

1 **PROPOSED AMENDED PROFESSIONAL INFORMATION**

2

3 **SCHEDULING STATUS**

4 **S4**

5

6 **1 NAME OF THE MEDICINE**

7 Victoza®

8

9 **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

10 1 ml of solution contains 6 mg of liraglutide*. One pre-filled pen
11 contains 18 mg liraglutide in 3 mL.

12 * human glucagon-like peptide-1 (GLP-1) analogue produced by
13 recombinant DNA technology in *Saccharomyces cerevisiae*.
14 For the full list of excipients, see section 6.1 List of excipients.

15

16 **3 PHARMACEUTICAL FORM**

17 Solution for injection in a pre-filled pen

18 Clear and colourless or almost colourless, isotonic solution;
19 pH = 8,15.

20

21 **4 CLINICAL PARTICULARS**

22 **4.1 Therapeutic indications**

23

24 Glycaemic control:

25 Victoza® is indicated as an adjunct to diet and exercise to achieve
26 glycaemic control in patients with type 2 diabetes mellitus. Victoza® is
27 indicated for once-daily administration as:

- 28 • monotherapy
- 29 • combination therapy with one or more oral antidiabetic
30 medicines (metformin, sulphonylureas, sodium-glucose
31 cotransporter 2 inhibitor (SGLT2i) or a thiazolidinedione) when
32 previous therapy does not provide adequate glycaemic control.
- 33 • combination therapy with insulin in patients not achieving
34 adequate glycaemic control with Victoza® and metformin.

35

36 Prevention of cardiovascular events:

37 Victoza® is indicated to prevent Major Adverse Cardiovascular Events
38 (MACE: cardiovascular death, non-fatal myocardial infarction, or non-
39 fatal stroke) in adults with type 2 diabetes mellitus at high
40 cardiovascular risk, as an adjunct to standard of care therapy (see
41 section 5 Pharmacological Properties).

42

43 **4.2 Posology and method of administration**

44 *Monotherapy*

45

46 To reduce gastro-intestinal adverse effects for all patients, Victoza®
47 should be initiated with a dose of 0,6 mg for at least one week, after
48 which the dose may be increased to 1,2 mg. Based on clinical
49 response and after at least one week the dose can be increased to 1,8

50 mg to achieve maximum efficacy. Daily doses higher than 1,8 mg are
51 not recommended.

52

53 *Combination therapy*

54 Victoza® can be used in combination with other glucose lowering
55 agents and no dose adjustments are required for metformin,
56 thiazolidinedione and SGLT2i therapy.

57

58 When Victoza® is added to a sulphonylurea therapy or insulin, a
59 reduction in the dose of sulphonylurea or insulin should be considered
60 to reduce the risk of hypoglycaemia (see section 4.4 Special warnings
61 and precautions for use).

62

63 Self-monitoring of blood glucose is not needed in order to adjust the
64 dose of Victoza®. However, when initiating treatment with Victoza® in
65 combination with a sulphonylurea or insulin, blood glucose self-
66 monitoring may become necessary to adjust the dose of the
67 sulphonylurea or insulin.

68

69 *Incompatibilities*

70 Substances added to Victoza® may cause degradation of liraglutide.
71 Victoza® must not be mixed with other medicinal products, e.g. infusion
72 fluids.

73

74 **Special populations**

75 *Elderly and Gender*

76 No dosage adjustment is required based on age and gender.

77

78 *Obesity*

79 Population pharmacokinetic analysis suggests that body mass index

80 (BMI) has no significant effect on the pharmacokinetics of liraglutide.

81

82 *Hepatic impairment*

83 No dose adjustment is required for patients with hepatic impairment

84 (see 4.4 Special warnings and precautions for use).

85

86 *Renal impairment*

87 No dose adjustment is required for patients with mild, moderate or

88 severe renal impairment.

89 There is no therapeutic experience in patients with end-stage renal

90 disease and Victoza® is therefore not recommended for use in these

91 patients (see 4.4 Special warnings and precautions for use).

92

93 **Paediatric population**

94 Victoza® has not been studied in paediatric patients below 18 years of

95 age (see 4.4 Special warnings and precautions for use).

96

97 **Method of administration**

98 Victoza® must not be administered intravenously or intramuscularly.

99

100 Victoza® is administered once daily at any time, independent of meals,
101 and can be injected subcutaneously in the abdomen, in the thigh or in
102 the upper arm.

103 Injection sites should always be rotated within the same region in order
104 to reduce the risk of cutaneous amyloidosis (see section 4.8
105 Undesirable effects).

106 The injection site and timing can be changed without dose adjustment.

107

108 **4.3 Contraindications**

- 109 • Hypersensitivity to liraglutide or any of its excipients
- 110 • A history of previous pancreatitis
- 111 • Type 1 diabetes mellitus
- 112 • Pregnancy and lactation (see section 4.6 Pregnancy)

113

114 **4.4 Special warnings and precautions for use**

115

116 Victoza® should not be used in patients with type 1 diabetes mellitus or
117 for the treatment of diabetic ketoacidosis.

118 Victoza® should not be administered intravenously or intramuscularly.

119 Victoza® is not a substitute for insulin.

120 Safety and efficacy of Victoza® in patients below 18 years of age has
121 not been established.

122

123 Patients above 70 years may experience more gastrointestinal effects
124 when treated with Victoza®. Patients with mild and moderate renal

125 impairment (creatinine clearance 60 – 90 ml/min and 30 – 59 ml/min,
126 respectively) may experience more gastrointestinal effects when
127 treated with Victoza®.

