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► **To cite this version:**

David Russell-Jones. The Safety and Tolerability of GLP-1 Receptor Agonists in the Treatment of Type 2 Diabetes. *International Journal of Clinical Practice*, 2010, 64 (10), pp.1402. 10.1111/j.1742-1241.2010.02465.x . hal-00566329

HAL Id: hal-00566329

<https://hal.science/hal-00566329v1>

Submitted on 16 Feb 2011

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Journal:	<i>International Journal of Clinical Practice</i>
Manuscript ID:	IJCP-02-10-0130.FT10.R1
Wiley - Manuscript type:	Non-Systematic Review
Date Submitted by the Author:	28-Apr-2010
Complete List of Authors:	Russell-Jones, David; Royal Surrey County Hospital, Cedar Centre
Specialty area:	



IJCP-02-10-0130.FT10
Russell-Jones

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The Safety and Tolerability of GLP-1 Receptor Agonists in the Treatment of Type 2

Diabetes

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Disclosure

Prof. Russell-Jones has received research grants, lecture fees or honoraria from Eli Lilly,
GlaxoSmithKline, Sanofi-Aventis, MSD, Novo Nordisk, Pharmacia, and Boehringer Ingelheim

Author contribution

Prof Russell-Jones was fully involved in the concept and design of this paper. He critically reviewed each draft of the article, at which time he analysed and interpreted the data, and approved the final product. He approved this version of the paper for submission. Nobody that qualifies for authorship has been excluded from the list of authors.

Prof. Russell-Jones received no honorarium or payment for authorship of this review.

Acknowledgements:

I would like to thank Andrew Horgan, PhD, and Patricia C. Abramo of AdelphiEden Health Communications for providing medical writing and editorial services, supported by Novo Nordisk.

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Keywords: liraglutide, GLP-1 analogue, type 2 diabetes mellitus, exenatide, incretin, DPP-4, human, once-daily

Abstract

Established therapies for type 2 diabetes effectively reduce blood glucose, but are often associated with adverse effects that pose risks to patient health or diminish adherence to treatment. Weight gain, hypoglycaemia, and gastrointestinal symptoms are commonly reported, and some agents may not be safe for use in patients with renal impairment or elevated cardiovascular risk. New treatments based on the action of the endogenous human hormone glucagon-like peptide-1 (GLP-1), including exenatide and liraglutide, are available. These therapies provide a novel pharmacologic approach to glycaemic control via multiple mechanisms of action, and accordingly exhibit different safety and tolerability profiles than conventional treatments. GLP-1 receptor agonists stimulate insulin release only in the presence of elevated blood glucose, and are therefore associated with a fairly low risk of hypoglycaemia. Gastrointestinal symptoms are common but transient, and there appears to be little potential for interaction with other drugs. GLP-1 receptor agonists are associated with weight loss rather than weight gain. As protein-based therapies, these agents have the potential to induce antibody formation, but the impact on efficacy and safety is minor. GLP-1 receptor agonists thus offer a new and potentially useful option for clinicians concerned about some of the common adverse effects of type 2 diabetes therapies.

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Review criteria

Information for this narrative review was collected for traditional oral antidiabetic agents and incretin-based therapies from literature indexed on PubMed or presented at recent professional Endocrinologist meetings. Data from relevant publications were analysed and reported descriptively.

Message for the clinic

- The novel, incretin-based, mechanism of action of GLP-1 receptor agonists mitigates common adverse effects associated with other type 2 diabetes therapies
- Safety and tolerability data on GLP-1 receptor agonists, together with their documented efficacy in lowering blood glucose, indicate that these agents provide a potentially valuable therapeutic option for type 2 diabetes

