is considered to be a non-genotoxic mechanism involving GLP-1 receptor activation to which rodents are particularly sensitive. Previously evaluated and newly submitted mechanistic studies showed considerably higher GLP-1 receptor expression in the mouse and rat thyroid compared with the human thyroid and increased responsiveness to GLP-1 receptor activation *in vitro* in cell-based functional assays. Treatment with lixisenatide did not produce thyroid proliferative lesions in dogs (≤2000 µg/kg/day for 12 months; relative exposure, ≤650). The human relevance of the rodent thyroid carcinogenicity findings cannot be entirely excluded, and it is appropriate that post-market monitoring for thyroid cancer is to be specifically included in the Australian Risk Management Plan (RMP).

Reproductive toxicity

Reproductive toxicity studies covered all stages (fertility, embryonic development, and pre- and post-natal development). Numbers of animals, the species used, and the timing and duration of treatment were appropriate.

Low levels of radioactivity were detected in the fetuses of rats and rabbits following SC administration of ^{14}C-lixisenatide, most of which was accounted for by degradants; ELISA for lixisenatide showed fetal:maternal plasma ratios of ≤0.14%. Similarly, only low amounts of ^{14}C-lixisenatide derived radioactivity were detected in the milk of lactating rats (≤3.2%) after SC administration, with ELISA assays again showing little of this corresponded to intact drug.

Relative exposure

Exposure ratios achieved in the reproductive toxicity studies are calculated below based on animal:human plasma AUC values for lixisenatide. High relative exposure levels were obtained in both species used (rats and rabbits).

Table 3. Exposure ratios achieved in the reproductive toxicity studies.

Species	Study	Dose (µg/kg/day)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio*
Rat (SD)	Fertility	4	3.1	0.4
		58	40.9	6
		828	481	66
	Embryofetal	5	3.9	0.5

Species	Study	Dose (µg/kg/day)	$AUC_{0-24\ h}$ (ng·h/mL)	Exposure ratio*
	development	70	49.4	7
		1000	581	80
	Pre-/postnatal development	4	3.1	0.4
		40	28	4
		400	232	32
Rabbit (Himalayan)	Embryofetal development	0.3	0.93	0.13
		2	16.0	2.2
		5	41.5	6
		50	293	40
		500	3899	538
Human (diabetic patients)	ACT6011	[20 µg/day]	7.25	–

* = animal:human plasma $AUC_{0-24\ h}$; SC administration in all studies; AUC values in the rat fertility and pre-/postnatal development studies are extrapolated from the embryofetal development study in the species.

Male and female fertility were unaffected in rats treated with lixisenatide at doses up to 828 µg/kg/day SC (estimated relative exposure, ≤66).

In the rat embryofetal development study, treatment with lixisenatide was associated with fetal growth retardation, malformations (including shortening and bending of long bones of fore- and hindlimbs and scapulae, misshapen clavicle and bent pelvic girdle), delayed ossification and skeletal variations at all dose levels (≥5 µg/kg/day; relative exposure, ≥0.5). These fetal effects occurred in the context of maternal toxicity (initial body weight loss and substantial inhibition of body weight gain, associated with decreased food consumption, and clinical signs of decreased motor activity and piloerection at all dose levels).

Two main embryofetal development studies were conducted in rabbits: the first involved dosing at 5–500 µg/kg/day and the second at 0.3–5 µg/kg/day. Post-implantation loss was increased with treatment at 500 µg/kg/day (relative exposure, 538). Five fetuses of lixisenatide-treated dams (compared with no controls) exhibited multiple major malformations in the first study. These consisted mainly of retardation and impaired formation or occlusion of cavities of the trunk, and were present at all dose levels, although the incidence was not dose-related. Impairment of ossification (all dose levels) and gall bladder defects (small or absent; ≥50 µg/kg/day) were additional findings. Increased incidences of sternebrae abnormalities and rib variations were observed at ≥50 µg/kg/day. No treatment-related increase in the incidence of fetal abnormalities was seen in the second study, and one control fetus showed similar adverse findings as seen in the earlier study (severe growth retardation associated with multiple malformations, including gallbladder aplasia) suggesting effects other than on sternebrae, ribs, ossification and post-implantation loss in the first study were incidental. A NOEL for embryofetal toxicity of 5 µg/kg/day (relative exposure, 6) is considered to be established in the rabbit. Doses ≥2 µg/kg/day were maternotoxic in the species (based on body weight loss, decreased food consumption, and clinical signs [hypoactivity and piloerection]; relative exposure, ≥2.2).

Treatment at >40 µg/kg/day in the rat pre-/postnatal development study (relative exposure, ≥4) was associated with decreased postnatal survival, an increased incidence of

insufficient suckling, decreased postnatal body weight gain in males and delayed coat growth. Tail abnormalities (shortened, part missing, tip necrotic, deformed or wavy [indicative of maternal cannibalisation]) and dead pups with retarded development and multiple skeletal malformations were seen at 400 µg/kg/day (relative exposure, 32). Learning and memory, and other developmental parameters (including reproductive function) were unaffected in pups of treated dams. The NOEL for pup development was 4 µg/kg/day (relative exposure, 0.4), while maternotoxicity was evident at all doses tested (≥4 µg/kg/day; as transient body weight loss, decreased body weight gain, hypoactivity and piloerection).

The adverse effects on development seen with lixisenatide are considered to have probably occurred secondary to maternal toxicity, a view supported by the very low placental transfer and excretion in milk of the drug.

Pregnancy classification

The sponsor has proposed Pregnancy Category B3.[14] This is considered to be appropriate given the adverse effects seen in the animal studies.

Local tolerance

Subcutaneous injection site reactions, consisting of reversible subdermal inflammation and fibrosis, were more pronounced in lixisenatide-treated mice, rats and dogs compared with saline controls in the repeat-dose toxicity studies. Acceptable tolerability was evident even with administration of very large multiples of the maximum recommended human dose of lixisenatide on a µg/kg body weight basis and using strengths of the drug well above the maximum proposed clinical strength (in the pivotal studies, up to 5 times [rats] and 20 times [dogs] higher than the maximum proposed clinical strength of 100 µg/mL lixisenatide). A specialised local tolerance study with the clinical formulation in rabbits also revealed good local tolerability after single SC administration. Additional local tolerance studies showed no dermal irritation by lixisenatide in rabbits, but severe ocular irritation was indicated in an *in vitro* test.

Antigenicity and immunotoxicity

Lixisenatide did not induce skin sensitisation in the murine local lymph node assay. There was no evidence of immunotoxicity in the repeat-dose toxicity studies. Neither lixisenatide nor GLP-1 stimulated T cell proliferation *in vitro* in cells from mice primed *in vivo* with lixisenatide dissolved in phosphate-buffered saline. T cell proliferation was seen, though, in cells from mice primed with lixisenatide in Complete Freund's Adjuvant but only at very high, non-therapeutic or non-physiological concentrations of lixisenatide or GLP-1.

Impurities

A number of peptide impurities specified above the applicable qualification threshold of 1.0% (British Pharmacopoeia) were adequately qualified in a 3 month SC study in rats, employing a stressed drug batch. Genotoxicity studies with the impurities were not submitted, nor are they required for peptides.

[14] Category B3 is defined as: *Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.*

Paediatric use

Lixisenatide is not proposed for paediatric use. In addition to decreased body weight gain (at all doses [≥10 µg/kg/day]; accompanied by reduced food consumption), an 8 month SC repeat dose toxicity study in juvenile dogs (approximately 4 months old at the start of dosing) revealed transient adverse clinical signs including emaciation, reduced skin elasticity, absence of food intake and ataxia and incoordination, trembling and twitching at ≥50 µg/kg/day BID. Reversible histopathological changes were observed in the testis (≥10 µg/kg/day) and epididymis (≥200 µg/kg/day), similar to the findings in adult dogs (discussed above).

Comments on the Safety Specification of the Risk Management Plan

Results and conclusions drawn from the nonclinical program for lixisenatide detailed in the sponsor's draft RMP are in general concordance with those of the nonclinical evaluator except with regard to the claimed absence of testicular toxicity in rodents. Microscopic findings in the testis, comprising seminiferous tubular atrophy and necrosis, spermatid stasis, mineralisation and chronic inflammation, were increased in incidence/severity in rats treated at 4000 µg/kg/day in the 6 month study (Study 2005-0085).

Nonclinical summary and conclusions

- The nonclinical data comprised an adequate set of studies to characterise the pharmacology, pharmacokinetics and toxicity of lixisenatide. Pivotal safety-related studies were conducted according to GLP.
- Lixisenatide is a 44 amino acid peptide that acts as GLP-1 receptor agonist. Nanomolar affinity for the human GLP-1 receptor was shown in binding experiments, and enhancement of glucose-stimulated insulin secretion was demonstrated in the isolated perfused rat pancreas. *In vivo*, lixisenatide improved oral glucose tolerance in mice, rats and dogs; and inhibited gastric emptying, and increased pancreatic β-cell volume and mRNA levels in mice.
- Screening assays for activity at other receptors and ion channels revealed no clinically significant secondary activities for the drug. Other secondary pharmacodynamic studies demonstrated a cardioprotective effect (Langendorff–perfused rat heart model of ischaemia/reperfusion injury) and anti-atherosclerotic and serum cholesterol lowering activity (ApoE knockout mice).
- Safety pharmacology studies covered the CNS, cardiovascular and respiratory systems. No CNS effects were observed in mice after single SC administration at up to 2000 µg/kg, but various CNS effects were observed in rats after IV administration of doses ≥1 µg/kg (yielding substantial multiples of the clinical Cmax). Increased mean arterial blood pressure was seen in rats (a recognised class effect); no cardiovascular or respiratory effects were noted in lixisenatide-treated dogs. Weak inhibitory activity was seen in the hERG K+ channel assay at a vast multiple of the clinical Cmax. Resting membrane potential and action potential duration were unaffected in isolated rabbit Purkinje fibres.
- Rapid absorption after SC administration was shown in laboratory animal species, as in humans (typical Tmax values, approximately 0.25–2.7 h). Terminal elimination half lives after SC administration ranged from 0.5–6 h. The development of anti-lixisenatide antibodies was associated with large increases in the measured exposure levels for total lixisenatide (that is, the sum of antibody-bound and unbound drug). Changes in the concentration of biologically active drug in plasma samples over the course of treatment (assessed in one species and one study only) did not parallel

changes in exposure, suggesting some neutralisation potential of the anti-lixisenatide antibodies; activity was not abolished, though, in antibody-positive samples, indicating at least that some free lixisenatide remains available. The absence of information on levels of free and/or pharmacologically active drug complicated the interpretation of toxicokinetic data.

- Low to moderate plasma protein binding was demonstrated for lixisenatide (rat, dog and human). Tissue distribution of radioactivity following SC or IV administration of radiolabelled drug in rats was rapid and wide; CNS penetration was low or negligible. Extensive metabolism of lixisenatide was evident following incubation with liver and kidney S9 fractions *in vitro* (mouse, rat, rabbit, dog and human). *In vitro* pharmacokinetic studies indicated no likely interactions mediated by effects of lixisenatide on CYPs or kidney or liver transporters.
- Single dose toxicity studies in mice, rats and dogs indicated a low order of acute toxicity by the SC and IV routes.
- Pivotal repeat-dose toxicity studies were conducted by the SC route in rats (6 months) and dogs (12 months). Additional shorter duration studies were conducted in mice, rats and dogs. The major findings were effects on body weight and food consumption, and microscopic changes in liver (increased or reduced vacuolation of hepatocytes; chronic periportal inflammation), and testis and epididymis (including seminiferous tubular dilation, hypospermatogenesis and spermatid stasis). The parotid glands were identified as a (non-neoplastic) target organ in a 2-year carcinogenicity study in mice (basophilic hypertrophic foci). Reactions at subcutaneous injection sites (subdermal inflammation and fibrosis) were of greater severity with lixisenatide cf. saline alone. Testicular toxicity was also evident in a study conducted in juvenile dogs.
- Lixisenatide was not genotoxic in the standard battery of tests.
- Lixisenatide caused thyroid C-cell adenomas in mice, and thyroid C-cell adenomas and C-cell carcinomas in rats, in 2-year subcutaneous carcinogenicity studies.
- Placental transfer (rats and rabbits) and excretion in milk (rats) were shown to be very limited for lixisenatide. Fertility was unaffected in rats. Adverse effects on embryofetal development were observed in rats (including growth retardation with multiple skeletal malformations, as well as delayed ossification and skeletal variations) and rabbits (skeletal abnormalities/variations and impaired ossification), in conjunction with maternal toxicity. Maternotoxic doses in the rat pre-/postnatal development study were associated with slightly decreased postnatal survival, insufficient suckling, decreased postnatal body weight gain and delayed coat growth.

Conclusions and recommendation

- While the nonclinical dossier contained no major deficiencies, the sponsor's characterisation of anti-lixisenatide antibodies in the animal studies, including their neutralising potential, and the effect of their development on levels of free/pharmacologically active drug in particular, was disappointing. However, as antibody development in the laboratory animal species is unavoidable with repeated SC dosing, and that the doses used were limited by adverse effects on body weight, the impact of this is to render uncertain the studies' predictive value, but not their adequacy *per se*.
- *In vitro* and *in vivo* primary pharmacology studies support the drug's use as an anti-diabetic agent.
- No clinically relevant hazards were identified in secondary pharmacodynamic or safety pharmacology studies.

- In the absence of definitive information on animal exposure to pharmacologically active drug in the wake of antibody formation following repeated administration, and with evidence of retention of pharmacological activity, but no marked increase in either pharmacological activity or toxicity evident to parallel the observed increase in exposure to total lixisenatide (antibody bound plus unbound), a conservative approach to estimating relative exposure achieved in the animal toxicity studies is warranted. Accordingly, exposure ratios have been calculated in this report based on plasma AUC values for lixisenatide in animals obtained in the early stages of treatment, prior to significant antibody formation and large increases in measured exposure (not necessarily representing actual increased exposure to active drug).
- Findings in the repeat-dose toxicity studies were mainly related to exaggerated pharmacological effects. Testicular toxicity with lixisenatide, to which dogs were found to be more sensitive cf. the other laboratory animal species tested (rats and mice), may also have a pharmacological basis given that sensitivity and GLP-1 receptor expression levels showed parallels (this remains to be established, however). While relative exposure at the NOEL in dogs is low (2.6), it is substantially higher in rats (116), and the demonstrated reversibility of the changes and the apparent absence of effects on sperm concentration in humans reduces concern regarding the clinical significance of the finding.
- The thyroid C-cell neoplasia observed in the mouse and rat carcinogenicity studies is consistent with similar observations with exenatide and liraglutide, and is thought to be caused by a GLP-1 receptor-mediated mechanism to which rodents are particularly sensitive. The relevance to humans is likely to be low, but cannot presently be completely excluded. Lixisenatide is not genotoxic.
- Adverse effects on embryofetal and pre-/postnatal development are considered most likely to have occurred secondary to maternotoxicity (that is, the pharmacologically mediated reduction in body weight gain and food consumption).
- Acceptable local tolerance by the SC route was shown in animals.
- There are no nonclinical objections to registration of lixisenatide for the proposed indication. No animal toxicity studies with lixisenatide in combination with other anti-diabetic agents were submitted. The safety of use of lixisenatide with the various proposed combinations has to be assessed from clinical data.

