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Glucagon-Like Peptide-1 Receptor Agonists in Type 2 Diabetes: Their Use and Differential Features

Katherine A. Lyseng-Williamson[1]

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Abstract

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are well established as effective adjuncts to lifestyle modification in the treatment of type 2 diabetes (T2D) as monotherapy or in combination with oral glucose-lowering drugs ± insulin. The six subcutaneous GLP-1RA formulations (i.e. twice-daily exenatide, once-daily liraglutide and lixisenatide, and once-weekly dulaglutide, exenatide and semaglutide) currently available in the EU and USA have many similarities, but also some unique features and properties. By stimulating GLP-1 receptors, GLP-1RAs increase insulin secretion and suppress glucagon release in a glucose-dependent manner, thereby improving clinical and patient-reported outcomes related to glycaemic control and weight. They also have been shown to reduce, or at least not increase, the risk of major cardiovascular outcomes. GLP-1RAs are generally well tolerated, with gastrointestinal and injection-site reactions being the most troublesome drug-related adverse events, and are associated with a very low intrinsic risk of hypoglycaemia. Treatment with GLP-1RAs should be customized to meet the clinical needs and personal preferences of the individual.

Key Points

GLP-1RAs improve glycaemic control, reduce patient weight and improve patient-reported outcomes when administered as monotherapy or add-on therapy to other glucose-lowering drugs

GLP-1RAs reduce, or at least not increase, the risk of major cardiovascular events

GLP-1RAs are generally well tolerated with a very low intrinsic risk of hypoglycaemia

Once-weekly administration of GLP-1RAs may improve treatment adherence and satisfaction relative to more frequent treatment

Consider clinical and administration differences between-GLP-1RAs and patient preferences when individualizing treatment

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✉ Katherine A. Lyseng-Williamson
DEcorrespondence@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Rationale for Using GLP-1RAs in Type 2 Diabetes

In many patients, the treatment of type 2 diabetes (T2D) requires the use of two or more glucose-lowering drugs [1, 2]. Unless contraindicated or poorly tolerated, metformin is commonly used as first-line therapy, but the addition of glucose-lowering drugs with different mechanisms of action is usually required to provide adequate glycaemic control.

Glucagon-like peptide-1 (GLP-1), an intestinal hormone with properties that include increasing insulin secretion after eating, plays has an important role in glucose homeostasis [3]. The effects of GLP-1 are impaired in patients with T2D, thereby providing the rationale for developing GLP-1 receptor agonists (GLP-1RAs) to treat T2D [3]. These agents have established efficacy in improving glycaemic control in patients with T2D and, unlike insulin and insulin secretagogues (e.g. sulfonylureas and meglitinides), induce weight loss and have a low intrinsic risk of hypoglycaemia [3].

This article reviews the features and properties of the six GLP-1RA formulations, which are administered subcutaneously twice daily [exenatide immediate release (IR)] [4, 5]; once daily (liraglutide [6, 7] and lixisenatide [8, 9]); or once weekly [dulaglutide [10, 11], exenatide extended release (ER) [12–14], and semaglutide [15, 16]] that are currently marketed in the EU and the USA. GLP-1RAs that have been

voluntarily withdrawn for commercial reasons (e.g. albiglutide), are currently available only in countries outside the EU/USA (e.g. taspoglutide) or are available as and fixed-dose combinations (e.g. insulin degludec/liraglutide and insulin glargine/lixisenatide) are not discussed in this review.

2 Pharmacological Properties of GLP-1RAs

Native GLP-1 has a very short half-life, as it is rapidly degraded by proteases, namely the dipeptidyl peptidase (DPP)-4 enzyme [17–19]. To overcome this, GLP-1RAs have been developed that are structurally similar to GLP-1 with regard to their amino-acid sequences, but with modifications that provide stabilization against DPP-4 degradation and/or minimise their renal clearance, thereby increasing their duration of activity (Table 1). Differences in the structure of GLP-1RAs may also determine accessibility to the CNS, which may partly explain differences between GLP-1RAs in weight loss (Table 2). The homology of the GLP-RAs to the structure of human GLP-1 (i.e. the proportion of amino acid sequence similar to native GLP) ranges from ≈50% with exenatide and lixisenatide (which are based on the exendin-4 molecule present in Gila monster venom) to 90–97% with lixisenatide, dulaglutide and semaglutide (which are modified from the human GLP-1 active fragment) [Table 1] [4–16].

GLP-1RAs selectively bind to and activate GLP-1 receptors in the same manner as native GLP-1 [4–16]. When blood glucose levels are high, activation of the GLP-1 receptors by GLP-1RAs stimulates insulin secretion and lowers inappropriately high glucagon secretion in a glucose-dependent manner, thereby improving glycaemic control. When blood glucose levels are low, GLP-1RAs do not stimulate insulin secretion and do not impair glucagon secretion, which also helps maintain glycaemic control by reducing the risk of hypoglycaemia [17–20]. Reduced feelings of hunger and lowered energy intake also help patients lose weight.

Individual GLP-1RAs differ with regard to their pharmacological profiles and duration of activity due to several factors, including the rate of absorption, degree of binding to albumin/plasma proteins, degree of protection against metabolic degradation and rate of renal clearance (Table 1) [17–20]. Based on their duration of activation of the GLP-1 receptor, exenatide IR and lixisenatide are classified as short-acting GLP-1RAs, whereas liraglutide, dulaglutide, exenatide ER and semaglutide are classified as long-acting GLP-1RAs (Table 1). [17–20]. Unlike long-acting GLP-1RAs, short-acting GLP-1RAs are associated with substantial delays in gastric emptying [19].

The half-life of the GLP-1RAs varies from a few hours to several days, with the long half-lives of dulaglutide and semaglutide allowing administration once weekly (Table 1) [4–16]. The ER formulation of exenatide also allows once-weekly administration, as the microspheres in the formulation release surface-bound exenatide initially, then gradually release exenatide from the microspheres (Table 1) [12–14].

3 Effects of GLP-1RAs on Glycaemic Control and Weight Loss

The efficacy of GLP-1RAs in controlling glycaemia in patients with T2D is well established. This section provides an overview of the results of randomized clinical trials (RCTs) that were pivotal in the approval of exenatide IR] [4, 5], liraglutide [6, 7], lixisenatide [8, 9], [dulaglutide [10, 11], exenatide ER [12–14], and semaglutide [15, 16] in the EU and the USA, as well as other relevant data.

3.1 Compared with Placebo, Oral Glucose-Lowering Drugs and Insulin

With regard to reducing glycosylated haemoglobin (HbA_{1c}) from baseline in RCTs in patients with T2D, monotherapy or add-on treatment with GLP-1RAs was significantly more effective than placebo [4–16]. GLP-1RA monotherapy or add-on treatment was also generally noninferior or more effective in reducing HbA_{1c} than several oral glucose-lowering drugs, including metformin, glimepiride (a sulfonylurea), sitagliptin (a DPP-4 inhibitor), pioglitazone (a thiazolidinedione) and dapagliflozin [a sodium-glucose cotransporter 2 (SGLT2) inhibitor], as well as insulin glargine (long acting) and insulins glulisine and lispro (rapid acting) [4–16]. The GLP-1RAs were also associated with significant or numerical improvements in other measures of glycaemic control, such as changes from baseline in mean fasting serum/plasma and 2-h post-prandial glucose levels [4–16].