128

129 There is no therapeutic experience in patients with end-stage renal
130 disease and Victoza® is therefore not recommended for use in these
131 patients.

132

133 There is no therapeutic experience in patients with congestive heart
134 failure New York Heart Association (NYHA) class IV and Victoza® is
135 therefore not recommended for use in these patients.

136

137 There is limited experience in patients with inflammatory bowel
138 disease and diabetic gastroparesis and Victoza® is therefore not
139 recommended for use in these patients. The use of Victoza® is
140 associated with gastrointestinal adverse reactions, including nausea,
141 vomiting and diarrhoea.

142

143 *Hypoglycaemia*

144 Patients receiving Victoza® in combination with a sulphonylurea or
145 insulin may have an increased risk of hypoglycaemia. The risk of
146 hypoglycaemia can be lowered by a reduction in the dose of
147 sulphonylurea or insulin.

148

149 *Immunogenicity*

150 Consistent with the potentially immunogenic properties of protein and
151 peptide pharmaceuticals, patients may develop anti-liraglutide
152 antibodies following treatment with Victoza®. On average, 8,6 % of
153 patients developed antibodies. Antibody formation has not been
154 associated with reduced efficacy of Victoza®.

155

156 *Injection site reactions*

157 Injection site reaction has been reported in approximately 2 % of
158 subjects receiving Victoza® in long-term (26 weeks or longer)
159 controlled trials. These reactions have usually been mild and did not
160 lead to discontinuation of Victoza®.

161

162 *Acute pancreatitis*

163 Acute pancreatitis has been observed with the use of GLP-1 receptor
164 agonists.

165 Patients should be informed of the characteristic symptoms of acute
166 pancreatitis. If pancreatitis is suspected, liraglutide should be
167 discontinued.

168 Once acute pancreatitis is confirmed, liraglutide or any other GLP-1
169 receptor agonist should never again be restarted. Caution should be
170 exercised in patients with a history of pancreatitis.

171

172 *Thyroid disease*

173 Thyroid adverse events, such as goitre, have been reported in clinical
174 trials, in particular in patients with pre-existing thyroid disease.

175 Victoza® should therefore be used with caution in these patients.

176

177 *Allergic reactions*

178 Allergic reactions including urticaria, rash and pruritus have been
179 reported from marketed use of Victoza®. Cases of anaphylactic
180 reactions with additional symptoms such as hypotension, palpitations,
181 dyspnoea and oedema have been reported with marketed use of
182 Victoza® (see 4.3 Contraindications).

183

184 *Dehydration*

185 Signs and symptoms of dehydration, including renal impairment and
186 acute renal failure have been reported in patients treated with
187 Victoza®. Patients treated with Victoza® should be advised of potential
188 risk of dehydration in relation to gastrointestinal side effects and take
189 precaution to avoid fluid depletion.

190

191 **4.5 Interaction with other medicines and other forms of**
192 **interaction**

193

194 *In vitro assessment of interaction studies*

195 Victoza® has shown a low potential involvement in pharmacokinetic
196 interactions with other active substances related to cytochrome P450
197 (CYP) and plasma protein binding.

198

199 *In vivo assessment of interaction studies*

200 Interaction has been investigated using paracetamol, digoxin, lisinopril,
201 griseofulvin and atorvastatin representing various degrees of solubility

202 and permeability properties. In addition, the effect of liraglutide on the
203 absorption of ethinyloestradiol and levonorgestrel administered in an
204 oral combination contraceptive medicine has been investigated (see
205 table 1 below).

206

207 The minor delay of gastric emptying caused by liraglutide did not affect
208 the absorption of orally administered medicines to any clinically
209 relevant degree and therefore no dose adjustment is required. Few
210 patients treated with Victoza® reported at least one episode of severe
211 diarrhoea. Diarrhoea may affect the absorption of concomitant oral
212 medicines.

213

214 *Warfarin and other coumarin derivatives*

215 No interaction study has been performed. A clinically relevant
216 interaction with active substances with poor solubility or with narrow
217 therapeutic index such as warfarin cannot be excluded. Upon initiation
218 of Victoza® treatment in patients on warfarin or other coumarin
219 derivatives, more frequent monitoring of INR (International Normalised
220 Ratio) is recommended.

221

222 *Insulin*

223 No pharmacokinetic or pharmacodynamic interactions were observed
224 between Victoza® and insulin detemir when administering a single dose
225 of insulin detemir 0,5 U/kg with Victoza® 1,8 mg at steady state in
226 patients with type 2 diabetes.

227

228 Table 1

Product	Dose	C _{max}	Median t _{max}	Comments
Paracetamol	Single dose of 1000 mg	Decreased by 31 %	Delayed up to 15 min	No dose adjustment for concomitant use of paracetamol is required
Atorvastatin	Single dose of 40 mg	Decreased by 38 %	Delayed from 1 h to 3 h	No dose adjustment of atorvastatin is required when given with Victoza [®]
Griseofulvin	Single dose of 500 mg	Increased by 37 %	Did not change	Dose adjustments of griseofulvin and other compounds with low solubility and high permeability are not required
Lisinopril	Single dose	Decreased by 27 %	Delayed from 6 h to 8 h	No adjustment of lisinopril

	of 20 mg			dose is required
Digoxin	Single dose of 1 mg	Decreased by 31 %	Delayed from 1 h to 1,5 h	No adjustment of digoxin dose is required
Oral Contraception:	Single dose		Delayed up to 1,5 h for both compounds	The contraceptive effect is anticipated to be unaffected when co-administered with Victoza®
Ethinylloes radiol		Decreased by 12 %		
Levonorge strel		Decreased by 13 %		

229

230 **4.6 Fertility, pregnancy and lactation**231 **Women of childbearing potential / Contraception in males and**
232 **females**

233 Apart from a slight decrease in the number of live implants, animal
234 studies did not indicate harmful effects with respect to fertility.