  Revisions to nonclinical aspects of the draft PI are recommended; details of these are beyond the scope of this AusPAR.

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

Lixisenatide (AVE0010) is a GLP-1 receptor agonist. Type 2 diabetes mellitus is a progressive chronic illness characterised by hyperglycaemia due to defective insulin secretion and resistance to insulin action. Native GLP-1 is known to stimulate insulin release from the pancreatic islet cells, suppress glucagon secretion, delay gastric emptying,

and reduce body weight.[15] Although GLP-1 levels are reduced in patients with T2DM, their response to exogenous GLP-1 remains intact.[16] The pancreatic effects are glucose dependent minimising the risk of clinically relevant hypoglycaemia.[17] Non pancreatic effects of GLP-1 include slowing of gastric emptying, reduction of food intake, and an increase in satiety, all of which contribute to improving glucose control and decreasing body weight. The endogenous, active, circulating form GLP-1 (7-36)-amide has a very short half-life in circulation (90 to 120 seconds) mainly because of rapid N-terminal cleavage and inactivation by the dipeptidyl peptidase-4 (DPP-4) enzyme. The sponsor claims that lixisenatide is resistant to enzymatic cleavage by DPP-4. This results in a longer duration of action making it possible to use lixisenatide for therapeutic purposes. It was thus developed as a new treatment option to achieve glycaemic control in patients with T2DM.

Guidance

In the pre-submission data assessment form it is noted that the evaluator should refer to the *Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus* CPMP/EWP/1080/00 (May 2002) which was adopted by the TGA in 2002. These Guidelines also refer to other guidelines, that is, studies in support of special populations: geriatrics; dose response information to support drug registration; statistical principles for clinical trials; choice of the control group in clinical trials; fixed combination medicinal products; pharmacokinetics (PK) studies in man; and the note for guidance on the investigation of drug interactions.

Contents of the clinical dossier

Scope of the clinical dossier

Modules 1 and 2 are in line with the TGA requirements for a category 1 submission.

In relation to Module 5, the following are submitted:

Clinical Pharmacology: 2 relative bioavailability studies; 4 relative bioavailability studies using admixture with insulin; 14 PK studies; 9 pharmacodynamic (PD) studies.

Efficacy: 10 efficacy and safety studies.

Comment: The scope of data provided in the clinical dossier is adequate for evaluation of this new chemical entity (NCE). Relevant individual patient data are submitted. It is noted that the author of the clinical summary reports in Module 2 is an employee of Sanofi-Aventis.

Good clinical practice

The sponsor states that the studies presented in this dossier have been undertaken in accordance with Good Clinical Practice (GCP), as required by the ICH E6 Guideline for Good Clinical Practice.

In 2 pivotal Phase III studies, 4 sites were terminated due to ongoing noncompliance with the clinical protocol and violations of GCP, in Study EFC 6016 and one of these sites was also involved in Study EFC 6019. One site (involving 5 subjects) was excluded based on a decision prior to database lock; this was due to a serious noncompliance. Other sites were

[15] Nauck MA. Incretin-based therapies for type 2 diabetes mellitus: properties, functions, and clinical implications. *Am J Med*. 2011;124(1 Suppl):S3-18.
[16] Salehi M *et al*. Effect of endogenous GLP-1 on insulin secretion in type 2 diabetes. *Diabetes* 2010; 59:1330-7.
[17] Vella A *et al*. Lack of effect of exendin-4 and glucagon-like peptide-1-(7,36)-amide on insulin action in non-diabetic humans. *Diabetologia*. 2002;45:1410-15.

included in all analyses as they were stated to be "non serious". The clinical evaluator requested the sponsor provide details of these violations in the sponsor's response to this report.[18]

Pharmacokinetics

Studies providing pharmacokinetic data

The table below lists the PK studies, and dose finding and efficacy studies with PK data. Pharmacokinetics data was also provided in PD and PK/PD studies.

Table 4. Submitted Pharmacokinetic Studies

PK topic	Subtopic	Study ID
PK in healthy adults	Bioequivalence different formulations: single dose	BEQ11094
	Bioavailability: obese, otherwise healthy subjects	BDR6864
	Bioavailability: given mixed with Lantus	BDR11540
PK in Special Populations	Renal impairment	POP6053
	Elderly	POP11814
	Healthy Chinese subjects	POP11320
PK Interactions	Warfarin	INT10408
	Atorvastatin	INT10409
	Ramipril	INT10782
	Digoxin	INT10783
	Paracetamol	INT6863

[18] The sponsor's response to the CER included the following clarification: In the 2 pivotal Phase 3 studies EFC6016 and EFC6019, research activities were terminated at 4 sites due to ongoing noncompliance with the clinical protocol and violations of GCP: sites due to ongoing noncompliance with the clinical protocol and violations of GCP: Site No. 630-625 (Puerto-Rico) in Study EFC6016 related to the management of patient safety. This site participated also in Study EFC6019 as Site No. 630--924 and was also closed in this study.; Site No. 840-608 (USA) in Study EFC6016 related to protocol adherence issues, Principal Investigator oversight, query resolution, and inappropriate source documentation practices; Site No. 840-910 (USA) in Study EFC6019 related to principal Investigator oversight, management of patient safety, and unavailability of patient clinic charts; Site No. 276-905 (Germany) in Study EFC6019 related to patients being allowed to continue taking antidiabetic medication, other than metformin, during study. Due to the seriousness of the noncompliance (intentional violation of inclusion criteria) at Site No. 276-905 (5 patients) in Study EFC6019, it was decided prior to database lock to exclude patient data from all efficacy and safety analyses in the clinical study report (CSR) and in the Clinical Summaries of Efficacy and Safety. Safety data of these patients were reported separately in the CSR. The patients from the other noncompliant sites were not excluded from the analyses because the noncompliance was considered to be non-intentional. Details are provided in the CSRs.

PK topic	Subtopic	Study ID
	Oral contraceptive: ethnyloestradiol/levonorgestrel	INT6052
Population Pk analyses	Healthy subjects, special populations and target population	poh0182
	Target population	poh0215
		poh0216
Other		
Summary of single dose PK in healthy subjects		
Summary of multiple dose PK in healthy subjects		
Pk data from a dose finding study in the target population		DRI6012
Pk data from efficacy studies in the target population		
Efficacy and safety as add on to sulfonylurea (with or without (±) metformin).		EFC6015
Efficacy and safety as add on to basal insulin or basal insulin with (+) metformin		EFC6016
Monotherapy		EFC6018
Efficacy and safety with 2 titration regimens as add on to metformin		EFC10743
Efficacy and safety in Asian patients insufficiently controlled with basal insulin with or without sulfonylurea		EFC10887
Safety and PK of 5 and 10 µg lixisenatide single doses; efficacy, safety and PK of lixisenatide for 5 or 6 weeks, with dose escalation from 5 to 30 µg in Japanese and Caucasian patients as add-on to sulfonylurea or sulfonylurea and metformin.		PDY6797

There were other PK studies submitted in this dossier that are not relevant to the formulation that applies to this application. Study TDU10121 investigated a prolonged release formulation which was found to be unsuitable for further clinical development. This is not discussed further.

Bioavailability studies BDR 10880, BDR 11038, BDR 11540 and BDR 11578 were performed to compare fixed mixtures of lixisenatide and insulin with separate administration of each drug. The sponsor has not proposed admixture with insulin and thus, this is of limited relevance.

Evaluator's conclusion on pharmacokinetics

There are 11 PK studies submitted. These were conducted in 367 healthy volunteers. There were two relative bioavailability studies; there were also 5 drug interaction studies.

The two dose strengths proposed for marketing (50 µg/mL and 100 µg/mL) have been shown to be bioequivalent using the accepted criteria for bioequivalence, that is, 90% confidence interval (90% CI) of 80-120%. These formulations are identical to the formulations used in the clinical trials.

Study BDR 6864 which examined the relative bioavailability of three sites (thigh, abdomen and arm) did not show bioequivalence in relation to Cmax relating to thigh versus abdomen. It is not possible to assess whether this is clinically significant as there is no absolute bioavailability study submitted. Thus, the PK of this product has not been fully characterised. Whether this formulation is optimally developed is not known[19]. Similarly, it is not known whether there is any modified release characteristics in this product or there is any degradation at the site of the injection.

The lack of absolute bioavailability and the lack of bioequivalence in relation to Cmax in the relative bioavailability study should be included in the PI.

The single dose PK studies in healthy and diseased subjects did not reveal a clear dose linear kinetics. Multiple dose studies also reflected similar findings; twice daily regimen had increased AUC compared with once daily regimen.

The terminal half life after multiple dose administration in healthy and diseased subjects ranged from 1 to 4 h. The total body clearance in those with T2DM was 20-67 L/h.

Lixisenatide is cleared renally. One study (POP6053) studies the effect of the PK of lixisenatide (5 µg) after a single dose in those (n=32) with varying degrees of renal impairment. Whilst those with mild renal impairment did not show any significant effect, the other categories of renal impairment showed increased exposure and decreased clearance. As this is a single dose study, it does not provide information on multiple dosing. The proposed PI only includes a precautionary statement that lixisenatide should not be used in those with creatinine clearance (Cr Cl) less than 30 mL/min. Unless the sponsor provides multiple dose studies showing it does not affect the PK significantly, lixisenatide should be contraindicated in those with any degree of renal impairment.

One single dose study on the elderly (POP11814) using 20 µg lixisenatide showed an increase in AUC in comparison to younger subjects. AUC ratio of elderly/ young: 1.29 (CI 1.06 to 1.57). The effect of multiple dosing is not known. This should be included in the PI; the statement that age had "no clinically relevant effect on PK based on population PK data" analysis should be removed as the weight of evidence of the above mentioned study contradicts this finding.

The studies on different ethnic backgrounds have been studied in Japanese, Chinese and Caucasian backgrounds. As these are studies with varying results, no conclusion can be drawn on the effect of lixisenatide on race. The statement in the PI that there were 'no clinically relevant effects' based on these studies should be qualified, as these studies that showed wide variability and of limited significance.

There are five PK studies examining interaction in those taking warfarin, atorvastatin, ramipril, dixogin, paracetamol and oral contraceptives. Since there is a delay in gastric emptying observed with this class of drugs, the timing of dosing of these drugs in relation to lixisenatide affected the PK. For example when paracetamol was administered 1 or 4 h after lixisenatide, the Tmax of paracetamol increased and the Cmax decreased. This was also seen with the oral contraceptive interaction study.

Antibody status also affected the PK of lixisenatide. The incidence of antibody formation in healthy adult (multiple dose) studies and T2DM studies ranged from 30–60%. There was a

[19] See *Response from Sponsor* under *Overall conclusions and risk/benefit assessment* for the sponsor's comments on this issue.

five to seven fold increase in AUC with the 20 µg dose; there was also an increase in Cmax (3-5 fold). The effects of these increases need to be examined in the Phase III studies.

Pharmacodynamics

Studies providing evaluable pharmacodynamics data

The table below lists the PD, PD/PK and population (pop) PK/PD studies.

Table 5. Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID
Primary pharmacology	Effect on glucagon and other counter regulatory hormones during hypoglycaemia in healthy subjects	PDY11941
	Effect on the first and second phase insulin response, second-phase C-peptide secretion responses and glucose disappearance rate, and on glucagon release in subjects with T2DM	PDY10433
	Effects of treatment with lixisenatide or liraglutide on the postprandial plasma glucose in patients with type 2 diabetes not adequately controlled with metformin.	PDY10931
Secondary pharmacology	Effect on gallbladder motility in healthy male and female subjects.	PDY11431
	Effect on sperm production in healthy subjects	TDR11215
	Effect on ventricular repolarisation in healthy subjects	TES6865
Population PD and PK/PD analyses	First in man; healthy subjects safety, tolerability, and maximum tolerated dose (MTD), single dose PK, effect on oral glucose tolerance, plasma insulin, unesterified free fatty acid, C-peptide, and glucagon levels	01016
	PD, safety, tolerability and PK in patients with T2DM	ACT6011
	PK/PD analysis of lixisenatide in Diabetes Type II patients in study PDY6797	PMH0051
	PK, PD safety and tolerability in patients with type 1 diabetes mellitus	BDR10880
		BDR11038
		BDR11578
	PK/PD Analysis of lixisenatide in Diabetes Type II patients in study DRI6012 and comparison to study PDY6797	PMH0050

Studies BDR10880, BDR11038 and BDR11578 are in patients with Type 1 DM and are therefore not relevant to this application as the proposed indication is for T2DM.

Evaluator's conclusions on pharmacodynamics

Single dose studies showed an insulin response which was dose related in the 10 to 40 µg dose range in response to glucose challenge. Glucagon levels were not significantly changed in these studies.

In the Phase II studies there was a dose related effect in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and other PD endpoints. This effect was seen in the range of 5-40 µg.

Minimum effective dose in relation to FPG and PPG appear to be 5 µg. This would need review in the Phase III studies based on HbA_{1c}. Maximum tolerated dose is in the range of 20 -30 µg based on the Phase II studies and the PD endpoints.

There are studies that examined gallbladder motility and spermatogenesis on healthy volunteers. It does not provide evidence that these factors are not affected in diseased subjects.