In keeping with their efficacy in reducing HbA_{1c} levels, GLP-1RAs were also associated with patients achieving their HbA_{1c} targets (i.e. $HbA_{1c} \leq 6.5$ or $< 7\%$) [4–16]. The proportion of patients who achieved their HbA_{1c} target varied depending on the design of the RCT (e.g. trial duration, background and comparator treatment, inclusion/exclusion criteria, GLP-1RA dosage, etc.). For example, where reported in the RCTs in Table 2, the proportions of patients who achieved the $HbA1_c < 7\%$ target at trial end were: 25–57% with exenatide IR, 35–58% with liraglutide, 25–50% with lixisenatide, 34–71% with dulaglutide, 27–73% with exenatide ER and 55–79% with semaglutide [4–16]. Overall, in individual RCTs, the proportion of patients achieving this target were generally significantly or numerically higher with GLP-1RA than with placebo (5–39%), and similar or somewhat higher with GLP-1RA than with oral glucose-lowering drugs (e.g. 48–52% with metformin, 30–40% with sitagliptin, 28–36% with glimepiride and 22–55% with

Table 1 Pharmacological properties of currently marketed glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Parameter	Twice daily	Once daily		Once weekly		
	Exenatide IR [4, 5]	Liraglutide [6, 7]	Lixisenatide [8, 9]	Dulaglutide [10, 11]	Exenatide ER [12–14]	Semaglutide [15, 16]
Structural properties						
Type of derivative or modification	Exendin-4 derivative	Human GLP-1 modification	Exendin-4 derivative	Human GLP-1 modification	Exendin-4 derivative	Human GLP-1 modification
Molecular weight	≈3300 Da	≈3700 Da	4858 g/mol	≈63,000 Da	≈3300 Da	4114 g/mol
% homology of AA sequence to human GLP-1	53	97	50	90	53	94
Modification of the N terminal sequence to ↑ resistance to DDP-4	Substitution of AA at position 2	None	Substitution of AA at position 2	Substitution of AA at position 8[a]	Substitution of AA at position 2	Substitution of AA at position 8[a]
Modification to ↓ renal clearance and ↑ duration of effect	None	C16 fatty acid + glutamic acid spacer added to AA at position 26	None	Linked to a modified human IgG4-Fc heavy chain[b]	None	C18 fatty di-acid + hydrophilic spacer added to AA at position 26 (↑ albumin binding)
Duration of activity[c]	Short	Long	Short	Long	Long	Long
Pharmacokinetic properties following subcutaneous injection						
Time to C_{max}	2.1 h	8–12 h	1–3.5 h	2 days	Wk 2 + wk 6–7[d]	1–3 days
Apparent V_d (L)	28.3	≈13	≈100	17–19	28.3	≈12.5
Plasma protein binding (%)		< 98	55			> 99 (albumin)
Apparent clearance (L/h)	9.1	1.2	35	0.01	9.1	0.05
Terminal half-life	2.4 h	13 h	3 h	≈5 days		≈1 wk

AA amino acid, *C_{max}* maximum plasma concentration, *DPP-4* dipeptidyl peptidase-4, *ER* extended-release, *GLP-1* glucagon-like peptide-1, *IR* immediate release, *V_d* volume of distribution, *wk* week(s), ↑ increase/s, ↓ decrease/s

[a]Equivalent to position 2 in exendin-4 derivatives

[b]Also ↓ immunogenicity

[c]Based on the duration of activation of the GLP-1 receptor

[d]Long-acting as microsphere formulation initially releases surface-bound exenatide (C_{max} at wk 2), followed by a gradual release of exenatide from the microspheres (C_{max} at wk 6–7) over a total period of ≈10 wk

Table 2 Clinical efficacy of currently marketed glucagon-like peptide-1 receptor agonists (GLP-1RAs) vs placebo and/or glucose-lowering drugs in phase 3 trials in > 250 patients with type 2 diabetes

Treatment type (study duration)	Comparators	No. of pts	HbA_{1c} (%)		Weight (kg)	
			BL (mean)	Mean change from BL	BL (mean)	Mean change from BL
Exenatide IR 5 or 10 μg twice daily [5]						
Add-on to metformin (30 wk)	Exenatide IR 5 μg twice daily	110	8.3	−0.5[a]***	100	−1.3[a]
	Exenatide IR 10 μg twice daily	113	8.2	−0.9[a]***	100	−2.6[a]
	Placebo	113	8.2	−0.0[a]	101	−0.2[a]
Add-on to sulfonylurea (30 wk)	Exenatide IR 5 μg twice daily	125	8.5	−0.5[a]***	95	−1.1[a]
	Exenatide IR 10 μg twice daily	129	8.6	−0.9[a]***	95	−1.6[a]
	Placebo	123	8.7	+0.1[a]	99	−0.8[a]
Add-on to metformin+ sulfonylurea (30 wk)	Exenatide IR 5 μg twice daily	245	8.5	−0.7[a]***	97	−1.6[a]
	Exenatide IR 10 μg twice daily	241	8.5	−0.9[a]***	98	−1.6[a]
	Placebo	247	8.5	+0.1[a]	99	−0.9[a]
Add-on to insulin glargine ± metformin and/or thiazolidinedione (30 wk)	Exenatide IR 10 μg twice daily	137	8.3	−1.7[a]***	95	−1.8[a]***
	Placebo	122	8.5	−1.0[a]	94	+1.0[a]
Add-on to insulin glargine + metformin (30 wk)	Exenatide IR 10 μg twice daily	315	8.3	−1.1[a]	90	−2.6[a]
	Insulin lispro	312	8.2	−1.1[a]	89	+1.9[a]
Liraglutide 1.2 or 1.8 mg once daily						
Monotherapy (1 year) [6]	Liraglutide 1.2 mg/day	251	8.2	−0.8[††]	92	−2.05[†††]
	Liraglutide 1.8 mg/day	246	8.2	−1.1[†††]	93	−2.45[†††]
	Glimepiride 8 mg/day	248	8.2	−0.5	93	+1.1
Add-on to metformin (26 wk) [6]	Liraglutide 1.2 mg/day	240	8.3	−1.0***[†††]	89	−2.6*[†††]
	Liraglutide 1.8 mg/day	242	8.4	−1.0***[†††]	88	−2.8*[†††]
	Placebo	121	8.4	+0.1	91	−1.5
	Glimepiride 4 mg/day	242	8.4	−1.0	89	+1.0
Add-on to glimepiride (26 wk) [6]	Liraglutide 1.2 mg/day	228	8.5	−1.1***[†††]	80	+0.3[†††]
	Liraglutide 1.8 mg/day	234	8.4	−1.1***[†††]	83	−0.2[†††]
	Placebo	114	8.4	+0.2	82	−0.1
	Rosiglitazone 4 mg/day	231	8.4	−0.4	81	+2.1
Add-on to metformin + rosiglitazone (26 wk) [6]	Liraglutide 1.2 mg/day	177	8.5	−1.5***	95	−1.0
	Liraglutide 1.8 mg/day	178	8.6	−1.5***	95	−2.0
	Placebo	175	8.4	−0.5	99	+0.6
Add-on to glimepiride + metformin (26 wk) [6]	Liraglutide 1.8 mg/day	230	8.3	−1.3***[††]	86	−1.8[†††]
	Placebo	114	8.3	−0.2	85	−0.4
	Insulin glargine	232	8.1	−1.1	85	+1.6
Add-on to metformin (26 wk) [7]	Liraglutide 1.2 mg/day	221	8.4	−1.2[a†††]	94	−2.7[a]
	Liraglutide 1.8 mg/day	218	8.4	−1.5[a†††]	94	−3.3[a]
	Sitagliptin 100 mg/day	219	8.5	−0.9[a]	94	−0.8[a]
Add-on to metformin ± sulfonylurea (26 wk) [7]	Liraglutide 1.8 mg/day	233	8.2	−1.1[a†††]	NR	≈3
	Exenatide IR 10 μg twice daily	231	8.1	−0.8[a]	NR	≈3
Lixisenatide 20 μg once daily [9]						
Add-on to metformin (24 wk)	Lixisenatide 20 μg/day	161	8.0	−0.7[a]****	90	−2.7 [a]**
	Placebo	162	8.0	−0.3[a]	88	−1.7[a]
Add-on to metformin (24 wk)	Lixisenatide 20 μg/day	318	8.0	−0.7[a]	94	−2.7[a]
	Exenatide IR 10 μg twice daily	316	8.0	−0.9[a†]	96	−3.7[a]
Add-on to sulfonylurea ± metformin (24 wk)	Lixisenatide 20 μg/day	573	8.3	−0.8[a]****	82	−1.6[a]**
	Placebo	286	8.2	−0.2[a]	84	−0.8[a]
Add-on to pioglitazone ± metformin (24 wk)	Lixisenatide 20 μg/day	323	8.1	−0.9[a]****	93	−0.1[a]
	Placebo	161	8.1	−0.4[a]	97	+0.3[a]