235

236 **Pregnancy**

237 Victoza® is contraindicated during pregnancy and lactation.
238 There is no adequate data for use of Victoza® in pregnant women.
239 Victoza® crossed the placental barrier in rabbits.
240 Studies in animals have shown reproductive toxicity and Victoza®
241 should therefore not be used during pregnancy. The use of insulin is
242 recommended.
243 If a patient wishes to become pregnant, or pregnancy occurs,
244 treatment with Victoza® should be discontinued.

245

246 **Breastfeeding**

247 It is not known whether Victoza® is excreted in human milk.
248 In lactating rats, up to 3 % of the maternal dose was present in breast
249 milk. Women on treatment with Victoza® should not breastfeed.

250

251 **4.7 Effects on ability to drive and use machines**

252 No studies on the effects on the ability to drive and use machines have
253 been performed. Victoza® may affect the ability to drive or use
254 machines. Patients should be advised to ensure that they are aware of
255 the effect of Victoza® on their abilities beforehand and to take
256 precautions to avoid hypoglycaemia while driving and using machines,
257 in particular when Victoza® is used in combination with a sulphonylurea
258 or insulin (see 4.8 Undesirable effects).

259

260 **4.8 Undesirable effects**

261 The most frequently reported adverse events during clinical trials were
262 gastrointestinal adverse events: nausea and diarrhoea (reported by >

10 % of patients) and vomiting, dyspepsia, upper abdominal pain, constipation, gastritis, flatulence, abdominal distension, gastro-oesophageal reflux disease and eructation (reported by $\geq 1\%$ and $\leq 10\%$ of patients).

Headache and upper respiratory tract infections were common.

Furthermore, hypoglycaemia was common and very common especially when Victoza® is used in combination with sulphonylurea.

Severe hypoglycaemia may occur uncommonly and has only been observed when combined with a sulphonylurea.

Table 2: Tabulated summary of side effects occurring during clinical trials and spontaneous (post-marketing) reports

Body system/ adverse reaction terms	Frequency of occurrence					
	Very Common ($\geq 1/10$)	Common ($\geq 1/100$, < $1/10$)	Uncommon ($\geq 1/1\,000$, < $1/100$)	Rare ($\geq 1/10\,000$, < $1/1\,000$)	Very Rare ($\leq 1/10\,000$)	Not known
Reactions						

Infections and infestations		Upper respiratory tract infection	Bronchitis Gastroenteriti s Osteomyelitis			
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)			Papillary thyroid cancer Prostate cancer Breast cancer			
Blood and the lymphatic system disorders			Thrombocyto penia			
Metabolism and nutrition disorders		Hypoglycae mia Anorexia Decreased appetite	Dehydration*			
Nervous system disorders		Headache Dizziness	Cerebrovasc ular accident Syncope Dysgeusia			

Eye disorders			Cataract			
Cardiac disorders		Increased heart rate*	Angina pectoris Acute myocardial infarction Coronary artery disease Atrial fibrillation Congestive cardiac failure Supraventricular tachycardia			
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism			

Gastro-intestinal disorders	Nausea Diarrhoea	Vomiting Dyspepsia Abdominal pain upper Constipation Gastritis Flatulence Abdominal distension Gastro-oesophageal reflux disease Eructation	Appendicitis with perforation Inguinal hernia Pancreatitis Delayed gastric emptying		Pancreatitis* (including necrotising pancreatitis)	
Musculoskeletal, connective tissue and bone disorders			Intervertebral disc protrusion Osteoarthritis			
General disorders and administration		Fatigue Injection site reactions	Chest pain Malaise*			

on site conditions						
Injury, poisoning and procedural complicatio ns			Fall			
Immune system disorders				Anaphyla ctic reaction*		
Hepatobilia ry disorders			Cholelithiasis Cholecystitis			
Skin and subcutane ous tissue disorders		Rash*	Urticaria* Pruritus*			Cutan eous amyloi dosis†
Renal and urinary disorders			Renal failure acute* Renal impairment*			
Investigatio ns		Increased lipase				

		Increased amylase				
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277 **spontaneous reports*

278 *†ADR from post marketing sources*

279

280 *Hypoglycaemia*

281 Most episodes of confirmed hypoglycaemia in clinical studies were

282 minor.

283 No episodes of severe hypoglycaemia were observed in the study with

284 Victoza® used as monotherapy. Severe hypoglycaemia may occur

285 uncommonly and has primarily been observed when Victoza® is

286 combined with a sulphonylurea (0,02 events/subject year). Very few

287 episodes (0,001 events/subject year) were observed with

288 administration of Victoza® in combination with a non-sulphonylurea.

289 In the LEADER® trial, severe hypoglycaemic episodes were reported at

290 a lower rate with liraglutide vs placebo (1,0 vs 1,5 events per 100

291 patient years of exposure; estimated rate ratio 0,69 [0,51 to 0,93]).

292 For patients treated with premix insulin at baseline and at least for the

293 following 26 weeks, the rate of severe hypoglycaemia for both

294 liraglutide and placebo was 2,2 events per 100 patient years of

295 exposure.