The effect of lixisenatide on ventricular repolarisation did not show and significant abnormalities in healthy subjects. However, the sponsor is now undertaking a "thorough QT/QTc[20] study" (Study TES11807) as per the adopted guidelines *Note for Guidance on Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (CHMP/ICH/2/04, May 2005[21]). The evaluator asked that the sponsor inform the TGA when the results will be made available.[22]

In one 28 day study where the PD effects of lxisenatide (20 µg once a day) was compared to liraglutide 1.8 mg once day in T2DM, there was a statistically significant change favouring lixisenatide over liraglutide in relation to the primary PD endpoint: change in plasma glucose.

Body weight: Mean weight reduction compared with placebo (ACT6011) in lixisenatide 10 or 20 µg groups did not show any statistically significant difference over 28 days. PDY10931 showed a reduction at 28 days in the lixisenatide group (1.6 kg) and liraglutide group (2.4 kg).

Dosage selection for the pivotal studies

There are 4 Phase II studies (ACT6011, DRI6012, PDY6797 and PDY 10931) included in this package.

Study DRI6012, is relevant for dose selection for the pivotal studies. This was a placebo-controlled, randomised, parallel-group dose response study in metformin treated T2DM subjects. There was a 2 week run-in and 13 weeks treatment period. The dose of lixisenatide used was 5 µg, 10 µg, 20 µg, or 30 µg either twice daily (before breakfast and before dinner) or once daily (before breakfast); subjects randomised to doses of 20 µg or 30 µg were to start with a dose of 10 µg and escalate the dose in weekly 5 µg steps to the assigned dose.

[20] The QT interval is the interval between the start of the Q and end of the T wave on an electrocardiogram; QTc is the QT interval duration corrected for heart rate.
[21] Adopted by TGA in 2006 with the following annotation: *QT prolongation would be of regulatory concern if either the estimated QT prolongation was >5ms OR the upper bound of the 95% confidence interval was >10ms*
[22] In the response to the CER, the sponsor stated that: "Study TES11807 has now been completed and the CSR is available upon request."

Based on the change in HbA_{1c} from baseline and the change in the secondary efficacy endpoints, the dose selection for the pivotal efficacy studies appears justified.

Efficacy

Studies providing evaluable efficacy data

The following Table includes the efficacy studies in support of the proposed indications. Whilst some studies have extension data for 76 weeks, the main efficacy analysis is performed at 24 weeks only. The studies are dealt with according to the requested indications.

Table 6. Clinical Phase III studies in patients with T2DM: Completed studies as of 30 April 2011

Study (background treatment)	Primary objective	Lixisenatide dose (number of randomized patients)	Lixisenatide dose, form, regimen	Control (number of randomized patients)	Design	Treatment period
Pivotal studies						
EFC6014/GetGoal-M (metformin) (see 5.3.5.1 [EFC6014])	Efficacy of lixisenatide on glycemic control (HbA_{1c}) when it is used in the morning within 1 hour prior to a meal over 24 weeks	20 µg QD (total= 510) Morning (n=255) Evening (n=255)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (total=170) Morning (n=85) Evening (n=85)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6015/GetGoal-S (SU ± metformin) (see 5.3.5.1 [EFC6015])	Effects of lixisenatide on glycemic control (HbA_{1c}) over 24 weeks	20 µg QD (n=573)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg)	Placebo (n=286)	Multinational, randomized, double-blind, 2-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6016/GetGoal-L (basal insulin ± metformin) (see 5.3.5.1 [EFC6016])	Efficacy of lixisenatide on glycemic control (HbA_{1c}) over 24 weeks	20 µg QD (n=329)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=167)	Multinational, randomized, double-blind, 2-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC6018/GetGoal-Mono (none) (see 5.3.5.1 [EFC6018])	Effects of lixisenatide on glycemic control (HbA_{1c}) over 12 weeks, using a 2-step dose increase regimen	20 µg QD (total=239) 2-step (n=120) 1-step (n=119)	- 2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) - 1-step (10 µg for 2 weeks, then maintenance dose of 20 µg QD)	Placebo (total=122) 2-step (n=61) 1-step (n=61)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel-group	12 weeks
EFC6019/GetGoal-X (metformin) (see 5.3.5.1 [EFC6019])	Efficacy of lixisenatide on glycemic control (HbA_{1c}) when it is used in the morning within 1 hour prior to a meal over 24 weeks	20 µg QD (n=318*)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Exenatide: 1-step dose increase (5 µg BID for 4 weeks, and maintenance dose of 10 µg BID) (n=316*)	Multinational, randomized, open-label, 2-arm, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC10743/GetGoal-F1 (metformin) (see 5.3.5.1 [EFC10743])	Effects of lixisenatide on glycemic control (HbA_{1c}) over 24 weeks, using a 2-step dose increase regimen	20 µg QD (total=322) 2-step (n=161) 1-step (n=161)	- 2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD) - 1-step (10 µg for 2 weeks, then maintenance dose of 20 µg QD)	Placebo (total=162) 2-step (n=80) 1-step (n=82)	Multinational, randomized, double-blind, 4-arm, unbalanced design, parallel-group	≥76 weeks (main efficacy analysis performed at the end of the 24-week main treatment period)
EFC10887/GetGoal-L-Asia (basal insulin ± SU) (see 5.3.5.1 [EFC10887])	Effects of lixisenatide on glycemic control (HbA_{1c}) over 24 weeks	20 µg QD (n=154)	2-step (10 µg QD for 1 week, then 15 µg QD for 1 week, then maintenance dose of 20 µg QD)	Placebo (n=157)	Multinational (Asia), randomized, double-blind, 2-arm, parallel-group	24 weeks

Evaluator's overall conclusions on efficacy

The following are relevant.

Site of administration

It is stated in the study protocols that, "the investigation product should be administered by deep subcutaneous injection, alternating between the left and right anterolateral and left and right posterolateral abdominal wall, thighs and upper arm. Within a given area, location should be changed (rotated) at each time to prevent injection site skin reaction". The draft PI is lacking in detail in relation to this. The above mentioned directions should be included in the PI.

Absolute efficacy versus placebo

In a double blind randomised 13 week study (EFC 6018) in treatment naive subjects[23], the absolute efficacy was modest in relation to HbA_{1c}: the least squares (LS) mean difference

[23] Sponsor clarification, provided in the response to the CER: Study EFC6018 was a 12 week study in treatment subjects not treated with antidiabetes agents for at least 3 months at screening.

versus placebo was -0. 54% (0.123) and - 0.66% (0.122) in the two and one step titration of lixisenatide groups respectively.

Dose selection for the pivotal studies

There is one placebo controlled randomised study, DRI6012 where groups of approximately 50 T2DM patients were administered once daily or twice daily 5, 10, 20 or 30 µg/day for 13 weeks, that suggests that the optimum maintenance dose is 20 µg. This was seen in relation to the primary efficacy parameter HbA_{1c}.

Racial mix of the recruited subjects

Most of the efficacy studies had a preponderance of Caucasians except Study EFC 6015 (44.8% Asian) and EFC 10887 (mostly Asian). Study EFC 6015 which had a reasonable mix of Asians showed that the LS mean change in HbA_{1c} from baseline to week 24 was greater in Asians than Caucasians (-0.93 and -0.61% respectively).[24] Thus, these studies do not reflect adequately the target population in Australia. In the presentation of study findings in the *Clinical Trials* section of the PI, the percentage of Caucasians and other racial groups should be specified.

Antibodies and their influence on efficacy

A meta-analysis of change in HbA_{1c} from baseline to week 24 by anti-lixisenatide antibody (Ab) status and measured antibody concentrations using combined data from EFC6015, EFC6016, EFC10743, and EFC10887, was presented. This included 998 patients, of whom 693 (69.4%) were antibody positive (Ab+ve). Antibody concentration was measured in 681, of whom 550 had been assessed as Ab+ve with Ab status not available in the remaining 131. The Ab concentration was less than the lower limit of quantitiation (<LLOQ; 3.21 nmol/L) in 477/681 (70.0%) patients.

There are discrepancies in the numbers of patients with Ab measurement with 998 and 986 noted in separate paragraphs of describing this analysis. Although this is a small difference, it suggests lack of clarity around Ab measurements. Also, it is concerning that samples were not adequate to measure Ab when this was a stated study objective.

Data from placebo controlled studies with an extension show there was an increase in the numbers of patients requiring rescue therapy over the entire treatment period compared with the 24 week period. In those receiving lixisenatide, a high proportion were Ab+ve prior to rescue. These data are tabulated below.

Table 7: Percentage of patients requiring rescue therapy and antibody status at the time of rescue

	Lixisenatide*		Ab+ve prior to rescue	Placebo*
	Morning	Evening		
ECF6015				
24 week period	4.0	-		12.6
Entire	27.0	-	104/148	38.8

[24] Sponsor clarification, provided in the response to the CER: "Most of the efficacy studies had a preponderance of Caucasians except Study EFC6015 (44.8% Asian) and EFC10887 (all Asian). Study EFC6015 which had a reasonable mix of Asians showed that the LS mean change in HbAlc from baseline to week 24 was -0.95% in Asians and -0.78% in Caucasians."

	Lixisenatide*				Ab+ve prior to rescue	Placebo*
	Morning		Evening			
period					(70.3%)	
EFC6016						
24 week period	5.8		-			7.2
Entire period	29.7		-		72/94 (76.6%)	41.6
ECF10743						
	A	B	A	B		
24 week period	3.1	1.3	-	-		4.4
Entire period	18.8	22.8	-	-	28/36 (77.8%)	38.4

*percentages of patients requiring rescue therapy
Study ECF10743: A = 2 step titration; B = 1-step titration
Ab+ve data: the number and percentage of patients receiving lixisenatide requiring rescue who were Ab+ve prior to rescue

It is recognised that these data are difficult to interpret as not all patients had Ab status assessed. Notwithstanding this, the results suggest that the presence of Ab may be associated with decreased efficacy. The sponsor notes that the increased requirement for rescue therapy is consistent with the patient population and progression of T2DM. However, decreased efficacy due to immunogenicity is referenced in the proposed PI.

Body weight changes

The reduction predictably varied in the studies. The mean for changes over placebo in the 'add on metformin' studies were -2.10 to 2.63 kg. In the exenatide comparator study, the change was -2.98 versus 3.98 kg (lixisenatide versus exenatide). The 'add on to insulin' studies, the values were -0.84 to -1.28. These were changes reported at 24 weeks and no study tested these changes independent of nausea and vomiting.

Add on to metformin

There were 2 placebo controlled double blind studies with a main treatment period of 24 weeks (EFC 6014 and EFC 10743).[25] These studies included sufficient number in each study arm to show superiority of lixisenatide over placebo. The absolute margin of difference in HbA_{1c} was 0.4% that was factored into the statistical testing to show superiority and this margin is generally acceptable.

The subjects were T2DM subjects who were on maximum dose of metformin (1500 mg/day). Their mean HbA_{1c} was approximately 8.16% also suggests that they were suitable for the addition of another antidiabetic agent (in this case, lixisenatide). They were significantly overweight with the mean body mass index (BMI) being over 32 and

[25] Sponsor clarification provided in the response to the CER: "There were 2 placebo controlled double blind studies with a **main treatment period** of 24 weeks (EFC6014 and EFC 10743).

33 kg/m^2. The population tended to be Caucasians in over 85% and does not reflect the other ethnic groups adequately.

The LS mean difference over placebo was approximately 0.41% to 0.48 % in relation to mean change from baseline of HbA_{1c}. Thus, predefined superiority was seen, though the magnitude is modest. The secondary endpoints showed similar trends. The change in HbA_{1c} appeared to be maintained over the 76 weeks.

There was a reduction of -2.0 to -2.6 kg in body weight over the 24 weeks in the lixisenatide group. The evaluator considered the change over placebo was not clinically significant. This endpoint is not independent of nausea and vomiting.

There was one active comparator study, EFC 6019 which used exenatide as the comparator at the dose that it is registered in Australia, which provides useful information. This was designed as a non-inferiority study and non-inferiority was demonstrated if the upper bound of the 2 sided 95%CI of the LS mean difference was less than of 0.4%. This is wider than it should have been as the placebo controlled superiority studies only included a margin of 0.4 to 0.5%. This is reinforced in the EMA *Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* CPMP/EWP/1080/00/Rev 1 (14 May 2012), where it is recommended that for a non-inferiority study, a margin of 0.3 % is generally acceptable. The sponsor was requested to justify the wider margin used in this study.[26]

These subjects also had a baseline HbA_{1c} of 8.03 % with a median duration of metformin of 2.49 years with maximum dose (≥ 1500mg/day) suggesting that the population was a suitable target population for add on therapy. Again the recruitment of 92.7% Caucasians does not reflect the T2DM population in Australia. Though this study showed non-inferiority in terms of the primary endpoint and efficacy endpoints relating to HbA_{1c}, exenatide fared better. This was also seen in relation to body weight loss. The draft PI should include the details of the non-inferiority margins in the study description. It should also have details of the study design, subject number and the primary efficacy endpoint and statistical testings included.

Analysis of efficacy by antibody status was provided in Study EFC 10743 in the modified intent to treat (mITT) population, where the mean change from baseline in HbA_{1c} was lower -0.76 % (0.83) in the Ab+ve group in the one step titration group versus -1.11% (0.99) in those without antibodies. This was also seen in those with the 2 step group. This was the results presented at 76 weeks.

This is a concern. These findings should be included in the PI. The sponsor should state how it proposes to monitor for lack of efficacy in patients administered lixisenatide over a prolonged period.[27]

Add on to sulfonylurea

As dual therapy, data are provided only in one good quality (randomised double blind placebo controlled study) Phase III study, EFC 6015, in a subgroup, only. This study included those on sulfonylurea with or without metformin. Those having sulfonylurea

[26] A justification was contained in the sponsor's response to the CER, which the following introductory paragraph: "The Phase 3 clinical development plan of lixisenatide, including Study EFC6019, was designed in 2007 based on relevant guidelines in force at this time, and studies were initiated in 2008. In accordance with EU, Study EFC6019 was an active-controlled study evaluating safety and efficacy of lixisenatide as compared to exenatide. Exenatide was selected as a relevant comparator since it belongs to the same class of GLP-1 receptor agonist, and was the only compound in this class approved at the time of study initiation (marketing authorisation application granted in November 2006 in the EU).

[27] In the response to the CER, the sponsor stated: "Usual standard of care recommends the assessment of HbA1c every 3 months in patients with type 2 diabetes (Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care, Vol 35, June 2012). This would detect potential lack of efficacy in patients administered over a prolonged period."

with lixisenatide included only 16% of those randomised, placebo (n=45, 15.8%) and lixisenatide (n=91, 15.9%). Analysis of efficacy in this subgroup was factored in the prestudy considerations. Statistically significant efficacy over placebo was seen in this subgroup (-0.85; 95% CI: -1.161, -0.543). Other data to support dual therapy was in PDY 6797 which was too small to yield conclusive findings.