Table 2 (continued)

Treatment type (study duration)	Comparators	No. of pts	HbA_{1c} (%)		Weight (kg)	
			BL (mean)	Mean change from BL	BL (mean)	Mean change from BL
Add-on to basal insulin ± metformin (24 wk)	Lixisenatide 20 µg/day	329	8.4	−0.7 [a]**	87	−1.6[a]
	Placebo	167	8.4	−0.3[a]	89	−0.4[a]
Add-on to basal insulin ± sulfonylurea (24 wk)	Lixisenatide 20 µg/day	154	8.5	−0.7[a]***	66	−0.5[a]
	Placebo	157	8.5	+0.1[a]	66	−0.03[a]
Add-on to insulin glargine + metformin ± thiazolidinedione (24 wk)	Lixisenatide 20 µg/day	223	7.6	−0.7[a]**	87	+0.3[a]*
	Placebo	223	7.6	−0.4[a]	87	+1.1[a]
Add-on to 1–3 oral glucose-lowering drugs (26 wk)	Lixisenatide 20 µg/day	298	7.8	−0.6[a]	90	−0.6[a†††b]
	Insulin glulisine once daily	298	7.7	−0.5[a]	88	+1.0[a]
	Insulin glulisine three times daily	298	7.8	−0.8[a‡‡‡]	90	+1.3[a]
Dulaglutide 0.75 or 1.5 mg once weekly [10]						
Monotherapy (1 year)	Dulaglutide 0.75 mg/wk	270	7.6	−0.5[†]	NR	−1.1
	Dulaglutide 1.5 mg/wk	269	7.6	−0.7[†]	NR	−1.9
	Metformin 1.5–2 g/day	268	7.6	−0.5	NR	−2.2[‡]
Add-on to metformin (2 years)	Dulaglutide 0.75 mg/wk	302	8.2	−0.7[†]	NR	−2.4
	Dulaglutide 1.5 mg/wk	304	8.1	−1.0[†]	NR	−2.9[††]
	Sitagliptin 100 mg/day	315	8.1	−0.3	NR	−1.7
Add-on to metformin (26 wk)	Dulaglutide 1.5 mg/wk	299	8.1	−1.4	NR	−2.9
	Liraglutide 1.8 mg/day	300	8.1	−1.4	NR	−3.6[‡‡]
Add-on to metformin + sulfonylurea (1.5 years)	Dulaglutide 0.75 mg/wk	272	8.2	−0.6	NR	−1.5[††]
	Dulaglutide 1.5 mg/wk	273	8.1	−0.9[†]	NR	−2.0[††]
	Insulin glargine	262	8.1	−0.6	NR	+1.3
Add-on to glimepiride (24 wk)	Dulaglutide 1.5 mg/wk	239	8.4	−1.4**	NR	−0.9
	Placebo	60	8.4	−0.1	NR	−0.2
Add-on to SGLTI ± metformin (24 wk)	Dulaglutide 0.75 mg/wk	141	8.0	−1.2**	NR	−2.6
	Dulaglutide 1.5 mg/wk	142	8.0	−1.3**	NR	−3.1
	Placebo	140	8.0	−0.5	NR	−2.3
Add-on to metformin + pioglitazone (1 year)	Dulaglutide 0.75 mg/wk	280	8.1	−1.1[†]	NR	+0.4
	Dulaglutide 1.5 mg/wk	279	8.1	−1.4[†]	NR	−1.1
	Exenatide IR 10 µg twice daily	276	8.1	−0.8		−0.8[‡]
Replace previous insulin (1 year)	Dulaglutide 0.75 mg/wk	293	8.4	−1.4[†]	NR	+0.9[††]
	Dulaglutide 1.5 mg/wk	295	8.5	−1.5[†]	NR	−0.4[††]
	Insulin glargine	296	8.5	−1.2	NR	+2.9
Exenatide ER 2 mg once weekly						
Monotherapy or add-on to 1 or 2 oral glucose-lowering drugs (24 wk) [12]	Exenatide ER 2 mg/wk	129	8.5	−1.6[†††]	97	−2.3
	Exenatide IR 10 µg twice daily	123	8.4	−0.9	94	−1.4
Monotherapy or add-on to 1 or 2 oral glucose-lowering drugs (30 wk) [12]	Exenatide ER 2 mg/wk	148	8.3	−1.9[†]	102	−3.7
	Exenatide IR 10 µg twice daily	147	8.3	−1.5	102	−3.6
Add-on to metformin (26 wk) [12]	Exenatide ER 2 mg/wk	160	8.6	−1.6[†c]	89	−2.3[†d]
	Sitagliptin 100 mg/day	166	8.5	−0.9	87	−0.8
	Pioglitazone 45 mg/day	165	8.5	−1.2	86	+2.8
Add-on to metformin ± sulfonylurea (26 wk) [12]	Exenatide ER 2 mg/wk	233	8.3	−1.5[†]	91	−2.6[†]
	Insulin glargine	223	8.3	−1.3	91	+1.4
Add-on to insulin glargine ± metformin (28 wk; 458) [12]	Exenatide ER 2 mg/wk	230	8.5	−1.0**	94	−1.0**
	Placebo	228	8.5	−0.2	NR	+0.5
Add-on to 1 or 2 oral glucose-lowering drugs (26 wk; 911) [13]	Exenatide ER 2 mg/wk	461	8.5	−1.3[a]	NR	−2.7[a]
	Liraglutide 1.8 mg/day	450	8.4	−1.5[a]	NR	−3.6[a]

Table 2 (continued)

Treatment type (study duration)	Comparators	No. of pts	HbA_{1c} (%)		Weight (kg)	
			BL (mean)	Mean change from BL	BL (mean)	Mean change from BL
Semaglutide 0.5 or 1.0 mg once weekly [15]						
Monotherapy (30 wk)	Semaglutide 0.5 mg/wk	128	8.1	−1.5***	90	−3.7***
	Semaglutide 1.0 mg/wk	130	8.1	−1.6***	97	−4.5***
	Placebo	129	8.0	0	90	−1.0
Add-on to basal insulin ± metformin (30 wk)	Semaglutide 0.5 mg/wk	132	8.4	−1.4***	93	−3.7***
	Semaglutide 1.0 mg/wk	131	8.3	−1.8***	93	−6.4***
	Placebo	133	8.4	−0.1	90	−1.4
Add-on to metformin and/or thiazolidinedione (56 wk)	Semaglutide 0.5 mg/wk	409	8.0	−1.3†††	90	−4.3†††
	Semaglutide 1.0 mg/wk	409	8.0	−1.6†††	89	−6.1†††
	Sitagliptin 100 mg/day	407	8.2	−0.5	89	−1.4
Add-on to metformin ± sulfonylurea or other (56 wk)	Semaglutide 1.0 mg/wk	404	8.4	−1.5†††	96	−5.6†††
	Exenatide ER	405	8.3	−0.9	95	−1.9
Add-on to metformin ± sulfonylurea (30 wk)	Semaglutide 0.5 mg/wk	362	8.1	−1.2†††	94	−3.5†††
	Semaglutide 1.0 mg/wk	360	8.2	−1.6†††	94	−5.2†††
	Insulin glargine	360	8.1	−0.8	93	+1.2
Add-on to metformin (40 wk)	Semaglutide 0.5 mg/wk	301	8.3	−1.5†††	96	−4.6 †††
	Dulaglutide 0.75 mg/wk	299	8.2	−1.1	96	−2.3
Add-on to metformin (40 wk)	Semaglutide 1.0 mg/wk	300	8.2	−1.8 †††	96	−6.5 †††
	Dulaglutide 1.5 mg/wk	299	8.2	−1.4	93	−3.0