296

297 *Cholelithiasis and cholecystitis*

298 Few cases of cholelithiasis (0,4 %) and cholecystitis (0,1 %) have been

299 reported during long-term, controlled phase 3a clinical trials with

300 Victoza®. In the LEADER® trial, the frequency of cholelithiasis and

301 cholecystitis was 1,5 % and 1,1 % for liraglutide and 1,1 % and 0,7 %
302 for placebo, respectively.

303

304 *Pancreatitis*

305 Few cases of acute pancreatitis (< 0,2 %) of acute pancreatitis have
306 been reported during long-term, controlled phase 3 during long-term
307 clinical trials with Victoza®. Pancreatitis was also reported from
308 marketed use. In the LEADER® trial, the frequency of acute
309 pancreatitis confirmed by adjudication was 0,4 % for liraglutide and
310 0,5 % for placebo, respectively.

311

312 *Reporting of suspected adverse reactions*

313 Reporting suspected adverse reactions after authorisation of the
314 medicine is important. It allows continued monitoring of the benefit/risk
315 balance of the medicinal product. Healthcare professionals are asked
316 to report any suspected adverse reactions via the “6.04 Adverse Drug
317 Reactions Reporting Form”, found online under SAHPRA’s
318 publications <https://www.sahpra.org.za/Publications/Index/8>.

319

320 **4.9 Overdose**

321 With overdose, the patients reported severe nausea, vomiting and
322 diarrhoea, but recovered without complications. Severe hypoglycaemia
323 has been observed. In the event of overdosage, appropriate supportive
324 treatment should be initiated according to the patient’s clinical signs
325 and symptoms. The patient should be observed for clinical signs of
326 dehydration and blood glucose should be monitored.

327

328 **5 PHARMACOLOGICAL PROPERTIES**329 **5.1 Pharmacodynamic properties**

330

331 Pharmacotherapeutic group: Drugs used in diabetes, glucagon-like
332 peptide-1 (GLP-1) analogues. ATC code: A10BJ02

333

334 *Mechanism of action*

335 Liraglutide is a human Glucagon-Like Peptide-1 (GLP-1) analogue with
336 97 % homology to human GLP-1 that binds to and activates the GLP-1
337 receptor.

338 The GLP-1 receptor is the target for native GLP-1, an endogenous
339 incretin hormone that potentiates glucose-dependent insulin secretion
340 from the pancreatic beta cells. Unlike native GLP-1, liraglutide has a
341 pharmacokinetic and pharmacodynamic profile in humans, suitable for
342 once daily administration.

343

344 Following subcutaneous administration, the protracted action profile is
345 based on three mechanisms: self association, which results in slow
346 absorption, and binding to albumin and enzymatic stability towards the
347 DPP-IV and NEP enzymes resulting in a long plasma half-life.

348

349 Liraglutide action is mediated via a specific interaction with GLP-1
350 receptors, leading to an increase in cAMP. Liraglutide stimulates
351 insulin secretion in a glucose-dependent manner and improves beta-
352 cell function. Simultaneously, liraglutide lowers inappropriately high

353 glucagon secretion, also in a glucose-dependent manner. Thus, when
354 blood glucose is high, insulin secretion is stimulated and glucagon
355 secretion is inhibited. Conversely, during hypoglycaemia liraglutide
356 diminishes insulin secretion and does not impair glucagon secretion.
357 The mechanism of blood glucose lowering also involves a delay in
358 gastric emptying.

359

360 Liraglutide reduces body weight and body fat mass through
361 mechanisms involving reduced hunger and lowered energy intake.

362

363 GLP-1 is a physiological regulator of appetite and calorie intake and
364 GLP-1 receptor (GLP-R) is present in several areas of the brain
365 involved in appetite regulation.

366 In animal studies, peripheral administration of liraglutide led to uptake
367 in specific brain regions including the hypothalamus, where liraglutide,
368 via specific activation of the GLP-1 receptor increased satiety and
369 decreased hunger signals, thereby leading to lower body weight.

370

371 Liraglutide has been shown *in vitro* to be a potent agent for specific
372 stimulation of beta cell proliferation and prevention of both cytokine
373 and free fatty acid induced beta-cell death (apoptosis). *In vivo*,
374 liraglutide increases insulin biosynthesis, and beta-cell mass in
375 diabetic animal models. When glucose is fully normalised, liraglutide
376 does not increase beta-cell mass.

377

378 *Pharmacodynamic effects*

379 Liraglutide has 24-hour duration of action and improves glycaemic
380 control by lowering fasting and postprandial blood glucose in patients
381 with type 2 diabetes mellitus.

382

383 The difference between liraglutide 1,8 mg/1,2 mg and placebo in
384 reduction of mean fasting glucose was found to be 3,90 mmol/l (70
385 mg/dl)/3,33 mmol/l (60 mg/dl). Following a standard meal, the
386 difference in mean 2-hour postprandial glucose concentration was 6,02
387 mmol/l (108 mg/dl)/5,63 mmol/l (101 mg/dl). In addition, liraglutide
388 decreased postprandial glucose excursion (incremental postprandial
389 glucose) on average by 1,1 mmol/l (20 mg/dl)/1,08 mmol/l (19 mg/dl).

390

391 **5.2 Pharmacokinetic properties**

392 *Absorption*

393 The absorption of liraglutide following subcutaneous administration is
394 slow, reaching maximum concentration 8 - 12 hours post dosing.