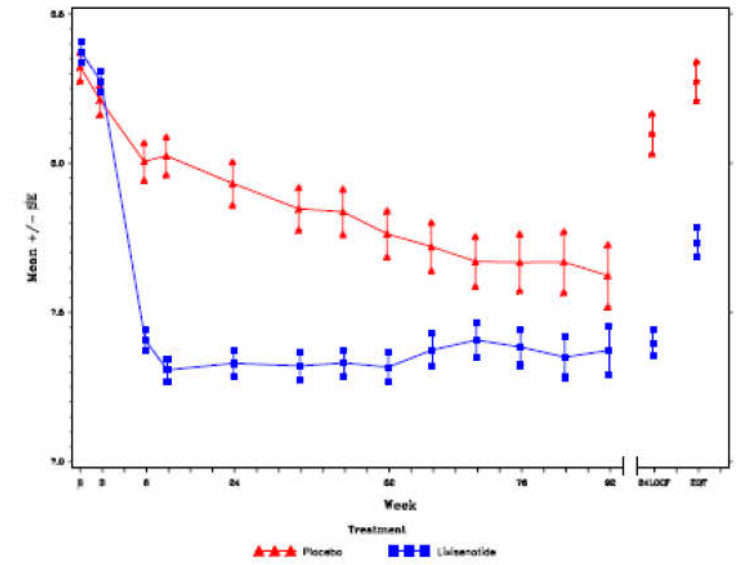
The efficacy data are not clinically significant as the numbers are too small. Further data are required to support use with sulfonylurea as dual therapy.

As triple therapy with sulfonylurea and metformin

The pivotal study was EFC 6015.This was double blind randomised placebo controlled study of T2DM subjects where 84% metformin and sulfonylurea at baseline. The mean HbA_{1c} at baseline was 8.36%; the median duration of diabetes mellitus was 8 years. These subjects were on maximum dose of sulfonylurea and metformin. Their baseline BMI was 30.22 kg/m^2 (6.22). This suggests that the target population was suitable for the addition of lixisenatide. This study also had a greater representation of Asians and Orientals (44.8%) and 52% Caucasians.

Overall, efficacy was statistically significant over placebo, and appeared to be maintained over the extension period of 76 weeks, see Figure below. These trends were also seen with the secondary efficacy endpoints.

Figure 2. Mean change in HbA_{1c} (%) from baseline by visit - mITT population: Study EFC 6015



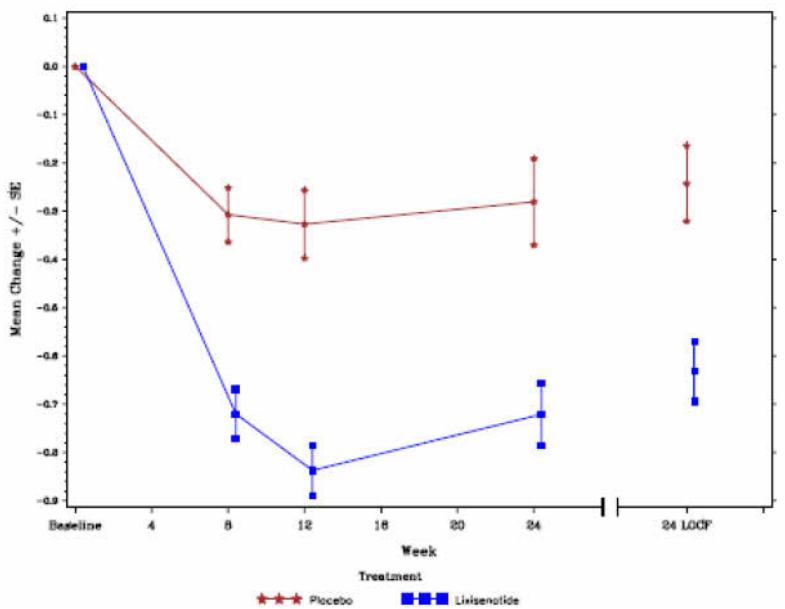
This study also showed that the magnitude of change in HbA_{1c} was less in those with the highest concentration of antibodies. However, this is difficult to interpret due to the small numbers.

Add on to insulin

There are two studies (EFC 6016 and EFC 10887) which were randomised placebo controlled studies on subjects with stable dose of insulin (≥ 30 units (U)) and metformin (≥1.5 g) in Study EFC 6016 and sulfonylurea in EFC 10887. Both studies were designed as superiority studies (over placebo) and this was achieved. There are no comparator (non-inferiority studies) with agents that are registered as add on regimen with insulin. The target population in Study EFC 6016 reflected the population that would generally require add-on treatment: mean duration of diabetes 12.6 years; on maximum treatment of metformin (2000 mg/day) for a median duration of 5.74 years; 20% had only insulin in Study EFC 6016. The subjects were overweight with a mean BMI of 32.13; mean HbA_{1c} was 8.48 (0.82). This study showed some insulin sparing (secondary efficacy endpoint).

In Study EFC 10887, the population was Asian (100%). This study was conducted in Asia and the treatment practices were somewhat different; the target population was those who had insulin added on to sulfonylurea. The mean baseline HbA_{1c} was less than that in the previous study being 8.17%. The mean duration of diabetes mellitus was also longer being 13.92 years. This study is supportive (in terms of reflecting the target population for this proposed indication in Australia). There was statistically significant difference over placebo in relation to the primary efficacy endpoint at 24 weeks as per Study EFC 6016. However the maximal change was seen at 12 weeks and the effect appeared to wane over time (see Figure below).

Figure 3. Mean change in HbA_{1c} (%) from baseline by visit and at endpoint – mITT population. Study EFC 6016



The use of lixisenatide with insulin alone is based on a subpopulation in these studies. It is 20% in EFC 6016 and 30% in EFC 10887. This number is inadequate to assess efficacy, especially as one of the studies did not reflect the target population in Australia.

Study EFC 6016 also tended to show that the presence of antibodies reduced the magnitude of efficacy in relation to the primary efficacy endpoint. The numbers were inadequate in Study 10887 to yield meaningful results.

Safety

Studies providing evaluable safety data

There were no pivotal studies that assessed safety as a primary outcome. Studies providing evaluable safety data in the dossier are:

- Clinical pharmacology studies in healthy subjects and patients with T2DM
- A study to select dosage in patients with T2DM
- A dosage escalation study in patients with T2DM
- 1 Phase III safety study
- 7 pivotal and 1 supportive Phase III efficacy studies

The safety variables assessed were**:** treatment emergent adverse events (TEAEs) coded using the Medical Dictionary for Regulatory Activities (MedDRA); AEs of special interest:

hypoglycaemia, allergic or allergic-like reactions, local tolerability, gastrointestinal (GIT) disorder, cardiovascular (CV), serum calcitonin, suspected pancreatitis; laboratory safety parameters; other safety parameters: physical examination, vital signs, body weight, height, and waist measurement and electrocardiogram (ECG). Serum calcitonin was an AE of interest due to reports of thyroid C-cell proliferation in animal studies with other GLP-1 agonists.

The safety analysis was undertaken on the safety population which included all randomised subjects who took at least 1 dose of the study medication. Adverse event data are presented with standard frequency tables. Descriptive statistics, number and percentage of subjects with potentially clinically significant abnormality (PCSAs) by treatment group and shift tables showing changes with respect to the PCSA between baseline and on-treatment period are presented for the laboratory safety variables. For vital signs, the number and percentage of normal, abnormal and missing findings from the physical examination at baseline and at endpoint are summarised by treatment and shift tables between baseline and endpoint presented.

An independent allergic reaction adjudication committee (ARAC) and CV adjudication committee were established to assess possible events of this type in the safety and efficacy studies.

The dossier also includes an integrated safety analysis (ISA) in the Summary of Clinical Safety. This included an analysis of CV safety. The statistical analysis plan and integrated data used in the ISA were also provided: *Reports of Analyses of Data from More than One Study: ISS*.

Exposure to lixisenatide

The total number of subjects exposed in the Phase 2 and 3 studies were: lixisenatide (n=3304) and placebo (n=1232); active comparator (n=548).

Evaluator's overall conclusions on safety

The absolute AE event incidence with lixisenatide can be ascertained from the monotherapy study EFC 6018 where lixisenatide (n=239) was compared to placebo (n=122), in treatment naive patients. The percentage of TEAEs was 53.6% (lixisenatide group) versus 45.1% in placebo. The most frequent event was vomiting (7.1%) versus 0 in placebo. In this study symptomatic hypoglycaemia was 1.6% in each group. Injection site reaction was 4.6% versus 0 in placebo, in this study.

The dose selection Study DRI 6012 suggests a dose response in relation to TEAEs. In relation to the AEs reported, it appears that the 20 µg is the optimum dose of lixisenatide.

Add on to metformin (EFC 6014, EFC 10743 and EFC 6019): dual therapy

In the two placebo controlled studies, 832 subjects were included in the lixisenatide group and 330 in the placebo group. The mean duration of treatment in these studies have been over 500 days. The studies have used the dose proposed in the draft PI and the population reflects the target population.

Nausea has been a common TEAE being 25-38% and vomiting 13-18%. The adjudicated allergic reactions were seen in 1.6% to 3.8% in the lixisenatide versus 1.6% in the placebo groups. There was also one report of anaphylactic reaction in the lixisenatide group. Symptomatic hypoglycaemia varied in these studies with lixisenatide always exceeding the placebo group.

The study versus exenatide (EFC 6019) where 319 were given lixisenatide and 316 given exenatide, provides valid comparison of drugs in the same class. The mean duration was over 410 days. Symptomatic hypoglycaemia was higher in the exenatide group (14.6%

versus 5.0%) in the lixisenatide group. Adjudicated allergic events, however were higher in lixisenatide group being 1.9% versus 0.9%.

Data to support use with sulfonylurea (EFC 6015) as dual therapy is only on a subpopulation in this study that involves placebo (n=46) and lixisenatide (n=88). This, in the opinion of the evaluator, is inadequate for a new chemical entity.

Add on to metformin and sulfonylurea (EFC 6015) as triple therapy

Here the number involved were 285 in the placebo group and 574 in the lixisenatide group; the mean duration was 570 days. The events were broadly similar to the previous studies. The addition of sulfonylurea appeared to increase the hypoglycaemic events (24.6% in lixisenatide group compared to previous studies on metformin as dual therapy; see above for reported rates). This is an expected finding.

Add on to basal insulin ± metformin or sulfonylurea (EFC 6016 and 10887)

This study (EFC 6016) included 167 subjects in the placebo group and 328 in the lixisenatide group and the mean duration was 510 days. The AE profile was similar to the previous studies. Study EFC 10887 was a study of similar design conducted in Asian subjects. This study included insulin and sulfonylurea in 70% of the subjects. Hypoglycaemia was higher in the lixisenatide group versus placebo (43.5% versus 23.6%). Cardiovascular events were also higher being 4.5% versus 0.65%. The data to support lixisenatide use with insulin alone is in 30% of Study EFC 6016 and EFC 10887. The issue with this small number is that it does not represent the target population in Australia adequately.

Adverse events of concern

In relation to AEs of concern to drugs for diabetes mellitus and of this drug class cardiac events showed a marginal increase in the lixisenatide groups versus placebo (2.0% versus 1.4%). The individual events are too small in number; their significance can only be ascertained in large post-market studies.

There was also a higher incidence of symptomatic hypoglycaemia in lixisenatide in the placebo controlled studies. There was also an increase seen in add on sulphonylurea study and basal insulin studies. This has been addressed in the *Precautions* section of the PI.

There are also hypersensitivity reactions above placebo (1.2% versus 0.7%). Injection site reaction was higher with lixisenatide (1% versus 0.2%).It is not possible to state whether these are due to the occurrence of antibodies.

List of questions

Questions and evaluation of sponsor responses

The clinical questions asked by the TGA and the clinical evaluator's evaluation of the sponsor's responses to these are provided below.[28]

Absolute Bioavailability Study

Question: The justification for not conducting an absolute bioavailability study does not address the question of why intravenous administration was not undertaken. Please provide the reasons (but not new data) for this (for example, pharmaceutical or safety reasons).

Response: This is essentially similar to the justification provided by the sponsor in the dossier. It also states that "the only (intrinsic) factor that was identified as having a

[28] Note: Questions relating only to revisions to text in the PI are not included in the AusPAR.

marked impact on the disposition of lixisenatide (but not on the efficacy) is the development of anti-lixisenatide antibodies. It is important to note that the development of anti-lixisenatide antibodies is believed to impact the distribution and clearance of lixisenatide, but not its absorption."

The sponsor concludes that taking into account the well established use of SC formulations for diabetes treatment and the scope and quantum of information provided in the clinical dossier is adequate for assessment of lixisenatide despite the absence of an absolute bioavailability study.

Evaluator's comment: No valid reasons are put forward. The PK is not well defined and it is not known if this product is optimally formulated. It is not known if there is degradation at the site of injection; the lack of equivalence in relation to Cmax observed in relation to thigh versus abdomen in Study BDR 6864 is not satisfactorily explained. This is a significant deficiency as these sites are the proposed sites of injection.

Immunogenicity

This **question** notes the proposed text in the PI on immunogenicity and, in particular, that this states that some Ab+ve patients had diminished efficacy. It was requested that the sponsor should indicate how this will be assessed if the product is approved for marketing and provide information on whether the Ab assay will be commercially available to assess efficacy failure.

Response: The following is noted.

Based on the meta-analysis performed on Studies EFC 6015, EFC 6016, EFC 10743, and EFC 10887 submitted within the original dossier, there is no signal for a progressive decline in efficacy at Week 24 triggered by Ab status; the LS mean change in HbA_{1c} was similar regardless of the patients' Ab status: LS mean (SE) of -0.81 (0.051) in Ab+ve patients and -0.83 (0.065) in antibody negative (Ab-ve) patients. (In this data set 693/998 (69.4%) were Ab+ve; 305/998 (30.6%) were Ab-ve).

Those with antibodies were categorised into 4 quartiles based on the antibody concentration. The LS mean change in HbA_{1c} from baseline to week 24 was -0.18% (95% CI: -0.428 to 0.075) for the group of patients with the highest Ab concentration, which may indicate a trend for diminished efficacy in the limited number of patients (51/998) with the highest Ab concentration.