For consistency in data between GLP-1RAs, results presented are for the intent-to-treat populations in randomized, controlled trials in > 250 pts and a duration of ≥24 wk reported in the EU [6, 10, 12, 15] and/or USA [5, 7, 9, 13] prescribing information (based on the completeness of the data reported). Trials are limited to those that evaluated approved dosages of GLP-1RA s as monotherapy or as a single addition to existing treatment (+ diet/exercise), and for which statistical data regarding BL and changes in BL for HbA_{1c} were reported. GLP-1RAs and optimized dosages of insulins were administered subcutaneously; other active comparators were administered orally

BL baseline, *HbA_{1c}* glycosylated haemoglobin, *NR* not reported, *pts* patients, *SGLT2I* sodium-glucose cotransporter 2 inhibitor, *wk* week(s)

*$p < 0.05$, **$p < 0.01$, ***$p < 0.0001$ for GLP-1RA vs placebo

†$p < 0.05$, ††$p < 0.01$, †††$p < 0.0001$ for GLP-1RA vs active comparator

‡$p < 0.05$ vs dulaglutide 0.75 mg/wk; ‡‡$p < 0.05$ vs dulaglutide 1.5 mg/wk, ‡‡‡$p = 0.0002$ vs lixisenatide 20 µg/day

[a]Least square mean

[b]Versus insulin glulisine three times daily

[c]$p < 0.0001$ for exenatide ER vs sitagliptin and $p < 0.05$ for exenatide ER vs pioglitazone

[d]$p < 0.05$ for exenatide ER vs sitagliptin and $p < 0.0001$ for exenatide ER vs pioglitazone

thiazolidinediones) and insulin (30–54% with insulins glargine, glulisine or lispro) [4–16].

Treatment with the GLP-1RAs was associated with weight loss in many RCTs (Table 2), which is an important consideration in the treatment of T2D. In most RCTs, weight decreased from baseline to a greater extent with GLP-1RAs than with placebo when taken as monotherapy or as an add-on to treatment with one or more glucose-lowering drugs [4–16]. Relative to add-on treatment with other oral glucose-lowering drugs and insulin, decreases from baseline in weight were significantly better with a GLP-1RAs in the following comparisons: liraglutide versus glimepiride, rosiglitazone and insulin glargine; lixisenatide versus insulin glulisine three times daily; dulaglutide versus sitagliptin and insulin glargine; exenatide ER versus sitagliptin, pioglitazone and insulin glargine; and semaglutide versus sitagliptin and insulin glargine (Table 2).

GLP-1RAs were also associated with decreases from baseline in waist circumference [21], according to network meta-analyses of 17 RCTs [21]. Waist circumference decreased to a greater extent with GLP-RAs than with placebo, thiazolidinediones and insulin, and somewhat greater than those with sitagliptin [21].

3.2 Comparisons Between GLP-1RAs

Given the pharmacological differences between individual GLP-1RAs (Table 1), the drugs in this class may have differences in their effectiveness [18–20, 22]. However, there are few RCTs that directly compare the relative efficacy

of drugs in this class (Table 2). In the available head-to-head comparisons, reductions from baseline in HbA_{1c} were significantly greater: with exenatide IR 10 µg twice daily than with lixisenatide 20 µg/day; with liraglutide 1.8 mg/day than with exenatide IR 10 µg twice daily; with dulaglutide 0.75 or 1.5 mg/week than with exenatide IR 10 µg twice daily; withsemaglutide 0.5 mg/week than with dulaglutide 0.75 mg/week; with semaglutide 1.0 mg/week than with dulaglutide 1.5 mg/week; and with semaglutide 1.0 mg/week than with exenatide ER; there were no significant differences between exenatide ER and liraglutide (Table 2).

Due to their effects in delaying gastric emptying, short-acting GLP-1RAs had greater effects on postprandial glucose levels than long-acting ones. However, the long-acting GLP-1RAs offer the pharmacological advantage of reducing plasma glucose levels across the 1-day or 1-week administration intervals [18, 20, 22]. In a meta-analysis of RCTs comparing a GLP-1RA with placebo or another GLP-1RA [23], dulaglutide, exenatide, liraglutide and lixisenatide improved HbA_{1c} and fasting plasma glucose levels relative to placebo (semaglutide data were not available at the time of the meta-analysis). Overall, the long-acting GLP-1RAs (once-weekly dulaglutide, liraglutide and exenatide ER) were superior to the short-acting agents (twice-daily exenatide and lixisenatide) with regard to improvements in glycaemic control, whereas no differences were shown in comparisons between either the various short-acting drugs or long-acting drugs [23]. Updated meta-analyses that include data for semaglutide would be of interest given the significantly better efficacy with semaglutide shown in head-to-head RCTs with the two other currently available weekly GLP-1RAs.

When added to oral glucose-lowering treatment, reductions in weight were more than twofold greater ($p < 0.0001$) with once-weekly semaglutide than with either once-weekly exenatide ER or once-weekly dulaglutide (Table 2). Weight reductions with once-daily liraglutide 1.8 mg were comparable to those with exenatide IR 10 µg twice daily, and significantly greater than those with dulaglutide 1.5 mg/week (Table 2). The clinical data are supported by results in the real-world setting [24]. In a retrospective cohort study in 2465 patients receiving once-weekly exenatide, dulaglutide or albiglutide, the overall mean decrease from baseline in HbA_{1c} at 6 months was 0.5%, with no significant differences between treatment groups [24]. However, weight loss with dulaglutide was significantly better with than with exenatide and albiglutide (2.7 vs 1.4 and 1.6 kg; $p = 0.001$) [24].

4 Effects of Once-Weekly GLP-1RAs on Patient-Reported Outcomes

Once-weekly GLP-1RAs improved most patient-reported outcomes (PROs) related to T2D treatment relative to baseline, with significant improvements relative to placebo or active comparators also being shown in some RCTs (Table 3) [25–32]. As these RCTs had differences in trial design (e.g. comparators, PRO measures, inclusion criteria and trial duration), results tend to vary between RCTs.

Overall, the currently available data suggest that treatment with a once-weekly GLP-1RA may improve Diabetes Treatment Satisfaction Questionnaire (DTSQ) total, treatment satisfaction and patient perception of the frequency of hyperglycaemia scores to a significantly greater extent than treatment with placebo (Table 3) [25–32], as well, in a few RCTs, some other glucose-lowering drugs (most frequently semaglutide vs sitagliptin or insulin glargine [28–32]) [Table 3]. With a few exceptions, DTSQ patient perception of the frequency of hypoglycaemia and weight-related PRO scores generally did not improve to a significantly greater extent with once-weekly GLP-1RAs than with placebo or glucose-lowering drugs (Table 3). In head-to-head comparisons of GLP-1RAs, improvements in some DTSQ scores were greater with once-weekly dulaglutide or exenatide ER than with exenatide IR [25, 26], and greater with semaglutide than with exenatide ER [31] (Table 3).