395 Estimated maximum liraglutide concentration was 9,4 nmol/l for a
396 subcutaneous single dose of liraglutide 0,6 mg. At 1,8 mg liraglutide,
397 the average steady state concentration of liraglutide ($AUC_{\tau/24}$) reached
398 approximately 34 nmol/l. Liraglutide exposure increased proportionally
399 with dose. The intra-subject coefficient of variation for liraglutide AUC
400 was 11 % following single dose administration. Liraglutide can be
401 administered subcutaneously in the abdomen, thigh, or upper arm.
402 Absolute bioavailability of liraglutide following subcutaneous
403 administration is approximately 55 %.

404

405 *Distribution*

406 The apparent volume of distribution after subcutaneous administration
407 is 11 – 17 l. The mean volume of distribution after intravenous
408 administration of liraglutide is 0,07 l/kg. Liraglutide is extensively bound
409 to plasma protein (> 98 %).

410

411 *Metabolism*

412 During 24 hour following administration of a single [3H]-liraglutide dose
413 to healthy subjects, the major component in plasma was intact
414 liraglutide. Two minor plasma metabolites were detected ($\leq 9\%$ and $\leq$
415 5 % of total plasma radioactivity exposure). Liraglutide is
416 endogenously metabolised in a similar manner to large proteins
417 without a specific organ as major route of elimination.

418

419 *Elimination*

420 Following a [3H]-liraglutide dose, intact liraglutide was not detected in
421 urine or faeces. Only a minor part of the administered radioactivity was
422 excreted as liraglutide-related metabolites in urine or faeces (6 % and
423 5 %, respectively). The urine and faeces radioactivity was mainly
424 excreted during the first 6 - 8 days and corresponded to three minor
425 metabolites, respectively.

426 The mean clearance following s.c. administration of a single dose
427 liraglutide is approximately 1,2 l/h with an elimination half-life of
428 approximately 13 hours.

429

430 *Renal impairment*

431 The pharmacokinetics of liraglutide was evaluated in subjects with
432 varying degrees of renal impairment in a single-dose trial. Subjects
433 with mild (estimated creatinine clearance 50 – 80 ml/min) to severe
434 (estimated creatinine clearance < 30 ml/min) renal impairment and
435 subjects with end stage renal disease requiring dialysis were included
436 in the trial. Renal impairment did not have any clinically relevant effect
437 on the pharmacokinetics of liraglutide.

438

439 **Paediatric population**

440 Victoza® has not been studied in paediatric patients below 18 years of
441 age (see 4.4 Special warnings and precautions for use).

442

443 **Clinical studies and mechanism of action**

444 *Post-hoc* analysis of serious major adverse cardiovascular events
445 (cardiovascular death, myocardial infarction, stroke) from all
446 intermediate and long-term phase 2 and 3 trials (ranging from 26 and
447 up to 100 weeks duration) including 5,607 patients (3,651 exposed to
448 Victoza®), showed no increase in cardiovascular risk (incidence ratio of
449 0,75 (95 % CI 0,35; 1,63)) for Victoza® versus all comparators.

450

451 The Liraglutide Effect and Action in Diabetes Evaluation of
452 Cardiovascular Outcome Results (LEADER®) trial, was a multicentre,
453 placebo-controlled, double-blind clinical trial. 9,340 patients were
454 randomly allocated to either liraglutide (4,668) or placebo (4,672), both
455 in addition to standards of care for HbA_{1c} and cardiovascular (CV) risk
456 factors.

457
458 Primary outcome or vital status at end of trial was available for 99,7 %
459 and 99,6 % of participants randomised to Victoza® and placebo,
460 respectively. The duration of observation was minimum 3,5 years and
461 up to a maximum of 5 years. The study population included patients ≥
462 65 years (n = 4,329) and ≥ 75 years (n = 836) and patients with mild (n
463 = 3,907), moderate (n = 1,934) or severe (n = 224) renal impairment.
464 The mean age was 64 years and the mean BMI was 32,5 kg/m². The
465 mean duration of diabetes was 12,8 years.
466 The primary endpoint was the time from randomisation to first
467 occurrence of any major adverse cardiovascular events (MACE): CV
468 death, non-fatal myocardial infarction, or non-fatal stroke. Victoza®
469 significantly reduced the risk of MACE vs placebo (Figure 1). The
470 estimated hazard ratio was consistently below 1 for all 3 MACE
471 components. Victoza® also significantly reduced the time to first
472 expanded MACE (primary MACE, unstable angina pectoris leading to
473 hospitalisation, coronary revascularisation, or hospitalisation due to
474 heart failure) and other secondary endpoints (Figure 2).
475