In the same meta analysis for results at week 76, the trend for diminished efficacy in patients with the highest Ab concentration is no longer observed; however, the change in HbA_{1c} was somewhat less in Ab+ve than Ab-ve patients (LS mean change: -0.75 [standard error (SE) 0.066] and -1.05 [SD 0.086], respectively). The reduction in HbA_{1c} by antibody concentration group was comparable among group 1 (LS mean change -0.68% [95% CI: -0.999 to -0.363%]) and group 4 (LS mean change -0.45% [95% CI: -0.783 to -0.124%]).

It is indicated that since submission of the original dossier, the Ab analysis for Study EFC6014 has been completed; results of the 2 meta-analyses at weeks 24 and 76 including these data are similar to those in the previous pool of studies.

Also, an additional analysis based on the Phase III placebo controlled studies submitted in the original dossier (EFC 6015, EFC 6016, EFC 10743, and EFC 10887) was provided in the response using a converse approach to present the Ab concentration data by category of HbA_{1c} change (change in HbA_{1c} < -1.2%, ≥-1.2 to < -0.4%, ≥-0.4% to < 0%, ≥ 0 to < 0.4%, ≥0.4%) in patients with quantifiable antibody concentration at weeks 24 and 76.

It was considered that these results show that the range of Ab concentrations is similar by category of HbA_{1c} change and noted that patients with relatively high Ab concentrations have a clinically relevant reduction in HbA_{1c}. Based on these data the sponsor considers that Ab concentration cannot predict HbA_{1c} change in an individual patient.

The sponsor concludes that based on the efficacy results for decrease in HbA_{1c} by Ab status and the analysis to assess whether Ab status and/or concentration is predictive for clinical efficacy, use of Ab measurement in clinical practice it is not recommended.

Therefore no commercial antibody assay is considered necessary since the main indicator of efficacy will remain the measurement of HbA_{1c}.

Evaluator comment: The following issues are of concern:

The sponsor has categorised into 4 quartiles, the number with varying concentrations of antibodies. They are referred to as groups, with group 4 having the highest concentration.

It is observed from the data, that the group with the largest concentration of antibodies showed the least magnitude of effect in terms of HbA_{1c} at 24 weeks. This was in the mITT group. This appeared to be maintained at 76 weeks. If data from study EFC 6014 (with recently completed findings on antibodies) is included, similar observations at 24 and 76 weeks are noted.

Hence, the sponsor has not addressed how it proposes to monitor for the potential lack of efficacy.[29]

PK data in the Ab+ve subjects and the implications of these for PD and safety

The **question** notes that for Study ACT 6011, the Clinical Study Report (CSR) presents PK data from the Day 29 Ab-ve group with data from the Day 29 Ab+ve group provided in an addendum. There was no discussion of the PK data for the Day 29 Ab+ve group. A comparison of the mean values of selected AUC, Cmax, Tmax and half life data in the AB-ve and Ab+ve groups suggest a higher exposure to lixisenatide in the Ab+ve group irrespective of the dosing regimen. Results of the PD and safety analyses included all subjects with no separate data by Ab status. The higher lixisenatide exposure in Ab+ve subjects could have implications for the PD effect and safety. The sponsor was requested to consider the PK data in the Ab+ve subjects and the implications of these for PD and safety.

The **response** indicates that in Appendix C of the CSR, descriptive statistics is presented for the main PD parameter, the postprandial blood-glucose AUC[0:14h-4:55h] by Ab status for breakfast/lunch/dinner. An extract of these data showing the median AUC[0:14h-4:55h] at the 20 µg dose (QD and BID) for breakfast/lunch/dinner by Ab status is provided and presented below.

Table 8. Median postprandial blood-glucose AUC[0:14h-4:55h] by antibody status for breakfast / lunch / dinner at dose level 20µg (QD and BID) in ACT6011.

AUC[0:14h-4:55h] [mg*h/dL]		Breakfast		Lunch		Dinner	
		ADA negative	ADA positive	ADA negative	ADA positive	ADA negative	ADA positive
Median	Placebo	883	-	870	-	553	-
	Lixisenatide 20µg QD	540	397	757	644	497	701
	Lixisenatide 20µg BID	535	395	705	706	379	506
Change from Baseline (Median)	Placebo	-113	-	23	-	1	-
	Lixisenatide 20µg QD	-519	-284	-276	-171	-181	-142
	Lixisenatide 20µg BID	-313	-311	-135	-226	-295	-239

This shows there are no major differences in the PPG between the Ab-ve and +ve patients in Study ACT6011.

The data on TEAEs by Ab status is also presented. These show a higher frequency of TEAEs in Ab+ve patients however the numbers are small.

[29] In the response to the CER, the sponsor stated: Usual standard of care recommends the assessment of HbA1c every 3 months in patients with type 2 diabetes (Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes, Diabetes Care, Vol 35, June 2012). This would detect potential lack of efficacy in patients administered over a prolonged period.

Evaluator comment: It is agreed that there are no major differences in the PPG data for Ab-ve and +ve subjects and the sponsor response is accepted. Of note however, these are small patient numbers and nearly 50% in the QD and BID groups were Ab+ve.

Data Query: EFC6014

The **question** notes that in the CSR for study EFC6016, it is indicated there were no protocol deviations resulting in a patient being excluded from the mITT population. However, the patient numbers in the results of the analysis for the primary efficacy variable are less than those in the mITT. The sponsor was requested to explain this apparent discrepancy.

Sponsor response: This indicates that 327 of 329 randomized patients in the lixisenatide and 166 of 167 placebo patients were included in the mITT population (section 5.3.5.1 EFC 6016 of CSR page 61 and page 72).

Evaluator comment: Results of the analysis for the primary efficacy variable in CSR table 12 on page 72 indicates there were 158 patients who received placebo and 304 who received lixisenatide. The discrepancy has not been explained.

Data Query: EFC10887

The **question** notes that in the CSR for Study EFC 10887, data provided for the changes in the daily basal and total insulin doses from baseline to week 24 are the same. The sponsor was requested to explain why the data provided for the daily basal and total insulin doses are the same.

Sponsor response: As in this study only basal insulin was allowed as background therapy the 2 analyses provided the same information. The results from the analysis of the change in daily total insulin dose are identical to those from the analysis of the change in daily basal insulin dose due to the fact that the rescue insulin usage was excluded from the analysis.

Evaluator comment: This is accepted.

Data Query: TES6865

The **question** notes that in the CSR for Study TES 6865, it is stated that 3 of the 4 subjects who discontinued the study were replaced. However, the analysis populations and subject numbers in the results are consistent with the numbers after taking into account those who discontinued. They do not appear to include the replacement subjects, x 2 with lixisenatide 20 µg QD and x 1 with lixisenatide 30 µg BID. These numbers are potentially material given the small numbers of subjects in each group. Please clarify this discrepancy.

Sponsor response: The sponsor response provides a detailed answer to this question explaining why discontinued patients were included in the analysis populations.

Evaluator comment: This is accepted.

Clinical summary and conclusions

Benefit-risk assessment

Assessment of benefit

To support add on to metformin there are two placebo controlled studies with an initial 6 months double blind period which shows lixisenatide is efficacious (compared with placebo). This was conducted on patients with T2DM on maximum dose of metformin. The statistically significant superiority over placebo was maintained over 24 weeks. One study which had an extension phase up to 76 weeks also showed that the efficacy was

maintained over the entire period. The secondary efficacy endpoints relating to glucose endpoints showed similar trends. The reduction in body weight over 6 months ranged from -2.0 to -2.6 kg. The placebo effect was -1.6 kg. The change in HbA_{1c} at 6 months was approximately 0.8% in the lixisenatide group.

The active controlled study (versus exenatide) was also of similar design. This was designed as a non-inferiority study. Whilst this study showed non-inferiority in relation to HbA_{1c}, the effect was greater with exenatide. The non-inferiority margin was also wider than that stipulated in the EU Guideline. Superior trends were also seen with the secondary efficacy endpoints.

To support add on to metformin and sulfonylurea (triple therapy) there was one pivotal study (EFC 6015) which recruited the target population and showed statistical superiority over placebo over 6 months. There was a subpopulation in this study that included sulfonylurea + lixisenatide only (dual therapy). The numbers were small and inadequate to support this indication in relation to efficacy and safety; (45 in the placebo group and 91 in the lixisenatide group which was approximately 16% of the entire population).

There were two placebo controlled studies that supported the use of lixisenatide as add on to basal insulin. Stable dose of insulin (>30 U) and metformin (≥1.5 g) reflected the target population that would require further add on therapy. The second study was conducted in Asia and included Asian patients and thus did not reflect the target group in Australia; this combination is not generally a recommended combination used in Australia. At 6 months, there was statistically significant difference over placebo in relation to HbA_{1c}. Maximum effect was seen at 12 weeks, then a waning of effect over 24 weeks was seen. Secondary efficacy endpoints showed similar changes; there was a reduction in the insulin dose seen. There was a tendency to decreased HbA_{1c} in those with the presence of antibodies. There is a request for the use of lixisenatide as add on to insulin monotherapy. The number of those given lixisenatide together with insulin is insufficient (20% in the first study and 30% in the second study) to support the efficacy and safety for this indication. Insulin is not generally used to treat T2DM; if there is contraindications to oral diabetic agents that would warrant such use, this population has not be tested in this study.

Assessment of risk

In relation to risks, the common effects were nausea and vomiting. There were adjudicated hypersensitive reactions which were higher than placebo (1.2% versus 0.7%). A higher increase of symptomatic hypoglycaemia was observed in the sulfonylurea study and also basal insulin studies. There was an increase in the hypersensitivity reactions and injection site reactions in those with antibodies. The relationship cannot be ascertained on the numbers involved; larger post-market studies are required to assess this. Cardiovascular effects were also higher (4.5% versus 0.65%). These risks are addressed in the PI and it is the evaluator's opinion that these are adequate provided the recommendations regarding the PI[30] are adopted by the sponsor.

Assessment of benefit-risk balance

Overall, there is a favourable risk benefit profile for the following indications; in combination with:

- metformin, or
- a combination of metformin and a sulphonylurea,

In combination with a basal insulin:

- in combination with metformin, or

[30] Details of recommended PI revisions are generally beyond the scope of the AusPAR.

· in combination with a sulphonylurea.

There is inadequate evidence for combination therapy with sulfonylurea; or in combination therapy with insulin alone.

Recommendation regarding authorisation

The following indications are recommended to be approved.

(Lyxumia) is indicated for treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients not adequately controlled ~~on oral antidiabetics and/or basal insulin~~: with diet and exercise, in combination with the following oral antidiabetics:

· metformin,

~~· a sulphonylurea, or~~

· a combination of metformin and a sulphonylurea,

In combination with a basal insulin:

~~· alone,~~

· in combination with metformin, or

· in combination with a sulphonylurea

The data to support the use with sulfonylurea is inadequate to support efficacy and safety of the proposed dual therapy.

The data to support the use with insulin (alone) is inadequate to support efficacy and safety of the proposed dual therapy.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Product Review (OPR). Documents reviewed were:

· EU RMP Version 1.0, dated 14OCT2011 [data lock date 30 APR 2011], with Australian Specific Annex Version 1, dated December 2011 (provided with initial application).

· EU RMP Version 1.1, dated 07MAY2012 [data lock data 30APR2011], with Australian Specific Annex Version 1.1, dated August 2012 (provided in response to a TGA request for further information).

The RMP evaluation report was based on RMP Version 1.0 with updates provided with RMP Version 1.1.

In summary, routine and additional pharmacovigilance activities are proposed by the sponsor to monitor and further inform 3 important identified risks, 7 important potential risks and 4 areas of important missing information associated with Lyxumia. In addition, routine risk minimisation activities are proposed by the sponsor to mitigate these ongoing risks.

Safety specification

The sponsor provided a summary of Ongoing safety Concerns which is shown at Table 9.

Table 9. Summary of the Ongoing Safety Concerns as specified by the sponsor

Important identified risks	Gastrointestinal events i.e. nausea, vomiting Systemic hypersensitivity reactions Hypoglycaemia [when used with a sulphonylurea or with a basal insulin + sulphonylurea]
Important potential risks	Cardiovascular events Acute pancreatitis Medullary thyroid cancer Malignant neoplasm Immunogenicity / neutralisation Dehydration / Acute renal impairment Off-label use in non Type II Diabetics for weight loss
Important missing information	Use in pregnant women Use in lactating women Use in children and adolescents < 18 years Use in patients with moderate and severe renal impairment

OPR reviewer comment:

It is noted that in the updated RMP Version 1.1 the sponsor has added the Important potential risk 'Off-label use in non Type II Diabetics for weight loss' and added use in patients with 'moderate' renal impairment as an area of important missing information (that is, previously only use in patients with severe renal impairment).

Based on the interpretation of the nonclinical comments on testicular toxicity in rodents, the Delegate may consider requesting the Sponsor to add this to the list of ongoing safety concerns in the RMP.

Pursuant to the evaluation of the clinical aspects of the safety specifications, the above summary of the Ongoing Safety Concerns is considered acceptable.

Pharmacovigilance plan

Routine and additional pharmacovigilance activities are proposed to monitor the safety concerns. The additional pharmacovigilance activities comprise a proposed patient registry/prospective cohort study, a proposed retrospective cohort study, and six randomised controlled clinical studies (one ongoing, three completed, two proposed).

The sponsor states: "*Whilst sites from Australia are not planned for all studies it is expected that due to similarities in populations, standards of care and indication, data generated from these studies will be applicable to the Australian healthcare setting.*"

Risk minimisation activities

The sponsor has assessed routine risk minimisation activities as sufficient for the defined important risks.

The sponsor also provides the following in regards to the evaluation of the need for risk minimisation activities in Australia "A summary of the proposed Australian RMP is

presented. The plan includes all of the routine pharmacovigilance and risk minimization activities described in the EU RMP. No specific additional measures are proposed beyond these routine measures."

OPR reviewer comment:

Routine risk minimisation activities are considered sufficient to mitigate the ongoing safety concerns associated with Lyxumia. No routine risk minimisation activities (that is statements in the PI) are proposed for the Important potential risk - Cardiovascular events. The sponsor states in the summary of planned minimisation actions in the RMP "*Based on the data collected in the clinical database, there is no evidence of a cardiovascular risk in lixisenatide-treated patients suggesting no significant potential public health impact.*" This is considered acceptable for the present time and it is noted that there is a long-term ongoing cardiovascular study to assess this risk.