General health-related quality-of-life (HR-QoL) was evaluated in several RCTs, with once-weekly GLP-1RAs showing consistent and significant improvements from baseline for most HR-QoL-related PROs, such as EuroQol 5 Dimension, Psychological General Well-Being Index and Short-Form-36 (SF-36) total and/or domain scores [25, 27, 29, 30, 32]. However, with a few exceptions, once-weekly GLP-1RAs did not consistently improve such outcomes to a significantly greater extent than placebo or active comparators [25, 27, 29, 30, 32].

Nevertheless, general HR-QoL-related PROs, as well as T2D-related PROs, may improve in conjunction with significant weight loss, such as that seen with semaglutide [33]. In pooled analyses of PROs in 2808 recipients of semaglutide 0.5 or 1.0 mg/week, patients with a weight loss of ≥ 5 or $\geq 10\%$ had significantly ($p < 0.01$) greater improvements in SF-36 version 2 physical component summary, general health and physical function scores than those without the corresponding weight-loss response [33]. DTSQ overall treatment satisfaction and perception of hyperglycaemia frequency scores were also significantly ($p < 0.01$) greater in patients who lost ≥ 5 or $\geq 10\%$ of their weight than those in patients who did not [33].

Adherence to treatment may be better with the once-weekly GLP-1RAs than with the once- or twice-daily options, leading to improvements in clinical outcomes [34]. Over a 6-month period in retrospective studies in the real-world setting, treatment adherence was significantly better with once-weekly exenatide ER

Table 3 Summary of patient-reported outcomes related to type 2 diabetes in randomized, controlled phase 3 trials of once-weekly glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Patient-reported outcome	Dulaglutide 0.75 or 1.5 mg/wk [25]	Exenatide ER 20 mg/wk [26, 27]	Semaglutide 0.5 or 1.0 mg/wk [28–32]
Diabetes Treatment Satisfaction Questionnaire (DTSQ) scores			
Total score	$p < 0.05$ vs placebo and exenatide IR (26 wk)	NS vs exenatide IR (30 and 52 wk), and sitagliptin and pioglitazone (26 wk)	$p < 0.05$ vs placebo and insulin glargine (30 wk), and sitagliptin or exenatide ER (56 wk)
	NS vs metformin and liraglutide (26 wk)		1.0 mg/wk: $p < 0.01$ vs exenatide ER (56 wk)
			NS vs dulaglutide (40 wk)
Current treatment satisfaction score		NS vs exenatide IR (30 and 52 wk), and sitagliptin and pioglitazone (26 wk)	$p < 0.05$ vs sitagliptin (56 wk)
			NS vs insulin glargine (30 wk) and dulaglutide (40 wk)
Perceived hyperglycaemia frequency score	$p < 0.05$ vs placebo and exenatide IR (26 wk)	$p < 0.05$ vs exenatide IR (30and 52 wk)	$p < 0.05$ vs insulin glargine (30 wk), dulaglutide (40 wk) and sitagliptin (56 wk)
	1.5 mg/wk: $p < 0.05$ vs metformin (26 wk)	NS vs sitagliptin and pioglitazone (26 wk)	
Perceived hypoglycaemia frequency score	$p < 0.05$ vs exenatide IR (26 wk)	NS vs exenatide IR (30 and 52 wk), and sitagliptin and pioglitazone (26 wk)	NS vs insulin glargine (30 wk), dulaglutide (40 wk) and sitagliptin (56 wk)
	NS vs placebo and metformin (26 wk)		
Weight-related scores			
Impact of Weight on Self-Perception score	NS vs placebo, metformin, exenatide IR and liraglutide (26 wk), and insulin glargine (52 wk)		
	1.5 mg/wk: $p < 0.05$ vs placebo (28 wk) and insulin glargine (26 wk)		
Impact of Weight on Quality of Life-Lite score	NS vs sitagliptin (52 wk)	$p < 0.05$ vs pioglitazone (26 wk)	
		NS vs exenatide IR (30 and 52 wk) and sitagliptin (26 wk)	

RCTs were 26–56 wk in duration [25–32]. GLP-1RAs and comparators were added to treatment with 1–3 glucose-lowering agents, with the exception of dulaglutide vs metformin monotherapy in one RCT [25]. Results presented are limited to total and key subscales scores for patient-reported outcomes related to type 2 diabetes that were assessed in more than one RCT. Unless otherwise indicated, results presented are for both dosages of dulaglutide and semaglutide. Active comparators were administered at a daily dosage of 1.5–2 g for metformin, 45 mg for pioglitazone, 100 mg for sitagliptin and 1.8 mg for liraglutide

ER extended-release, *NS* no significant difference between GLP-1RA and comparator, *RCT* randomized, controlled trial, *wk* week(s)

than with twice-daily exenatide IR [35, 36] and/or once-daily liraglutide [35–37], and treatment adherence and persistence rates were significantly higher, and discontinuation rates were significantly lower, with once-weekly dulaglutide than with once-daily liraglutide and once-weekly exenatide [38].

5 Effects of GLP-1RAs on Major Cardiovascular Outcomes

As patients with T2D have an increased risk of adverse cardiovascular (CV) outcomes, current management of T2D includes the reduction of CV risk factors including, but not limited to, hyperglycaemia [39, 40]. GLP-1RAs, as a class, provide beneficial effects with regards to several CV risk factors by improving glycaemic control and promoting weight loss (Sect. 3), as well as improving factors that are independent of changes in blood glucose [39–42].

RCTs evaluating major adverse CV events (MACE) with once-daily or -weekly GLP-1RAs in patients with T2D have found the incidence of MACE to be significantly reduced (liraglutide [43], dulaglutide [44] and semaglutide [45]), or at least not increased (lixisenatide [46] and exenatide ER [47]) relative to placebo, with hazard ratios ranging to 0.74–1.02 (Table 4). The primary MACE component appearing to be driving the reduction in MACE was CV death with liraglutide [43], and non-fatal stroke with dulaglutide [44] and semaglutide [45], with no other significant differences in the risk of individual MACE components shown between individual GLP-1RAs and placebo (Table 4). The risk of all-cause death was significantly lower with liraglutide and exenatide ER than with placebo (Table 4).

Between-trial discrepancies may be explained by factors such the heterogeneity across the RCTs, the definitions of composite and individual outcomes, GLP-1RA pharmacokinetics and the degree to which each GLP-1RA may impact modifiable CV risk factors [39–42, 44]. According to a meta-analysis of RCTs of lixisenatide, liraglutide, exenatide ER and semaglutide investigating CV outcomes, overall these GLP-1RAs significantly reduced the risk of MACE by 10%, CV mortality by 13% and all-cause mortality by 12% relative to placebo [48].

6 Tolerability Profiles of GLP-1RAs

Overall, GLP-1RAs are well tolerated, with gastrointestinal effects being the most common adverse drug reactions (ADRs; Table 5) [19, 49–51]. Of note, as the effects of GLP-1RAs are glucose-dependent, they do not have an intrinsic risk of hypoglycaemia. In RCTs, GLP-1RAS were associated with very low rates of major/severe hypoglycaemia when used as monotherapy or in combination with other glucose-lowering drugs [4–16]. However, when a GLP-1RA is added to an existing regimen, the dosage of insulin or an insulin secretagogue may need to be reduced, in order to decrease the potential for hypoglycaemic episodes [4–16].