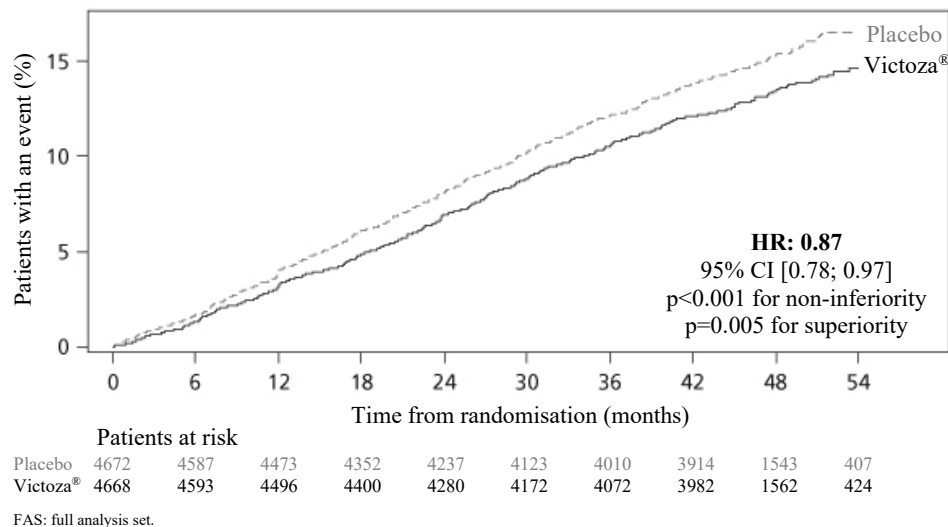


Figure 1 Kaplan Meier plot of time to first MACE - FAS population

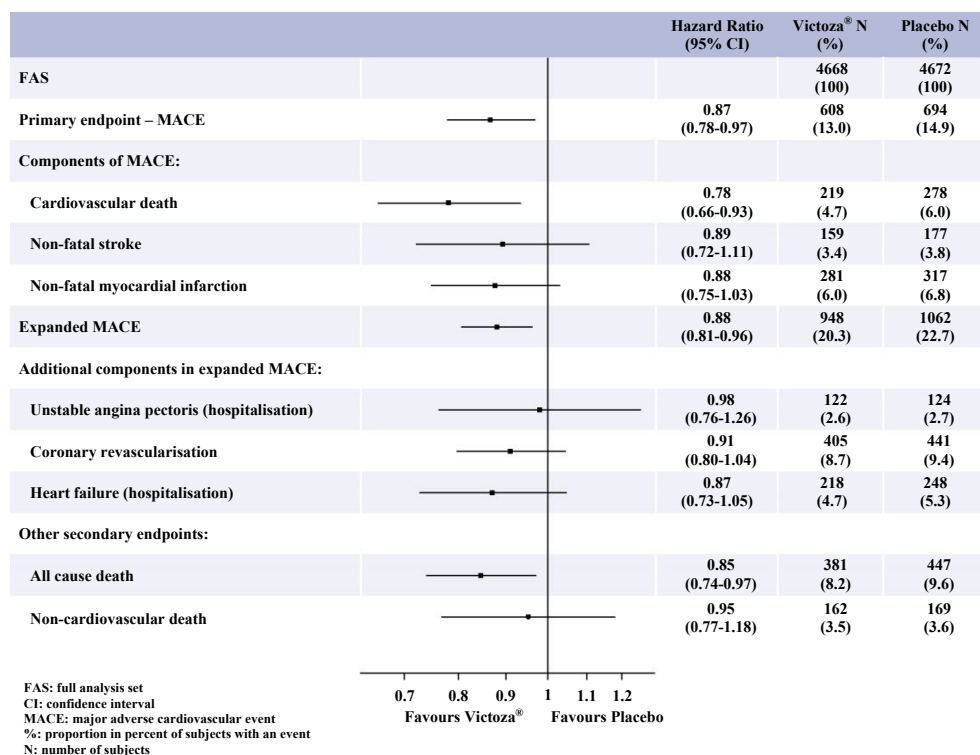


Figure 2 Forest plot of analyses of individual cardiovascular event types - FAS population

483

484 A significant and sustained reduction in HbA_{1c} from baseline to month
485 36 was observed with Victoza® vs placebo, in addition to standard of
486 care (-1,16 % vs -0,77 %; estimated treatment difference [ETD] -
487 0,40 % [-0,45; -0,34]). The need for treatment intensification with
488 insulin was reduced by 48 % with Victoza® vs placebo in insulin-naïve
489 patients at baseline (HR 0,52 [0,48; 0,57]). A significant and sustained
490 reduction in body weight from baseline to month 36 was also seen with
491 Victoza® vs placebo (-2,74 kg vs -0,47 kg, respectively; ETD -2,26 [-
492 2,54; -1,99]). The adverse event profile reported was overall
493 comparable to that observed in completed Victoza® clinical trials in
494 type 2 diabetes mellitus (see section 4.8 Undesirable effects).

495

496 *Blood pressure and heart rate*

497 Victoza® reduced systolic blood pressure with a mean range of 2,3 –
498 6,7 mmHg within the first two weeks of treatment in long-term clinical
499 trials. Victoza® reduced the occurrence of metabolic syndrome
500 according to the Adult Treatment Panel III (ATPIII) definition. The
501 reduction in systolic blood pressure occurred before weight loss.

502

503 In the LEADER® trial, systolic blood pressure was reduced with
504 Victoza® vs placebo (-1,4 mmHg vs -0,2 mmHg; ETD: -1,29 mmHg [-
505 1,92; -0,48]) whereas diastolic blood pressure decreased less with
506 liraglutide vs placebo (-0,8 mmHg vs -1,4 mmHg, respectively, ETD:
507 0,59 [0,19; 0,99]) after 36 months. A mean increase in heart rate from
508 baseline of 2 to 3 beats per minute has been observed with Victoza® in

509 long-term clinical trials including LEADER®. In the LEADER® trial, no
510 long-term clinical impact of increased heart rate on the risk of
511 cardiovascular events was observed.