In regard to the proposed routine risk minimisation activities, the OPR reviewer commented that the draft PI and CMI documents are considered satisfactory.

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application:

It is recommended that the Delegate consider:

- implementing EU RMP Version 1.1, dated 07MAY2012 [data lock data 30APR2011] and any future updates as a condition of registration.
- request the Sponsor add testicular toxicity to the list of ongoing safety concerns in the RMP, based on the interpretation of the nonclinical comments on testicular toxicity in rodents.

It is recommended to the Delegate that the sponsor:

- commit to providing full protocols and implementation of the proposed Patient Registry and Retrospective database study prior to marketing in Australia. If marketing authorisation is delayed/not approved in the EU, it is recommended that the sponsor commit to providing full protocols and implementation of alternative pharmacovigilance activities to these proposed studies. Study milestones such as the planned date for submission of final data to the TGA of should also be provided.
- Commit to providing an estimated sample size for the Lyxumia patient registry and power calculations for the outcomes of interest (acute pancreatitis, pancreatic cancer and thyroid cancer) prior to marketing in Australia.
- Commit to providing annual incidence data for pancreatitis, pancreatic cancer and thyroid cancer in the annual status reports from the patient registry provided to the TGA
- Provide justification on how the duration of follow-up for the patient registry study (5 year exposure) will be adequate to inform potential cancer risks with Lyxumia.
- Confirm when final study reports for studies EFC 11321, EFC 6017 and EFC 10781 will be available and submitted to the TGA.

VI. Overall conclusion and risk/benefit assessment

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

Background

Lixisenatide is a new chemical entity and was not registered in any overseas country at the time this overview was prepared. It is a GLP-1 receptor agonist. The GLP-1 receptor is a target for native GLP-1 which is an endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic b cells.

At present, liraglutide and exenatide are GLP-1 agonists that are registered in Australia.

Quality

The drug substance is chemically synthesised. All chemistry and quality control issues relating to the drug product have been satisfactorily resolved.

The PSC considered this submission at its 146th meeting. The subcommittee expressed concerns regarding the lack of absolute bioavailability data. The subcommittee also raised concerns about the occurrence of lixisenatide antibodies. There was no indication of the percentage of subjects who developed antibodies and when these antibodies developed. There was a likelihood of these antibodies affecting the efficacy.

Nonclinical

There are no nonclinical objections to registration of lixisenatide for the proposed indication. The recommendation notes that no animal toxicity studies with lixisenatide in combination with other anti-diabetic agents were submitted.

Clinical

Bioavailability and pharmacokinetics

The submission did not include an absolute bioavailability study. Two relative bioavailability studies supporting the use of different sits of administration and the two solution strengths were provided. The former compared a dose of 10 μg SC to the thigh, upper arm and abdomen. The results suggested bioequivalence between the arm and abdomen but the Cmax was lower for the thigh.

The sponsor should in its response to this overview, state the number included in the Phase III studies that had injections in the thigh and provide results for the primary efficacy outcome for this group. The clinical evaluator recommends that the lack of bioequivalence in relation to Cmax should be included in the PI. This is supported.

In the second study the two strengths proposed for marketing (50 μg/mL and 100 μg/mL) were shown to be bioequivalent. These formulations are identical to the formulations used in the clinical trials.

In pharmacokinetic clinical trials the terminal half-life of lixisenatide in healthy volunteers and patients ranged from 1 to 4 h. The total body clearance in T2DM patients was in the range 20 to 67 L/h. Lixisenatide being a polypeptide, has simple metabolism to smaller chains and amino acids which are cleared via renal route are also subject to reabsorption.

One study (POP 6053) investigated the pharmacokinetics of a single dose of lixisenatide in patients with varying degrees of renal impairment. There was no effect lixisenatide exposure in mild renal impairment did not show any significant effect. In severe renal impairment, the ratio estimate for AUC_{last} compared to normal renal function was 1.67 (90% CI 1.12 to 2.51) and for Cmax was 1.29 (90% CI 0.90 to 1.86). The clinical evaluator is of the view that as this was only a single (5 µg) dose study, lixisenatide should not be used with any degree of renal impairment until more information is available based on multiple dosing. This is supported.

Another single dose PK study (POP 11814) compared on elderly with younger subjects using 20 µg lixisenatide dose. The AUC ratio of elderly/young was 1.29 (90% CI 1.06 to 1.57). The effect of multiple dosing is not known. This should be reflected in the PI rather than the proposed statement that age had no effect on the PK.

There were six PK drug-drug interaction studies (warfarin, atorvastatin, ramipril, dixogin, paracetamol and oral contraceptives) to assess coadministration with lixisenatide. The delay in gastric emptying observed with GLP-1 agonists appeared to impair PK of oral administration of paracetamol, digoxin and oral contraceptive to an extent which may have clinical consequences.

The incidence of antibody formation in healthy adult (multiple dose) studies and T2DM studies ranged from 30 to 60%. There was a five to seven fold increase in AUC with the 20 µg dose. The increase in Cmax ranged from 3 to 5 fold.

Pharmacodynamics

In single dose studies dose related insulin response was shown in the 10 to 40 µg dose range in response to a glucose challenge. Glucagon levels were not significantly changed in these studies. In the Phase II studies, dose related effect was shown in fasting, post-prandial plasma glucose and other PD outcomes, in the 5 to 40 µg dose range. The minimum effective dose (FPG and PPG) appeared to be 5 µg and the maximum tolerated dose 20-30 µg (FPG and PPG).

Effect on gallbladder motility and spermatogenesis was also examined in healthy volunteers. It is recommended that the findings regarding spermatogenesis (20 µg/day for 6 months; placebo corrected treatment difference in proportion of subjects with at least 50% reduction in sperm count was 5%; 95% CI -1.6% to 12.4%) be included in the PI. The effect of lixisenatide on QT interval prolongation did not show significant abnormalities in healthy subjects. However a thorough QTc study is currently underway.

In a 28 day PD study, lixisenatide was compared to liraglutide in poorly controlled T2DM patients on metformin. Lixisenatide produced a reduction in plasma glucose of -227.25 h.mg/dL (95%CI -246.88 to -207.61) compared to liraglutide (-72.83 h.mg/dL; 95% CI -93.19 to -52.46). The treatment difference was statistically significant in favour of lixisenatide.

The mean weight reduction with lixisenatide 10 or 20 µg did not show statistically significant difference over 28 days compared to placebo. In another study a reduction of 1.6 kg with lixisenatide compared to 2.4kg with liraglutide was shown at 28 days.

Dose selection

Dose selection, with respect to HbA_{1c}, was investigated in study DRI 6012 (placebo controlled, 13 weeks study) with the results as follows:

Table 10. Mean change in HbA_{1c} (%) from baseline to endpoint – ITT population

		AVE0010							
HbA1C (%)	Placebo (N=108)	5 µg QD (N=55)	10 µg QD (N=51)	20 µg QD (N=53)	30 µg QD (N=52)	5 µg BID (N=51)	10 µg BID (N=54)	20 µg BID (N=52)	30 µg BID (N=53)
Change									
N	107	55	50	53	51	51	54	52	53
Mean (SD)	-0.21 (0.71)	-0.50 (0.58)	-0.52 (0.55)	-0.73 (0.73)	-0.78 (0.63)	-0.68 (0.64)	-0.80 (0.44)	-0.80 (0.62)	-0.88 (0.55)
Median	-0.10	-0.40	-0.55	-0.80	-0.70	-0.70	-0.80	-0.80	-0.90
Min : Max	-2.5 : 2.6	-1.8 : 0.6	-1.8 : 0.8	-2.2 : 3.0	-2.7 : 1.0	-1.9 : 1.3	-1.7 : 0.2	-2.6 : 0.7	-2.1 : 0.4
LS Mean (SE)	-0.18 (0.073)	-0.47 (0.090)	-0.50 (0.095)	-0.69 (0.093)	-0.76 (0.094)	-0.65 (0.093)	-0.78 (0.091)	-0.75 (0.093)	-0.87 (0.095)
LS Mean difference (SE) vs. Placebo	-	-0.28 (0.097)	-0.31 (0.100)	-0.50 (0.098)	-0.57 (0.099)	-0.47 (0.099)	-0.59 (0.098)	-0.57 (0.099)	-0.69 (0.098)
95% CI	-	(-0.472 to -0.091)	(-0.508 to -0.115)	(-0.695 to -0.310)	(-0.768 to -0.377)	(-0.661 to -0.271)	(-0.784 to -0.401)	(-0.760 to -0.372)	(-0.878 to -0.492)
P-value*									
Step down linear trend test									
(QD)		0.0056	0.0033	<.0001	<.0001				
(BID)						<.0001	<.0001	<.0001	<.0001

The dose selection for the pivotal studies appears justified based on these results.

Clinical efficacy

In a double blind randomised 12 week study (EFC 6018) in treatment-naive T2DM patients, the absolute efficacy in relation to HbA_{1c} was -0.66% (95% CI -0.903 to -0.423) in the 1-step[31] lixisenatide group and -0.54% (95%CI -0.785 to -0.300) in the 2-step group.[32] Note that use in treatment-naive patients as monotherapy is not a requested indication.

The studies supporting the requested indication were as follows. The main results were reported at 24 weeks but data up to 76 weeks were also included. The patient population was adult T2DM patients with poor glycaemic control despite adequate and stable metformin therapy (and a second drug in case of triple therapy). The trials were appropriately designed, randomised, double blind, placebo (with existing anti-diabetic medications) or active control studies:

- *Add on to metformin:* Two pivotal placebo-controlled (EFC 6014 and EFC 10743) and one pivotal active (exenatide) controlled (EFC 6019) study to support the use of lixisenatide with metformin (dual therapy).
- *Add on to sulfonylurea with or without metformin:* one pivotal study (EFC 6015) to support the use of lixisenatide with sulfonylurea (dual therapy) or with sulfonylurea and metformin (triple therapy).
- *Add on to basal insulin with or without metformin:* one pivotal study (EFC 6016) to support the use of lixisenatide with basal insulin (dual therapy) or with basal insulin and metformin (triple therapy).
- *Add on to basal insulin with or without sulfonylurea:* one study (EFC 10887) in Asia to support the use of lixisenatide with basal insulin (dual therapy) or basal insulin and metformin (triple therapy).

The doses of lixisenatide used in the clinical trials were consistent with those proposed for registration.

Add on to metformin

Patients with T2DM who were on maximum dose of metformin (1500 mg/day) were included, with mean HbA_{1c} > 8% at baseline. At 24 weeks the main results in Study EFC 6014 were as follows:

[31] 10 µg daily for 2 weeks, then maintenance dose of 20 µg daily.
[32] 10 µg daily for one week, then 15 µg daily for 1 week, then maintenance dose of 20 µg daily.

Table 11. Study EFC 6014: main efficacy results at 24 weeks

Treatment group	Placebo	Lixisenatide morning	Lixisenatide evening
Number of patients	170	255	255
HbA_{1c} change from baseline: LS Mean (SE)	-0.38 (0.075)	-0.87 (0.065)	-0.75 (0.066)
2-hour PPG change from baseline: LS Mean (SE)	-1.41 (0.588) [a]	-5.92 (0.415)	-
FPG change from baseline: LS Mean (SE)	-0.25 (0.166)	-1.19 (0.145)	-0.81 (0.146)
Body weight change from baseline: LS Mean (SE)	-1.64 (0.269)	-2.01 (0.234)	-2.02 (0.236)

At 24 weeks the main efficacy outcomes in study EFC 10743 were as follows:

Table 12. Study EFC 10743: main efficacy results at 24 weeks

Primary endpoint	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
HbA_{1c}	LS Mean difference	-0.41	-0.49
	95% CI	-0.583 to -0.232	-0.670 to -0.317
	P-value	<0.0001	<0.0001
Secondary endpoints	Comparison groups	Lixisenatide 2-step versus Placebo	Lixisenatide 1-step versus Placebo
FPG	LS Mean difference	-0.67	-0.65
	95% CI	-1.035 to -0.301	-1.019 to -0.275
	P-value	0.0004	0.0007
Body weight	LS Mean difference	-1.05	-1.00
	95% CI	-1.727 to -0.371	-1.687 to -0.317
	P-value	0.0025	0.0042

The change in HbA_{1c} appeared to be maintained over the 76 weeks.

Analysis of efficacy by antibody status was also provided in Study EFC 10743 at 76 weeks where mean change from baseline in HbA_{1c} was lower (-0.76 %) in the antibody positive group compared to -1.11% in the antibodies negative patients in the 1-step titration group. This was also seen in those with the 2-step group.

In the active comparator study against exenatide (5 µg BID for 4 weeks, then 10 µg BID, consistent with the Australian approved dosage), the primary efficacy outcome at 24 weeks was as follows:

Table 13. Study EFC 6019: main efficacy results at 24 weeks

HbA1c (%)	Lixisenatide (N=315)	Exenatide (N=315)
Change from baseline to week 24 (LOCF)		
Number	295	297
Mean (SD)	-0.80 (0.88)	-0.95 (0.87)
Median	-0.80	-0.90
Min : Max	-3.1 : 3.8	-3.3 : 3.4
LS Mean (SE) [a]	-0.79 (0.053)	-0.96 (0.054)
LS Mean difference (SE) vs. Exenatide [a]	0.17 (0.067)	
95% CI	(0.033 to 0.297)	

This was a non-inferiority design (pre-defined non-inferior upper border of 95% CI 0.4%). However, the treatment difference was statistically superior in favour of exenatide (0.17%, 95% CI 0033 to 0.297). The results for some secondary outcomes were as follows:

Table 14. Study EFC 6019: Selected secondary outcomes

Secondary endpoints	Comparison groups	Lixisenatide versus Exenatide
FPG [a]	LS Mean difference	0.23
	95% CI	-0.052 to 0.522
Body weight [a]	LS Mean difference	1.02
	95% CI	0.456 to 1.581
Rescue therapy [a]	Risk difference	-1.6
	95% CI	-4.41 to 1.16
[a] No formal interferential testing		

Add on to sulphonylurea with or without metformin

As dual therapy, the data in the study EFC 6015 are limited (16% of randomised) to a subgroup of only 42 placebo patients and 86 lixisenatide patients although based on prospective design.