Although many ADRs appear to be class effects, the tolerability profiles of individual GLP-1RAs are affected by differences in their structure and duration of effect with regard to some ADRs, especially with regard to gastrointestinal ADRs and injection-site reactions (Table 5) [19, 49, 50].

In head-to-head RCTs, significant differences in the rates of gastrointestinal ADRs were found only with liraglutide versus exenatide ER [65], and exenatide IR versus dulaglutide 0.75 (but not 1.5) mg/week [53]. A meta-analysis found no significant differences in the rates of nausea and discontinuation for ADRs between exenatide ER and dulaglutide, exenatide IR, liraglutide and lixisenatide as add-ons to metformin [66]. Another meta-analysis found that the once-weekly GLP-1RAs (semaglutide data were not included) had similar risks of diarrhoea, but the risk of nausea was greater with dulaglutide than with exenatide ER [23]. In a head-to-head RCT, the rate of nausea was higher with semaglutide 1.0 mg/week than with dulaglutide 1.5 mg/week (83.2 vs 45.4/100 patient-years), but the rate of all gastrointestinal ADRs was similar (43 vs 44% of patients) [32].

The relative incidences of injection-site reactions with GLP-1RAs are difficult to determine as their frequency and characteristics in RCTs are inconsistently reported and lack statistical analysis [19, 51]. In head-to-head RCTs, exenatide ER recipients had a higher rate of injection-site reactions than exenatide IR recipients [12–14] and semaglutide recipients had a lower rate of injection-site reactions than exenatide ER recipients [31]. Rates of injection-site reactions were similar between dulaglutide and liraglutide [67], as well as between dulaglutide and semaglutide [32].

With some exceptions, dosage changes are generally not required in patients with hepatic impairment or mild renal impairment (Table 6). However, due to limited data, the use of GLP-1RAs in patients with more severe renal impairment usually requires caution or is not recommended (Table 6). Dosage changes are not required on the basis of age (limited data in patients aged ≥70 or 75 years), but treatment in elderly patients should take into account any age-related renal impairment. The use of GLP-1RAs is not recommended in women who are pregnant or breastfeeding. Precautions should also be taken in patients at risk of acute kidney disease, pancreatitis or thyroid disease (Table 5).

7 Approved Indications of GLP-1RAs

Six GLP-1RA formulations (i.e. twice-daily exenatide IR, once-daily liraglutide and lixisenatide, and once-weekly dulaglutide, exenatide ER and semaglutide) are approved for the treatment of T2D in the EU and/or USA (Table 6) [4–16]. They are all indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2D in combination with other glucose-lowering drugs (including insulin) when current treatment + diet/exercise do not provide adequate

Table 4 Results of randomized, placebo-controlled trials evaluating the effects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) on major adverse cardiovascular events (MACE)

	Once-daily GLP-1RAs		Once-weekly GLP-1RAs		
	Liraglutide 1.8 mg/day vs PL) [6, 7, 43]	Lixisenatide 20 µg/day vs PL [8, 9, 46]	Dulaglutide 0.5/1.0 mg/wk vs PL [44]	Exenatide ER 20 mg/wk vs PL [12, 47]	Semaglutide 0.5/1.0 mg/wk vs PL [15, 45]
Trial design					
No. of patients	9340	6068	9901	14,752	3297
Antidiabetic treatment to which GLP-1RA was added	Standard of care	Standard of care (after recent ACS)	1–2 oral antidiabetics ± basal insulin	Standard of care	Standard of care
Treatment duration	Median: 3.5 years	Median: 22.4 vs 23.3 months	82 vs 83% of the time to MACE/follow-up	Median: 27.8 months	2 years
Follow-up duration	3.5–5 years	Median: 25.8 vs 23.3 months	Median: 5.4 years	Median: 38.7 months	
MACE and its components					
Composite outcome[a] [% of pts (HR; 95% CI)]	**13.0 vs 14.9 (0.87; 0.78–0.97)**	13.4 vs 13.2 (1.02; 0.89–1.17)	**12.0 vs 13.4 (0.88; 0.79–0.99)**	11.4 vs 12.2 (0.91; 83-1.00)	**6.6 vs 8.9 (0.74; 0.58–0.95)**
CV death [% of pts (HR; 95% CI)]	**4.7 vs 6.0 (0.78; 0.66–0.93)**	5.1 vs 5.2 (0.98; 0.78–1.22)	6.4 vs 7.0 (0.91; 0.78–1.06)[b]	4.6 vs 5.2 (0.88; 0.76–1.02)	2.7 vs 2.8 (0.98; 0.65–1.48)
Non-fatal stroke [% of pts (HR; 95% CI)]	3.4 vs 3.8 (0.89; 0.72–1.11)	2.2 vs 2.0 (1.12; 0.79–1.58)	**2.7 vs 3.5 (0.76; 0.61–0.95)**	2.5 vs 2.9 (0.85; 0.70–1.03)	**1.6 vs 2.7 (0.61; 0.38–0.99)**
Non-fatal myocardial infarction [% of pts (HR; 95% CI)]	6.0 vs 6.8 (0.88; 0.75–1.03)	8.9 vs 8.6 (1.03; 0.87–1.23)	4.1 vs 4.3 (0.96; 0.79–1.16)	6.6 vs 6.7 (0.97; 0.85–1.10)	2.9 vs 3.9 (0.74; 0.51–1.08)
Hospitalization for unstable angina [% of pts (HR; 95% CI)]		0.4 vs 0.3 (1.11; 0.47–2.62)			
Other secondary endpoints					
All-cause death [% of pts (HR; 95% CI)]	**8.2 vs 9.6 (0.85; 0.74–0.97)**		10.8 vs 12.0 (0.90; 0.80–1.01)	**6.9 vs 7.9 (0.86; 0.77–0.97)**	3.8 vs 3.6 (1.05; 0.74–1.50)

Results reported in the full-analysis-set (liraglutide, dulaglutide and semaglutide) or intent-to-treat populations (exenatide ER and lixisenatide). Bolded values indicate significant between-treatment differences favouring the GLP-1RA over PL

ACS acute coronary syndrome, *CV* cardiovascular, *ER* extended-release, *HR* hazard ratio, *PL* placebo, *pts* patients, *wk* week

[a]Primary endpoint comprising the time from randomization to the first occurrence of one of the components of MACE

[b]Also included deaths of unknown cause

glycaemic control. Some GLP-1RAs are also indicated as an adjunct to diet and exercise as monotherapy, or as monotherapy when the use of metformin is considered inappropriate due to intolerance or contraindications (Table 6) [4–16].

All of the GLP-1RAs are injected subcutaneously to the abdomen, thigh or upper arm, with a different injection site being used each time when injecting in the same region [4–16]. Their use differs with regard to some parameters, such as dosage, administration and dose preparation (Table 6) [4–16].

8 Current Clinical Position of GLP-1RAs

Current treatment guidelines recommend GLP-1RAs as an option for T2D management, most commonly as add-on therapy in patients not achieving glycaemic targets with lifestyle interventions plus metformin and/or other glucose-lowering drugs [1, 2]. As a class, GLP-1RAs offer some potential advantages over other classes of glucose-lowering drugs. Outcomes related to glycaemic control and weight loss improved to at least, or better, extent with a GLP-1RA than metformin, sulfonylureas, DPP-4 inhibitors, thiazolidinediones, SGLT2 inhibitors and long-and rapid-acting insulins (Sect. 3). The beneficial effects of the GLP-1RAs on glycaemic control, including the low intrinsic risk of hypoglycaemia, and loss of weight are associated with improvements in PROs pertaining to diabetes treatment satisfaction, perception of weight and perceived frequency of hyper- and hypoglycaemia (Sect. 4).