512

513 *Microvascular evaluation*

514 In the LEADER® trial, microvascular events comprised nephropathy
515 and retinopathy outcomes. The analysis of time to first microvascular
516 event for liraglutide vs placebo had a HR of 0,84 [0,73, 0,97]. The HR
517 for liraglutide vs placebo was 0,78 [0,67, 0,92] for time to first
518 nephropathy event and 1,15 [0,87, 1,52] for time to first retinopathy
519 event. The estimated treatment ratio for change in urinary
520 albumin/creatinine excretion from baseline to month 36 was 0,81 [0,76,
521 0,86].

522

523 In the LEADER® trial, Victoza® significantly reduced deterioration in
524 patient reported quality of life compared to placebo (as measured by
525 EQ5D index, ETD 0,018 [0,001; 0,035] and VAS score, ETD 1,302
526 [0,101; 2,504]).

527

528 GLP-1 receptors are also expressed in specific locations in the heart,
529 vasculature, immune system, and kidneys. Human and animal studies
530 have shown that activation of these receptors with liraglutide may
531 mediate cardiovascular and microvascular effects, including reduced
532 inflammation. Animal studies show that liraglutide attenuates the
533 development of atherosclerosis.

534

535 Glycaemic control

536

537 Table 3 Victoza® clinical phase 3 trials in monotherapy (52 weeks)

538 and in combination with oral antidiabetics (26 weeks)

	N	Mean baseline HbA _{1c} (%)	Mean HbA _{1c} change from baseline (%)	Patient s (%) achievi ng HbA _{1c} <7%	Mean baseline weight (kg)	Mean weight change from baseline (kg)
Monotherapy						
Liraglutide 1,2 mg	251	8,18	-0,84*	42,8 ¹ , 58,3 ³	92,1	-2,05**
Liraglutide 1,8 mg	246	8,19	-1,14**	50,9 ¹ , 62,0 ³	92,6	-2,45**
Glimepirid e 8 mg/day	248	8,23	-0,51	27,8 ¹ , 30,8 ³	93,3	1,12
Add-on to metformin (2,000 mg/day)						
Liraglutide 1,2 mg	240	8,3	-0,97 [†]	35,3 ¹ , 52,8 ²	88,5	-2,58**
Liraglutide 1,8 mg	242	8,4	-1,00 [†]	42,4 ¹ , 66,3 ²	88,0	-2,79**
Placebo	121	8,4	0,09	10,8 ¹ , 22,5 ²	91,0	-1,51

Glimepirid e 4 mg/day	242	8,4	-0,98	36,3 ¹ , 56,0 ²	89,0	0,95
Add-on to glimepiride (4 mg/day)						
Liraglutide 1,2 mg	228	8,5	-1,08 ^{**}	34,5 ¹ , 57,4 ²	80,0	0,32 ^{**}
Liraglutide 1,8 mg	234	8,5	-1,13 ^{**}	41,6 ¹ , 55,9 ²	83,0	-0,23 ^{**}
Placebo	114	8,4	0,23	7,5 ¹ , 11,8 ²	81,9	-0,10
Rosiglitazo ne 4 mg/day	231	8,4	-0,44	21,9 ¹ , 36,1 ²	80,6	2,11
Add-on to metformin² (2,000 mg/day) + rosiglitazone (4 mg twice daily)						
Liraglutide 1,2 mg	177	8,48	-1,48	57,5 ¹	95,3	-1,02
Liraglutide 1,8 mg	178	8,56	-1,48	53,7 ¹	94,9	-2,02
Placebo	175	8,42	-0,54	28,1 ¹	98,5	0,60
Add-on to metformin² (2,000 mg/day) + glimepiride (4 mg/day)						
Liraglutide 1,8 mg	230	8,3	-1,33 [*]	53,1 ¹	85,8	-1,81 ^{**}
Placebo	114	8,3	-0,24	15,3 ¹	85,4	-0,42

Insulin glargine ⁴	232	8,1	-1,09	45,8 ¹	85,2	1,62
Add on to SGLT2i⁵ ± metformin (≥ 1500 mg/day)						
Liraglutide 1,8 mg	203	8,00	-1,02	54,8	91,0	-2,92
Placebo	100	7,96	-0,28	13,9	91,4	-2,06

539 *Superiority (p<0.01) vs active comparator; **Superiority (p<0.0001) vs active
 540 comparator; †Non-inferiority (p<0.0001) vs active comparator

541 ¹all patients; ²previous OAD monotherapy; ³previous diet treated patients

542 ⁵Victoza® add on to SGLT2i was investigated at all doses approved of
 543 SGLT2i.

544 ⁴the dosing of insulin glargine was open-labelled and was applied according
 545 to Guideline for titration of insulin glargine. Titration of the insulin glargine
 546 dose was managed by the patient after instruction by the investigator:

547

548 **Table 4: Guideline for titration of insulin glargine:**

Self-measured FPG	Increase in insulin glargine
≤ 5,5 mmol/l (≤ 100 mg/dl)	No adjustment
> 5,5 and < 6,7 mmol/l (> 100	0 – 2 ^a
≥ 6,7 mmol/l (≥ 120 mg/dl)	2

549 ^a According to the individualised recommendation by the investigator at the
 550 previous visit for example depending on whether subject has experienced
 551 hypoglycaemia.

552

Victoza[®] monotherapy for 52 weeks resulted in statistically significant ($p < 0.0014$) and sustained reductions in HbA_{1c} compared with patients receiving glimepiride (Figure 3).