At 24 weeks, the results as dual therapy (sulphonylurea with lixisenatide) with respect to change in HbA_{1c} were as follows:

Table 15. Study EFC 6015: change in HbA_{1c} at 24 weeks: sulphonylurea with lixisenatide

Subgroups	N	LS Mean[a]	SE[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]
Sulfonylurea alone					
Placebo	42	0.08	0.135		
Lixisenatide	86	-0.77	0.102	-0.85 (0.158)	[-1.161, -0.543]

As triple therapy with sulfonylurea and metformin, the results at 24 weeks in this trial with respect to change in HbA_{1c} were as follows:

Table 16. Study EFC 6015: main efficacy results: sulfonylurea, metformin and lixisenatide

Subgroups	N	LS Mean[a]	SE[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]
Sulfonylurea + Metformin					
Placebo	232	-0.20	0.067		
Lixisenatide	458	-0.92	0.054	-0.72 (0.068)	[-0.857, -0.591]

Results for some secondary outcomes were as follows:

Table 17. Study EFC 6015: Selected secondary outcomes

Secondary endpoints	Ccmparison groups	Lixisenatide versus Placebo
2-hour PPG [a]	LS Mean difference	-5.98
	95% CI	-6.912 to -5.043
	P-value	<0.0001
FPG	LS Mean difference	-0.63
	95% CI	-0.919 to -0.346
	P-value	<0.0001
Body weight	LS Mean difference	-0.84
	95% CI	-1.250 to -0.421
	P-value	<0.0001

Overall efficacy appeared to be maintained over the extension period of 76 weeks.

Add on to basal insulin with or without metformin or with or without sulphonylurea

Note there are no studies of lixisenatide against agents that are registered as add-on regimen with insulin.

The results at 24 weeks with respect to change in HbA_{1c} in the study EFC 6016 (basal insulin with or without metformin) were as follows:

Table 18. Study EFC 6016: Change in HbA_{1c} at 24 weeks

Subgroups	N	LS Mean[a]	SE[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]
Basal Insulin alone					
Placebo	32	-0.11	0.185		
Lixisenatide	55	-0.80	0.147	-0.70 (0.217)	[-1.123, -0.271]
Basal Insulin + Metformin					
Placebo	126	-0.49	0.110		
Lixisenatide	249	-0.77	0.086	-0.28 (0.107)	[-0.489, -0.070]

The study EFC 10887 (basal insulin with or without sulphonylurea) was carried out solely in Asian population. The results with respect to change in HbA_{1c} at 24 weeks were as follows:

Table 19. Study EFC 10887: Change in HbA_{1c} at 24 weeks

Subgroups	N	LS Mean[a]	SE[a]	LS Mean Treatment Difference(SE)[ab]	95% CI[ab]
Basal Insulin alone					
Placebo	45	0.02	0.193		
Lixisenatide	43	-0.85	0.188	-0.87 (0.221)	[-1.305, -0.436]
Basal Insulin + Sulfonylurea					
Placebo	109	0.19	0.134		
Lixisenatide	103	-0.70	0.151	-0.89 (0.141)	[-1.164, -0.607]

Study EFC 6016 also showed that presence of antibodies tended to reduce the magnitude of efficacy in relation to the primary efficacy endpoint.

Rescue medication

The clinical evaluator has noted that data from placebo controlled studies with an extension showed increase in the numbers of patients requiring rescue therapy over the entire treatment period compared with the initial 24 week period. As well, in patients receiving lixisenatide a high proportion were anti-lixisenatide antibodies positive prior to rescue. The sponsor is requested to include an appropriate tabulation in the response to this overview.

Antibodies and their influence on efficacy

A pooled analysis (EFC 6015, EFC 6016, EFC 10743 and EFC 10887) of change in HbA_{1c} from baseline to week 24 by anti-lixisenatide antibody status included 998 patients. The results were as follows:

Table 20. Change in HbA_{1c} from baseline to week 24 by anti-lixisenatide antibody status: Pooled analysis

	Lixisenatide			
	n/N (%)	LS Mean[b]	SE[b]	95% C.I.[b]
Anti-lixisenatide antibody status[a]				
Positive	693/998 (69.4%)	-0.81	0.051	(-0.914 to -0.714)
Negative	305/998 (30.6%)	-0.83	0.065	(-0.962 to -0.708)

The clinical evaluator has observed a number of discrepancies in this analysis. The sponsor is requested to provide comment in its response to this overview.

Clinical safety

The absolute (placebo-corrected) incidence of AEs based on the 12 weeks monotherapy Study EFC 6018 in treatment-naive T2DM patients, in which 239 patients were exposed to lixisenatide, was 53.6% in lixisenatide group compared to 45.1% in placebo group. The most frequent event was vomiting (7.1%) in patients on lixisenatide, versus zero on placebo. The incidence of symptomatic hypoglycaemia was 1.6% in both groups. Injection site reaction was 4.6% in the lixisenatide group versus zero in the placebo group. The Study DRI 6012 indicated a dose response in relation to TEAEs.

The overall summary of TEAEs (in Studies 6014, 6015, 6016, 6018, 10743 and 108887) during the main treatment period (12 weeks in Study 6018 and 24 weeks in all others) is as follows:

Table 21. Overall summary of TEAEs during the main treatment period

	Placebo (N=1061)	Lixisenatide (N=2127)
Patients with any TEAE	660 (62.2%)	1475 (69.3%)
Patients with any serious TEAE	43 (4.1%)	68 (3.2%)
Patients with any TEAE leading to death	1 (<0.1%)	3 (0.1%)
Patients with any TEAE leading to permanent treatment discontinuation	34 (3.2%)	157 (7.4%)

In placebo controlled two add-on studies to metformin, 832 patients were exposed to lixisenatide with mean treatment duration of over 500 days. Nausea (25-38%) and vomiting (13-18%) were common TEAEs. The adjudicated allergic reactions were seen in 1.6% to 3.8% in the lixisenatide compared to 1.6% placebo treated patients. There was also one report of anaphylactic reaction in the lixisenatide group.

In the Study EFC 6019, a total of 319 and 316 patients were exposed to lixisenatide and exenatide, respectively. The mean duration was over 410 days. The adjudicated allergic events were higher in lixisenatide (1.9%) compared to exenatide (0.9%).

In add-on to metformin and sulfonylurea Study EFC 6015 (triple therapy), a total of 574 in the patients were exposed to lixisenatide treatment. The mean duration was 570 days. The events were broadly similar to the previous studies.

The add-on to basal insulin with or without metformin or sulfonylurea studies were EFC 6016 and EFC 10887. In study EFC 6016, a total of 328 patients were exposed to lixisenatide over a mean duration of 510 days. The AE profile was similar to the previous studies. In Study EFC 10887, a total of 157 Asian patients were exposed to lixisenatide. This study included insulin and sulfonylurea in 70% of the subjects. The cardiovascular events were higher with lixisenatide treatment (4.5% versus 0.65%).

The absolute incidence of symptomatic hypoglycaemia in the main treatment period (Study EFC 6018) was as follows:

Table 22. Incidence of symptomatic hypoglycaemia in the main treatment period (Study EFC6018)

Background therapy Treatment	Symptomatic hypoglycemia		
	Any symptomatic hypoglycemia	Blood glucose <60 mg/dL	No blood glucose reported
Monotherapy[a]			
Placebo (N=122)	2 (1.6%)	2 (1.6%)	0
Lixisenatide (N=239)	4 (1.7%)	2 (0.8%)	2 (0.8%)

The incidence of symptomatic hypoglycaemia in the main treatment period by background therapy in other Phase III controlled studies was as follows:

Table 23. Incidence of symptomatic hypoglycaemia in the main treatment period by background therapy

Background therapy Treatment	Symptomatic hypoglycemia Any symptomatic hypoglycemia	Blood glucose <60 mg/dL	No blood glucose reported
Metformin from placebo - controlled studies[b]			
Placebo (N=330)	2 (0.6%)	1 (0.3%)	1 (0.3%)
Lixisenatide (N=832)	26 (3.1%)	25 (3.0%)	2 (0.2%)
Metformin from exenatide - controlled study[c]			
Lixisenatide (N=318)	8 (2.5%)	7 (2.2%)	1 (0.3%)
Exenatide (N=316)	25 (7.9%)	20 (6.3%)	7 (2.2%)
Metformin from sitagliptin - controlled study[d]			
Lixisenatide (N=158)	1 (0.6%)	1 (0.6%)	0
Sitagliptin (N=161)	3 (1.9%)	1 (0.6%)	2 (1.2%)
Sulfonylurea[e]			
Placebo (N=46)	4 (8.7%)	2 (4.3%)	2 (4.3%)
Lixisenatide (N=88)	16 (18.2%)	11 (12.5%)	8 (9.1%)
Sulfonylurea + metformin[e]			
Placebo (N=239)	31 (13.0%)	22 (9.2%)	9 (3.8%)
Lixisenatide (N=486)	72 (14.8%)	59 (12.1%)	15 (3.1%)
Basal insulin ± metformin[f]			
Placebo (N=167)	36 (21.6%)	35 (21.0%)	1 (0.6%)
Lixisenatide (N=328)	91 (27.7%)	87 (26.5%)	9 (2.7%)
Basal insulin[g]			
Placebo (N=46)	13 (28.3%)	11 (23.9%)	2 (4.3%)
Lixisenatide (N=46)	15 (32.6%)	13 (28.3%)	3 (6.5%)
Basal insulin + sulfonylurea[g]			
Placebo (N=111)	24 (21.6%)	21 (18.9%)	9 (8.1%)
Lixisenatide (N=108)	51 (47.2%)	46 (42.6%)	12 (11.1%)

[a] EFC6018. [b] EFC6014 and EFC10743. [c] EFC6019. [d] EFC10780. [e] EFC6015. [f] EFC6016. [g] EFC10887.
Main treatment period:12 weeks for EFC6018 and 24 weeks for other studies.

Severe symptomatic hypoglycaemia was reported in the following studies:

Table 24. Incidence of severe symptomatic hypoglycaemia

Background therapy Treatment	Severe symptomatic hypoglycemia Any severe symptomatic hypoglycemia	Blood glucose <36 mg/dL	No blood glucose reported
Sulfonylurea + metformin[e]			
Placebo (N=239)	0	0	0
Lixisenatide (N=486)	1 (0.2%)	0	1 (0.2%)
Basal insulin ± metformin[f]			
Placebo (N=167)	0	0	0
Lixisenatide (N=328)	4 (1.2%)	3 (0.9%)	1 (0.3%)

Risk management plan

The Delegate considered the evaluation of the RMP reviewed by the OPR area of the TGA (see section V *Pharmacovigilance findings*, above).

Risk-benefit analysis

Delegate considerations

Lixisenatide PK and PD were adequately investigated. The deficiencies in the dossier include lack of an absolute bioavailability study. Such comparison of time-concentration of the SC drug with its IV profile would be useful in view of relatively short half-life of the drug and its proposed once daily dosing.

The efficacy of lixisenatide in patients with inadequate glycaemic control while on metformin alone, investigated in placebo-controlled trials, was modest but adequate and was nominally lower but non-inferior against exenatide based on pre-defined criterion. These data support add-on lixisenatide to metformin. However, there are no data to ascertain the relative place of metformin/lixisenatide dual combination among the currently approved and recommended dual combinations (based on diabetes mellitus treatment guidelines). This appears to be an accepted norm for regulatory purposes in the development of new anti-diabetic medications. In this instance, the Delegate considers that at least the estimate of relative efficacy with exenatide (which is available from data in this dossier) should be objectively noted in the PI.

Addition of lixisenatide as triple therapy in patients with poor glycaemic control while on dual therapy (metformin, a sulphonylurea, a basal insulin) is also supported by the evidence provided in this dossier. The patient population is considered appropriate based on regulatory practice. Again, however, despite inadequate glycaemic control with two drugs, the patients are rather unselected. There does not appear to be an effort to start a new agent with investigation in more narrowly defined, hard to treat patient group, or gain wider exposure post-market before moving to a less selected population. And this is despite the fact that anti-diabetics are approved based on (validated) surrogate endpoints without requiring demonstration of benefit on long-term mortality and morbidity outcomes.

The use of lixisenatide dual therapy with a sulfonylurea or with a basal insulin is not supported due to small number of patients exposed in the trials investigating this use included in the dossier. The Delegate supported the view that the data are grossly insufficient for a new chemical entity.

One particular concern with this drug is the observed risk of development of anti-lixisenatide antibodies in the clinical trials. The long-term impact of these antibodies on safety and efficacy is currently unknown and will require active post-market monitoring.

Proposed action

In agreement with the clinical evaluator, the Delegate supported approval of lixisenatide, with appropriate restrictions in the PI as noted by various evaluation areas, and the recommendations for the RMP. The supported indication is:

> *treatment of adults with T2DM to achieve glycaemic control in patients not adequately controlled with diet and exercise:*
>
> *In combination with:*
>
> - *metformin (dual therapy)*
> - *metformin and a sulphonylurea (triple therapy)*
> - *a basal insulin and metformin (triple therapy)*
> - *a basal insulin and a sulphonylurea (triple therapy)*

Advice requested from ACPM

In addition to any matter on which ACPM may wish to provide advice, the Delegate requested comment on:

1. The overall adequacy of the package to support initial registration,
2. The proposed indication and advice on any implicit hierarchy or sequence, and
3. The post-market requirements with respect to the risk of antibodies development.

Response from Sponsor

In accordance with TGA procedures, the sponsor receives final evaluation reports for comment on errors and omissions. This procedural step is intended to allow the Delegate to consider the sponsor responses prior to finalisation of the overview.

The sponsor submitted comments on the CER together with a revised PI to address recommendations made by the clinical evaluator. However, as the CER was subject to multiple delays, the Delegate advised that the sponsor comments on the CER were not considered prior to finalisation of the Delegates overview. The Delegates overview therefore includes reference to items that were addressed in the sponsor's CER response and does not refer to the revised indication that formed part of the updated PI provided with that response.