GLP-1RAs, SGLT2 inhibitors, DPP-4 inhibitors and thiazolidinediones are often indicated as add-on options to current therapies at the same step of treatment guidelines [1, 2]. Although both GLP-1RAs and DPP-4 inhibitors are incretin-based therapies, GLP-1RAs have direct

Table 5 Summary of the overall tolerability profiles of glucagon-like peptide-1 receptor agonists (GLP-1RAs)

Gastrointestinal effects	Most common type of ADR; most frequent at the beginning of treatment, then ↓ gradually [19, 50–52]
	Use is not recommended in pts with inflammatory bowel disease or diabetic gastroparesis [4–16]
	Nausea: very common[a] (reported in up to 50% of pts); generally mild to moderate in severity and dose-dependent [49]
	Short-acting GLP-1RAs[b]: ↑ risk due to substantial delays in gastric emptying; ↓ slowly over several months; may lead to treatment discontinuation (long-acting GLP-1RAs do not delay gastric emptying; nausea rapidly resolves) [19, 49, 52]
	Other common[a] events: dyspepsia, constipation, abdominal pain [52]; vomiting is more common with dulaglutide than with exenatide IR [53]
Cardiovascular-related effects	No significant ↑ in the risk of cardiovascular effects (Sect. 5) [44, 48, 54–56]
	May cause small ↑ in heart rate (2.1–3.3 beats/min) and moderate ↓ in systolic blood pressure (1.8– 4.6 mmHg) vs PL [56]
	No significant ↑ in rates of hypertension [56], atrial fibrillation [55] or heart failure [54]; no effect on QT interval [49]
Microvascular effects	Diabetic retinopathy: ↑ risk of early worsening with semaglutide (consistent with early worsening that occurs with insulin; associated with rapid and sizeable improvements in glycaemic control) [57], but not other GLP-1RAs [58, 59]
	Nephropathy: ↓ risk [58, 59]
Lipid levels	Exenatide IR/ER, liraglutide and lixisenatide provided generally modest ↓of high-density lipoprotein cholesterol (0.06–0.13 mmol/L), low-density lipoprotein cholesterol (0.08–0.16 mmol/L) and total cholesterol (0.16–0.27 mmol/L) [60]
Immunogenicity and allergic reactions	Potential for antibody production is greater with GLP-1RAs whose structure is based on exendin-4, as they are less homologous to human GLP-1 than those based on human GLP-1 (Table 1) [19, 49]
	Incidence of antibody formation: ≈ 45% of exenatide IR and ER, 70% of lixisenatide, 9% of liraglutide and ≈1–2% of dulaglutide and semaglutide recipients [4–16]
	Antibodies have little impact on efficacy, with the possible exception of pts with high antibody titres [19, 49]
	Severe anaphylactic reactions: uncommon[a] with lixisenatide; rare[a] with liraglutide and very rare[a] with exenatide
	Rare[a] reports of pruritus, urticaria and angioneurotic oedema [49]
Injection-site reactions	Common[a] ADR due to subcutaneous injection; generally presents as pruritus at the injection site; generally mild and transient; may be more frequent in pts who develop antibodies against the drug [19, 49, 50]
	Exenatide ER recipients may have small (diameter generally < 0.05 cm) raised bumps on their abdomen, which are due to the polymer microspheres present in the formulation; the bumps usually resolve within 4-8 weeks, are not symptomatic and do not lead to treatment discontinuation [12–14]
Hypoglycaemia	GLP-1RA alone or + metformin: does not ↑ the risk of hypoglycaemia [49]
	GLP-1RA + sulfonylurea ± metformin or + insulin ↑ the risk of hypoglycaemia, although still low overall [49]
	Advisable to ↓ the dosage of sulfonylurea or insulin when initiating a GLP-1RA to ↓ the risk of hypoglycaemia
Acute kidney injury	Probably caused by volume contraction and dehydration due to gastrointestinal symptoms [61]
	Reported with exenatide IR/ER and liraglutide; no causal relationship with acute interstitial nephritis [19, 49]
	Advisable to avoid the use of GLP-1RAs in pts with uncontrolled type 2 diabetes, polyuria or polydipsia, or who develop severe gastrointestinal symptoms (e.g. vomiting and diarrhoea) or are receiving drugs (i.e. renin-angiotensin system inhibitors) that predispose them for volume depletion [20, 49]
Pancreatitis and pancreatic cancer	Current data do not support a link between these conditions and incretin-based drugs [62, 63]
	As a precautionary measure, do not use GLP-1RAs in pts with pancreatic cancer or acute pancreatitis [20, 49, 51]
Thyroid C-cell tumours	GLP-1RAs caused thyroid C-cell tumours at clinically relevant exposures in rodent, but not primate, studies; unknown whether GLP-1RAs cause thyroid C-cell tumours, including medullary thyroid carcinoma, in humans (relevance of rodent studies in humans is likely to be low, but cannot be excluded) [4–16]
	USA: use is contraindicated (black-box warning) in pts with a personal or family history of medullary thyroid carcinoma or in pts with multiple endocrine neoplasia syndrome type 2 [5, 7, 9, 11, 13, 14, 16]
Others	Infections and headache: frequently reported in RCTs, but no causal association with GLP-1RA treatment [49]
	↑ risk of bone fractures: linked to exenatide but not liraglutide [64]; causality is controversial [49]
	EU: ↑ risk of thyroid ADRs (e.g. goitre); reported in RCTs, particularly in pts with pre-existing thyroid disease; use with caution in such pts [4, 6, 8, 10, 12, 15]

ADR adverse drug reaction, *IR* immediate release, *PL* placebo, *pts* patients, *RCT* randomized, controlled trial, ↑ increase(s), ↓ decrease(s)

[a]Very common ADRs reported in ≥ 10% of pts, common in ≥ 1 to < 10%, rare in ≥ 0.1 to < 1%, and very rare in ≥ 0.01 to < 0.1%

[b]Exenatide IR and liraglutide are short-acting; lixisenatide, dulaglutide, exenatide ER and semaglutide are long-acting

intrinsic effects on the incretin system, whereas DPP-4 inhibitors work indirectly to prevent the inactivation of endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) through competitive inhibitor of the DPP-4 enzyme [72–74]. Both drug classes have a low risk of hypoglycaemia and weight gain; however, GLP-1RAs provide better glycaemic control than DPP-4 inhibitors, and promote weight loss instead of being weight neutral. In patients who have a compelling need to lose weight, treatment with a GLP-1RA or an SGLT2 inhibitor

Table 6 Selected features of glucagon-like peptide-1 receptor agonists (GLP-1RAs) [4–16]