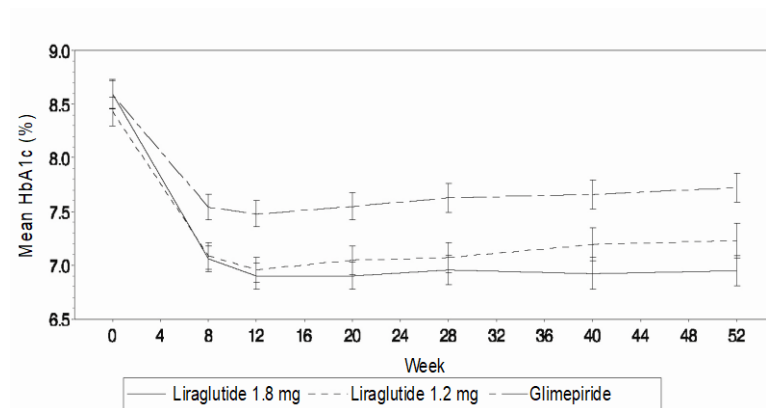


Figure 3 HbA_{1c} level reduced to below 7% and sustained over 12 months when Victoza[®] is administered to patients previously treated with diet and exercise (Trial 1573).

Postprandial glucose
Victoza[®] reduced postprandial glucose across all three daily meals by 1, 68 – 2, 71 mmol/l (31 – 49 mg/dl).

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology, repeat-dose toxicity or genotoxicity.

Non-lethal thyroid C-cell tumours were seen in 2-year carcinogenicity studies in rats and mice. In rats, a no observed adverse effect level (NOAEL) was not observed. These tumours were not seen in monkeys treated for 20 months. These findings in rodents are caused by a non-

573 genotoxic, specific GLP-1 receptor-mediated mechanism to which
574 rodents are particularly sensitive. The relevance for humans is likely to
575 be low but cannot be completely excluded. No other treatment-related
576 tumours have been found.

577 Animal studies did not indicate direct harmful effects with respect to
578 fertility but slightly increased early embryonic deaths at the highest
579 dose. Dosing with Victoza® during mid-gestation caused a reduction in
580 maternal weight and foetal growth with equivocal effects on ribs in rats
581 and skeletal variation in the rabbit. Neonatal growth was reduced in
582 rats while exposed to Victoza® and persisted in the post-weaning
583 period in the high dose group. It is unknown whether the reduced pup
584 growth is caused by reduced pup milk intake due to a direct GLP-1
585 effect or reduced maternal milk production due to decreased caloric
586 intake.

587

588 **6 PHARMACEUTICAL PARTICULARS**

589 **6.1 List of excipients**

590 Disodium phosphate dihydrate

591 Propylene glycol

592 Phenol

593 Water for injections

594

595 **6.2 Incompatibilities**

596 Substances added to Victoza® may cause degradation of liraglutide.

597 Victoza® must not be mixed with other medicinal products, e.g.,

598 infusion fluids.

599

600 **6.3 Shelf life**

601 30 months.

602 After first use: 1 month.

603

604 **6.4 Special precautions for storage**

605 Store in a refrigerator (2 °C – 8 °C).

606 Do not store in the freezer or directly adjacent to the refrigerator
607 cooling element.

608 Do not freeze Victoza® and do not use Victoza® if it has been frozen.

609 After first use of the Victoza® pen, the product can be stored for 1
610 month at room temperature (not above 30 °C) or in a refrigerator at
611 (2 °C – 8 °C).

612 Victoza® should be protected from excessive heat and sunlight.

613 Always remove the injection needle after each injection and store the
614 Victoza® pen without an injection needle attached. This prevents
615 contamination, infection and leakage. It also ensures that the dosing is
616 accurate.

617 Recap the pen to protect from light.

618 Keep out of reach and sight of children.

619

620 For storage conditions after first opening of the medicine, see section
621 6.3 Shelf life.

622

623 **6.5 Nature and contents of container**

624 Pre-filled (multidose, disposable) light blue pen, comprising of a slim
625 pen-shaped injector assembled with a cartridge (3 ml). The cartridge is
626 made of colourless glass (type 1), containing a bromobutyl rubber
627 closure shaped as a plunger and closed with a bromobutyl/
628 polyisoprene rubber closure.

629 The pen injector is made of polyolefin and polyacetal.

630

631 Each pen contains 3 ml of solution, delivering 30 doses of 0,6 mg, 15
632 doses of 1,2 mg or 10 doses of 1,8 mg.

633

634 Pack sizes of 2 or 3 pens are packed in a cardboard box.

635

636 **6.6 Special precautions for disposal and other handling**

637 Victoza® should not be used if it does not appear clear and colourless
638 or almost colourless.

639 Victoza® should not be used if it has been frozen.

640 Victoza® can be administered with needles up to a length of 8 mm and
641 as thin as 32G. The pen is designed to be used with NovoFine® or
642 NovoTwist® disposable needles.

643 Needles are not included.

644 The patient should be advised to discard the injection needle in
645 accordance with local requirements after each injection and store the
646 pen without an injection needle attached. This prevents contamination,
647 infection and leakage. It also ensures that the dosing is accurate.

648

649 For detailed instructions for use, see the Instructions for using the
650 Victoza[®] pen.

651

652 **7 HOLDER OF CERTIFICATE OF REGISTRATION**

653

654 Novo Nordisk (Pty) Ltd

655 150 Rivonia Road

656 10 Marion Street Office Park,

657 Building C1 Sandton,

658 Johannesburg, 2196

659

660 **8 REGISTRATION NUMBER(S)**

661 43/21.13/0781

662

663 **9 DATE OF FIRST AUTHORISATION**

664 25 November 2011

665

666 **10 DATE OF REVISION OF THE TEXT**

667 23 October 2025