Key information included in the CER response relevant to the Delegates overview are summarised below:

- information pertaining to the justification for not completing an absolute bioavailability study for inclusion in the application
- assessment of effects on spermatogenesis in Study TDR 11215 conducted in healthy subjects
- confirmation of the completion of the 2nd comprehensive QTc study (TES 11087)
- explanation for the differences in numbers of patients for antibody analyses
- corrections/clarification of information relevant to requested statements in the PI by the clinical evaluator
- a revised indication in the updated PI reflecting the wording recommended for approval in the EU, following adoption of a positive opinion at the November CHMP meeting as outlined below:

  *Lyxumia is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see **CLINICAL TRIALS and PRECAUTIONS (Risk of Hypoglycemia**) for available data on the different combinations).*

- The EU indication wording is aligned with the revised CHMP guideline on *Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* which was issued on 14 May 2012 and recently came into effect in the EU (on 15 November 2012) and is anticipated to be adopted in Australia.

As agreed with the Delegate, to ensure the ACPM can take into consideration the additional information submitted by the sponsor a complete copy of the response to the CER was provided to the ACPM.

Sponsor's comments on evaluations

The sponsor comments on the matters for which the advice of the ACPM is sought, as outlined in the Delegate's overview, as well as proposals for updates to the PI recommended by the clinical evaluator and endorsed by the Delegate, are presented below.

Overall adequacy of the package to support initial registration

The initial registration package submitted in Australia was the same as submitted in the EU for which a positive opinion for approval has been issued by the CHMP in November 2012. A copy of the proposed EU SmPC is provided as part of the pre-ACPM response.

The Delegate has stated that the lack of an absolute bioavailability study is a deficiency in the dossier based on the view shared with the clinical evaluator that comparison of the SC and IV profile will be useful in further characterizing the pharmacokinetics. Based on the population PK data analysis conducted, it became evident that the PK of lixisenatide when administered subcutaneously, is absorption rate limited, as indicated in the original dossier (POH0182, including POH0063), the population mean absorption time (MAT) of 2.7 h was longer than the population mean elimination time (V/CL) of 1.15 h. This absorption limitation applies to the large majority of patients when comparing individual parameters. In this flip-flop kinetic situation, the terminal half-life ($t_{½z}$) for most patients corresponded to the absorption process and had to be calculated as log(2)*MAT. An IV administration that circumvents the identified absorption limitations, would thus not substantially add to the full characterisation of the PK of lixisenatide. It should also be noted that no requirement to submit this data was made as part of the recent CHMP Opinion recommending approval of Lyxumia in the EU.

In addition, in order to clarify the PK properties of lixisenatide when administered simultaneously with another drug as part of the development program for a potential combination product, the sponsor recently completed a bioavailability study for lixisenatide, which included an IV arm, and for which a report was issued at the end of October 2012. The high-level information of this study BDR 12546 is as follows: The absolute bioavailability of the SC administration of the 100 µg/mL formulation when administered in the abdomen was 32% (90% CI: [24% to 42%]) for total lixisenatide.

Based on these data, the sponsor maintains that the information captured in this report does not add substantially to complete understanding of the PK of lixisenatide when being administered SC and that the original justification for not conducting an absolute bioavailability study remains valid. Importantly, the efficacy and safety data from the pivotal Phase III trials confirm an overall favourable benefit/risk for the intended commercial formulation of lixisenatide administered SC once daily in the proposed patient population. The Sponsor can provide a copy of the above report to the TGA post-approval.

In relation to the completed relative bioavailability studies and the noted lower Cmax using the thigh, rather than arm and abdomen sites of administration, the sponsor included a revised PI statement reflecting the results of this bioavailability study as follows: *Following subcutaneous administration of a single 10µg dose of lixisenatide in the abdomen, thigh and arm, mean Cmax was 56.7 pg/mL, 48.6 pg/mL (ratio thigh versus abdomen: 0.86; CI: 0.79-0.94) and 56.9 pg/mL [ratio arm versus abdomen: 1.00; CI: 0.92-1.09], respectively.*

In Phase III studies, recommendation was given per protocol to administer the study drug alternating between the left and right anterolateral and left and right posterolateral abdominal wall and thighs and upper arms. Within a given area, the location should be changed (rotated) each time to prevent injection site skin reactions. Therefore, no further information is available to address the Delegate's request to state the number of patients included in the Phase III studies that had injections in the thigh and provide results for the

primary efficacy outcome for this group. The sponsor does not consider this as a deficiency as it reflects the same approach used in routine clinical practice for insulin therapies with which clinicians and patients are familiar.

Overall, the sponsor concurs with the Delegate that the registration package is sufficient to support an approval recommendation for Lyxumia. Considering the similarity in patient populations and clinical practice between the EU and Australia and the common regulatory framework based on adoption of the CHMP guidelines, the sponsor considers the EU regulatory decision further supports and validates the Delegate's opinion on the overall adequacy of the package for initial registration of lixisenatide.

Proposed indication and advice on any implicit hierarchy or sequence

As outlined above, the sponsor has proposed an alternative indication to that included in the Delegates overview, aligned with that recommended for approval in the EU SmPC:

> *Lyxumia is indicated for the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control (see CLINICAL TRIALS and PRECAUTIONS (Risk of Hypoglycemia) for available data on the different combinations).*

The proposed text addresses the comments of the clinical evaluator that the indication wording was confusing in presentation and is consistent with the revised CHMP guideline on *Clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus* which is anticipated to be adopted in Australia. The indication specifically refers the prescriber to the 'Clinical Trials' and 'Precautions' section of the PI so that the full clinical data set is considered in making the most appropriate treatment choice for an individual patient. In considering the ongoing developments in the diabetes area, ensuring the most recent Clinical Trial information is taken into account is considered important to support quality use of medicines.

Whilst acknowledging the comments of the Delegate and clinical evaluator on the patient numbers and data from Asian populations supporting dual therapy with a sulfonylurea (SU) or basal insulin, the Sponsor disagrees with the conclusion that safety and efficacy have not been adequately demonstrated to support use in clinical practice. on the following grounds:

- Based on current clinical practice the majority of patients who will be candidates for lixisenatide therapy will be receiving metformin or basal insulin and metformin, reflecting the primary focus of the clinical development program. (Pharmaceutical Benefits Scheme (PBS) data Type 2 Diabetes June 2012; GLP-1+ SU = 0.042%; GLP-1+basal insulin = 0.007%).
- Statistically and clinically significant improved glycemic control based on comparisons of difference in HbA_{1c} between lixisenatide and placebo added to SU or basal insulin alone were demonstrated in a sufficient number of patients to justify the relevance of the data to the general target patient population.
  - Additional supportive analyses demonstrate overall improvements in key secondary efficacy parameters (responder rates on HbA_{1c}, FPG, 2 h PPG and body weight).
- As reflected in the PI, ethnic origin had no clinically relevant effect on the pharmacokinetics of lixisenatide and there were no clinically significant differences in efficacy or safety profile between the Asian and Caucasian populations.
- The Population National Summary derived from the 2011 census data [Australia Bureau of Statistics Cat. 4102.0] indicates people born in East, Central or Southern Asian countries make up 9.1% of the ethnic mix in Australia with increasing levels of

immigration from these countries evident over the period 1998-2011. These estimates exclude second generation born Australians and thus are conservative from a clinical practice perspective.

- Information from studies conducted in Asian patients is relevant to patient management in clinical practice in Australia. The sponsor has revised the 'Clinical Trials' section of the PI to specify data generated in Asian populations to ensure prescriber awareness
- Reassurance on the safety profile of lixisenatide when used as dual therapy is provided by the evidence of safety when used in triple therapy regimens:
  - 725 patients treated with SU + metformin were randomised in Study EFC 6015, including 486 exposed to lixisenatide
  - 611 patients treated with basal insulin + oral anti-diabetic drug (OAD) were randomised in Studies EFC 6016 and EFC 10887, including 369 exposed to lixisenatide (safety populations).
- The recent CHMP recommendation for Lyxumia includes use as dual therapy. The similarity in clinical practice and populations between Australia and the EU, which numbers almost half a billion citizens, enhances the ability as part of routine global pharmacovigilance to identify any potential signals and implement appropriate risk mitigation measures, thus ensuring safe and effective use in Australian clinical practice.

Data supporting use of lixisenatide dual therapy with SU

Overall 134 patients treated with SU alone were randomised in Study EFC 6015, and 88 of these were exposed to the lixisenatide treatment (safety population). Lixisenatide significantly improved glycaemic control in this subgroup of patients. The LS mean difference in HbA_{1c} between lixisenatide and placebo in this subgroup was clinically meaningful and statistically significant: -0.85%, (95% CI: -1.161 to -0.543). To address the Delegate concerns, additional supportive analyses of the main secondary efficacy endpoints were completed (responders rates [HbA_{1c} ≤6.5% or <7%], FPG, 2 h PPG and body weight) which show an effect generally meaningful and comparable in the subgroup of patients treated with SU alone.

A subgroup analysis by metformin use (yes/no) in Study EFC 6015 indicates no relevant difference in the incidence and the distribution of AEs between subgroups. The same was observed for symptomatic hypoglycaemia. This confirms there is no rationale for the safety profile of lixisenatide to be worse in patients treated with SU alone compared to patients treated with SU + metformin.

Data supporting use of lixisenatide dual therapy with a basal insulin

Use of lixisenatide with basal insulin alone was investigated in two Phase III studies: the EFC 6016 Study (global study to support use of lixisenatide in add-on to basal insulin and/or metformin) and the EFC 10887 Study (Asian study to support use of lixisenatide in add-on to basal insulin and/or sulfonylurea). Overall 195 patients (safety population) treated with basal insulin alone were randomised in Studies EFC 6016 and EFC 10887, including 113 in the lixisenatide group.

Lixisenatide significantly improved glycaemic control in this subgroup of patients. In both studies, the LS mean difference in HbA_{1c} between lixisenatide and placebo was clinically meaningful and statistically significant in the subgroups of patients treated with basal insulin alone: -0.70% (95% CI: -1.123 to -0.271) in EFC 6016; -0.87% (95% CI: -1.305 to -0.436) in EFC 10887. To address the Delegate concerns, additional supportive analyses of the main secondary efficacy endpoints were completed (responders rates [HbA_{1c} ≤6.5% or

<7%], FPG, 2 h PPG and body weight) which show an effect generally meaningful and comparable in the subgroups of patients treated with basal insulin alone.

A subgroup analysis by metformin use (yes/no) in Study EFC 6016 and by SU use (yes/no) in Study EFC 10887 indicates no relevant difference in the incidence and the distribution of AEs between subgroups. In particular in study EFC 6016 the incidence of hypoglycaemia on lixisenatide treatment was similar in patients regardless of metformin use (41.8% with metformin use versus 43.3% without metformin use), and in Study EFC 10887, the incidence of symptomatic hypoglycaemia was similar to placebo in patients treated with basal insulin alone. This confirms there is no rationale for the safety profile of lixisenatide to be worse in patients treated with basal insulin alone compared to patients treated with basal insulin + OAD.

Overall, considering the patient populations and clinical practice in Australia, the available data are appropriate to demonstrate a suitable efficacy and safety profile of lixisenatide dual therapy with SU or a basal insulin to support the proposed indication for use.

Post market requirements with respect to risk of antibodies development.

The potential risk of immunogenicity/neutralisation associated with anti-lixisenatide antibodies is included in the proposed RMP. To address the risk, both routine and additional pharmacovigilance measures are included to assess the effects of antibodies. These include further analysis of anti-lixisenatide antibodies in ongoing clinical trials (EFC 6017, EFC 10781, EFC 11321, EFC 11319/ELIXA) and special attention to events potentially associated with antibody formation, for example, hypersensitivity, in Periodic Benefit-Risk Evaluation Reports (PBRERs). Especially, the antibody development and consequences will be further assessed in the ongoing long term (176 weeks) cardiovascular outcome study (EFC 11319/ELIXA) planned to include 6000 patients, and as per the RMP, the sponsor has committed to submit results from these studies post-approval. Overall, the sponsor considers the existing measures are sufficient to proactively identify any new signals and enable mitigation of any potential risks with respect to antibody development. It should be also noted that these same measures are also included in the RMP recently recommended for approval in EU by the CHMP in November 2012.

Anti-lixisenatide antibodies

As requested by the Delegate, tabular summaries were provided at the last on-treatment value prior to rescue in patients who had at least one anti-lixisenatide antibody status measurement (prior to rescue for patients with rescue therapy) in the pooled data: (1) 24 week treatment period based on the pooled data of 5 placebo-controlled studies (EFC 6014, EFC 6015, EFC 6016, EFC 10743 and EFC 10887), and (2) the entire treatment period in the pooled data of 4 studies with at least 76 weeks of treatment (EFC 6014, EFC 6015, EFC 6016 and EFC 10743). These results showed that the incidence of patients being antibody positive was generally similar between patients who initiated rescue therapy versus patients without any rescue therapy during the study.

An explanation of differences in numbers for antibody analyses was included in the response to the CER.

Proposed product information updates

Details of these are beyond the scope of this AusPAR.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the delegate and considered these products to have an overall positive benefit–risk profile for the following revised indication**:**

For treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in patients not adequately controlled with diet and exercise:

In combination with:

- *Metformin (dual therapy)*
- *Metformin and a sulphonylurea (triple therapy)*
- *A basal insulin and metformin (triple therapy)*
- *A basal insulin and a sulphonylurea (triple therapy)*

In making this recommendation, the ACPM noted the potential for drug interactions and the adverse effect on spermatogenesis and agreed that immunogenicity should be the subject of detailed post-marketing study.

The ACPM agreed with the delegate to the proposed amendments to the PI and CMI.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Lyxumia / Lyxumia Treatment initiation pack / Lixisenatide Sanofi / Lixisenatide Sanofi Treatment initiation pack / Lixisenatide Winthrop / Lixisenatide Winthrop Treatment initiation pack, containing Lixisenatide injection solution 0.05 mg/mL and 0.01 mg/mL for:

> *the treatment of adults with type 2 diabetes mellitus to achieve glycaemic control in combination with metformin, metformin and sulphonylurea, basal insulin and metformin, basal insulin and sulphonylurea when these, together with diet and exercise, do not provide adequate glycaemic control (see sections Clinical Trials and Precautions (Risk of Hypoglycaemia)) for available data on the different combinations.*

Condition of registration applicable to these goods

The implementation in Australia of the LYXUMIA (lixisenatide) 10 µg and 20 µg solution for injection injector pens Risk Management Plan (included with submission PM-2011-03163-3-5) identified as the EU RMP Version 1.5, dated 14 November 2012 [data lock point 30 April 2011], including Australian Specific Annex Version 1.4 dated January 2013, and any subsequent revisions as agreed with the TGA and its Office of Product Review.

Attachment 1. Product Information

The Product Information for Lyxumia approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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