Parameter	Twice daily	Once daily		Once weekly		
	Exenatide [4, 5]	Liraglutide [6, 7]	Lixisenatide [8, 9]	Dulaglutide [10, 11]	Exenatide [12–14]	Semaglutide [15, 16]
Approval details						
Tradename	Byetta®	Victoza®[a]	Lyxumia®[b] (EU); Adyxin®[b] (USA)	Trulicity®	Bydureon®/Bydureon® BCise®[c]	Ozempic®
Initial approval	2009	2009	2013	2014	2011/2017	2017
Monotherapy	✓	✓[d]	✗ EU; ✓ USA	✓[d] EU; ✗ USA	✗	✓[d]
Combination therapy	✓	✓	✓	✓	✓	✓
Dosage and administration						
Initial dosage	5 µg twice daily	0.6 mg/day	10 µg/day	0.75 or 1.5 mg/wk[e]	2 mg/wk	0.25 mg/wk
Dosage ↑	May ↑ to 10 µg twice daily at ≥1 month	May ↑ to 1.2 mg/day at ≥1 wk	Should ↑ to 20 µg/day at 15 days	May ↑ to 1.5 mg/wk		Should ↑ to 0.5 mg/wk at 4 wk
Further ↑ if needed		1.8 mg at ≥1wk				1 mg/wk at ≥ 4 wk
Administration restricted with regard to meals	✓: ≤1 h before 2 main meals ≥6 h apart	✗; at about the same time each day	✓; ≤1 h before any (EU) or 1st (USA) meal	✗; same day each wk	✗; same day each wk	✗; same day each wk
Available dose/pen (no. of doses/pen)	300 µg (60 × 5 µg)	18 mg (10 × 1.8, 15 × 1.2 or 30 × 0.6 mg)	140 µg/pen (14 × 10 µg)	0.75 mg (1 × 0.75 mg)	2 mg (1 × 2 mg)	2 mg (4 × 0.25 or 0.5 mg)
	600 µg (60 × 10 µg)		280 µg/pen (14 × 20 µg)	1.5 mg (1 × 1.5 mg)		4 mg (4 × 1 mg)
Requirements for preparation of a dose						
Reconstitute or mix	✗	✗	✗	✗	✓	✗
Prime device before use	✓	✓	✓	✗	✗	✓
Select dose	✓	✓	✓	✗	✗	✓
Attach needle (included)	✓ (✗)	✓ (✗)	✓ (✗)	✗ (✓ PHN)	✓ (✗)/✗ (✓PHN)	✓ (✓)
Storage						
Before use	2–8 °C	2–8 °C or < 30 °C × ≤ 1 month	2–8 °C	2–8 °C or < 30 °C × ≤ 14 days	2–8 °C or < 30 °C (< 25 °C Bydureon USA) × ≤ 4 wk	2–8 °C
After 1st use	< 25 °C	2–8 °C or < 30 °C	< 30 °C	NA	NA	2–8 °C or < 30 °C
Discard date after 1st dose	30 days	30 days	14 days	NA	NA	6 wk EU; 8 wk USA
Use in patients with renal impairment						
Mild	✓	✓	✓	✓	✓	✓
Moderate	↑ dose with caution	✓	✓	✓	↑ dose with caution	✓
Severe	NRC	✓	NRC	✓	NRC	✓
End-stage renal disease	NRC	NRC	NRC	NRC EU; caution USA		NRC
Use in patients with hepatic impairment						
Mild to moderate	✓	✓	✓	✓ EU; caution USA	✓	✓
Severe	✓	NRC	✓	✓ EU; caution USA	✓	Caution

Unless otherwise indicated, details pertain to both the EU and USA. All GLP-1RAs are used as an adjunct to diet and exercise

NA not applicable, *NRC* not recommended, *PHN* pre-attached hidden needle, *wk* week(s), ✓ approved/required, ✗ not approved/not required

[a]Also available as a once-daily fixed-dose combination with insulin degludec (Xultophy®) [68, 69]

[b]Also available as a once-daily fixed-dose combination with insulin glargine (Suliqua® in the EU) [70]; Soliqua® in the USA [71])

[c]Refers to both Bydureon injection and Bydureon® BCise pre-filled pen unless otherwise indicated

[d]If metformin cannot be used due to intolerance or contraindications

[e]0.75 mg/wk is the starting dosage for monotherapy and potentially vulnerable populations (i.e. patients aged ≥75 years) in the EU and combination therapy in the USA; 1.5 mg/wk is the starting dosage for combination therapy in the EU

(which also promote weight loss), therefore, could be preferred over a DPP-4 inhibitor; if weight is not a concern, oral administration is desired or GLP-1RA treatment is not tolerated, treatment with a DPP-4 inhibitor may sometimes be preferred.

Treatment with a GLP-1RA or an SGLT2 inhibitor with proven CV benefits may also be preferred over other options in patients at risk of atherosclerotic CV events [2]. In RCTs of GLP-1RAs assessing CV outcomes, semaglutide, dulaglutide and liraglutide significantly reduced the risk of MACE by 26%, 13% and 12%, respectively, and exenatide ER and lixisenatide at least did not increase the risk of MACE (Table 4). These are important findings as the treatment of T2D should manage aspects of T2D beyond achieving glycaemic control. Overall, current evidence regarding efficacy in reducing CV events is greatest with liraglutide, followed by semaglutide and then by exenatide ER [2]. Of note, SGLT2 inhibitors have also shown CV benefits relative to placebo and other oral glucose-lowering drugs (i.e. metformin, sulfonylureas, thiazolidinediones and DPP-4 inhibitor) [75], with evidence being moderately stronger for empagliflozin than for canagliflozin [2]. In patients in whom heart failure or chronic kidney disease (CKD) predominates, treatment with an SGLT2 inhibitor with evidence of reducing heart failure and/or CKD is preferable in patients with adequate renal function; a GLP-1RA with proven CV benefits can be added if an SGLT2 inhibitor is not tolerated/contraindicated or if renal function is less than adequate [2].

In patients without established atherosclerotic CV disease or CKD and in whom the cost of glucose-lowering drug treatment is a major issue, the addition of a sulfonylurea or thiazolidinedione to metformin may generally be preferred over the addition of a GLP-1RA, SGLT2 inhibitor or DPP-4 inhibitor, with the addition of a glucose-lowering drug in the newer, and more costly, drug classes being reserved for subsequent treatment lines (consider treatment with the drug with the lowest acquisition cost) [2].

GLP-1RAs must be administered subcutaneously, which is a disadvantage relative to the convenient oral administration of most other classes of glucose-lowering drugs. Clinical outcomes in individuals with T2D are worse in those with low treatment adherence, which can be particularly problematic with injectable glucose-lowering drugs, such as GLP-1RAs and insulin. Concerns about injections (e.g. pain, fear of needles, needle size) and the burden/inconvenience of injections are common barriers to using and continuing injectable glucose-lowering drug treatment [76]. GLP-1RAs that are administered once weekly (i.e. dulaglutide, exenatide ER and semaglutide) may be preferred by some patients over the GLP-1RAs that are administered once or twice daily.

No one GLP-1RA has yet been shown to be clearly better overall than the other GLP-1RAs. However, long-acting GLP-1RAs consistently reduce glucose levels across the 1-day or 1-week dosage interval (Sect. 3), and may offer some clinical benefits in selected patients. In meta-analyses, improvements in glycaemic control with long-acting GLP-1RAs were superior those with the short-acting agents, and both short- and long-acting agents reduced weight. No overall clinically meaningful differences were consistently shown between individual short-acting GLP-1RAs. In contrast, of the long-acting GLP-1RAs, semaglutide was significantly more effective in lowering HbA_{1c} levels and reducing weight than the other once-weekly GLP-1RAs (dulaglutide and exenatide ER; Table 2).

Overall, GLP-1RAs are generally well tolerated (Sect. 5), but the common gastrointestinal ADRs can be troublesome and may lead to treatment discontinuation. Such events are generally transient and decrease in frequency over a period of a few weeks or months. More gradual dosage titration may help reduce their frequency and intensity. Injection-site reactions are also common, but transient, and may occur more frequently in patients with relatively high titres of antibodies to the GLP-1RA. Comparative data from the real-world setting would help clarify the relative effectiveness, tolerability and acceptance of this drug class.

Differences in the pharmacological, effectiveness, tolerability and administration profiles of GLP-1RAs should be considered, together with patient preferences, when these drugs are added to lifestyle modifications ± other glucose-lowering drugs. Patients should be advised on the correct use of the GLP-1RA device, as well as the potential for and management of treatment-related ADRs. When used appropriately, GLP-1RAs are a valuable and effective class of glucose-lowering drugs, especially in patients who have difficulty managing T2D with diet/exercise ± metformin and other glucose-lowering drugs.

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Compliance with Ethical Standards

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