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3 **Introduction: Safety and tolerability considerations in the pharmacotherapy of type 2**
4 **diabetes**
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7 The conventional pharmacotherapies currently available for the treatment of type 2 diabetes
8 include insulin sensitizers (metformin, thiazolidinediones), insulin secretagogues
9 (sulphonylureas, glinides), α -glucosidase inhibitors, insulin, insulin analogues, and the amylin
10 analogue pramlintide. These treatments have a clearly established ability to reduce blood
11 glucose levels, and are generally safe and well tolerated. However, used as monotherapy or in
12 combination, these medications often result in adverse effects that may reduce glucose-lowering
13 efficacy, pose a risk to patient health, or compromise patient adherence to therapy (Table 1)
14 [1,2]. As used here, the term “safety” will refer to adverse effects that substantially threaten
15 patient health; the term “tolerability” will be applied to adverse effects that primarily impact
16 medication adherence.
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27 Weight gain occurs with the use of sulphonylureas, insulin [3], thiazolidinediones [4,5], and
28 glinides [6]. Studies of insulin show that weight gain following the initiation of diabetes therapy
29 may result in increased insulin resistance, elevated cardiovascular risk, and reduced patient
30 compliance [7]. An increased risk of hypoglycaemic episodes is a well-recognized adverse
31 effect of sulphonylureas, glinides, and insulin, and gastrointestinal adverse effects occur with
32 the use of metformin, α -glucosidase inhibitors, and pramlintide [1]. Furthermore, not every
33 agent is safe for use in all patients. Sulphonylureas, glinides (with the exception of repaglinide),
34 and metformin, for example, should be used cautiously or avoided altogether in patients with
35 renal impairment [8], a common condition in patients with type 2 diabetes. A need consequently
36 exists for new treatment options that may avoid some of these obstacles to effective glucose
37 control.
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3 **Glucagon-like peptide-1–based therapies: mechanisms of action and implications for**
4 **safety and tolerability**
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7 New treatments for type 2 diabetes achieve glucose lowering by novel mechanisms based on the
8 action of the endogenous human hormone glucagon-like peptide (GLP)-1. These agents would
9 accordingly be expected to have different safety and tolerability profiles than other antidiabetes
10 drugs. Physiologic mechanisms of action of GLP-1 suggest specific areas in which GLP-1-
11 based therapies may have advantages or disadvantages relative to other medications.
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17 *Physiology of GLP-1*
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20 GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) are two known endogenous
21 human incretin hormones that play a major role in the maintenance of glucose homeostasis. In
22 healthy individuals, incretins are released from the gastrointestinal tract in response to meal
23 ingestion and stimulate pancreatic insulin secretion. GLP-1 and GIP induce insulin release in a
24 glucose-dependent manner, and thus do not interfere with the normal physiologic counter-
25 response to hypoglycaemia [9].
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32 Incretins reduce glycaemia by additional mechanisms. GLP-1 has been shown to inhibit gastric
33 emptying, thereby slowing the intestinal absorption of nutrients after ingestion [10,11]. The
34 hormone also decreases appetite and food intake via stimulation of anorexigenic neural
35 pathways [12]. Finally, GLP-1 suppresses inappropriately high postprandial levels of glucagon,
36 a characteristic feature of type 2 diabetes [13,14]. Glucagon secretion, which raises blood
37 glucose levels, is activated during hypoglycaemia in healthy individuals, and is suppressed as
38 blood glucose levels rise. In persons with type 2 diabetes, glucagon release is not inhibited in
39 the presence of elevated blood glucose, and consequently exacerbates hyperglycaemia [15].
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3 The glucose-lowering effect of incretin hormones seems to be impaired in type 2 diabetes. In a
4 clinical study of insulin secretion by pancreatic beta-cells, the action of incretin hormones
5 accounted for approximately 60% of the insulin response in healthy subjects following oral
6 glucose ingestion, but for less than 10% in patients with type 2 diabetes [16]. Given that
7 circulating human GLP-1 is degraded rapidly by the enzyme dipeptidyl peptidase (DPP)-4 [17],
8 exhibiting a half-life of only ~2 minutes [18], continuous infusion of GLP-1 would be necessary
9 for effective glycaemic control. As a more practical therapeutic alternative, agents that augment
10 or extend the action of native GLP-1 were developed.

11 *Dipeptidyl peptidase-4 inhibitors*

12  The DPP-4 inhibitors approved for clinical use include saxagliptin, sitagliptin, and vildagliptin.

13 These agents suppress the degradation of endogenous GLP-1 by the enzyme DPP-4. The
14 enzyme DPP-4 is widely expressed in many human tissues; thus, DPP-4 inhibition has a
15 theoretical potential to induce numerous adverse effects [9]. Given the physiologic differences
16 between GLP-1 receptor agonism and DPP-4 inhibition, and the fact that the efficacy and safety
17 of DPP-4 inhibitors have been reviewed recently [19], this paper will focus solely on GLP-1
18 receptor agonists.

Comment [A1]: This paragraph has been moved from below to improve the flow.

19 *GLP-1-based therapies*

20 The GLP-1-based therapies now in clinical use include twice-daily exenatide and once-daily
21 liraglutide, both GLP-1 receptor agonists. These agents stimulate human GLP-1 receptors, but
22 have substantially longer half-lives than endogenous GLP-1 (exenatide: 2.4 hours; liraglutide:
23 13 hours) [20,21]. An extended-release, once-weekly formulation of exenatide, exenatide LAR,
24 is being assessed in phase 3 trials. Several other GLP-1 receptor agonists, including
25 tasoglutide, AVE0010, and albiglutide, are in various stages of development; available data on
26 these agents are limited.

The multiple glucose-lowering mechanisms of GLP-1 receptor agonists promise a potentially valuable place for these agents in the treatment of type 2 diabetes, and their efficacy has in fact been amply documented in large-scale clinical trials (Table 2) [22–34]. The wide distribution of GLP-1 receptors in human tissues, however, suggests a potential for unintended effects. In addition to the pancreas, GLP-1 receptors have been found in the central nervous system, digestive tract, and kidneys, and are weakly expressed in the thyroid gland [35]. The pharmacologic properties of GLP-1 receptor agonists appear to affect the risk/benefit profiles of these agents in several key ways. Given that the stimulation of pancreatic insulin secretion by GLP-1 is dependent on blood glucose levels [36], GLP-1-based therapies offer a decreased risk of hypoglycaemic episodes compared to other treatments. Inhibition of gastric emptying and appetite by GLP-1 not only supports the beneficial effects of GLP-1 receptor agonists on weight, but may also explain the undesirable gastrointestinal symptoms seen with these treatments. As protein-based treatments, GLP-1 receptor agonists carry the possibility of antibody induction and, consequently, of reduced efficacy and/or safety. Finally, concerns have been raised about the potential effects of GLP-1 receptor agonists on the pancreas and the thyroid. The following sections will review recently published data on incidences of adverse effects, to help determine the place of GLP-1 receptor agonists in type 2 diabetes therapy.

Safety

Hypoglycaemia

Similarly to human GLP-1, GLP-1 receptor agonists at clinical doses have been shown to stimulate pancreatic insulin secretion only in the presence of elevated plasma glucose [37,38], and they do not inhibit the counter-regulatory release of glucagon in response to hypoglycaemia [37,39]. GLP-1 receptor agonists would therefore be expected to carry a reduced risk of hypoglycaemic episodes compared to other antidiabetes medications.

Deleted: DPP-4 Inhibitors¶

The DPP-4 inhibitors approved for clinical use include sitagliptin, vildagliptin, and saxagliptin. These agents suppress the degradation of endogenous GLP-1 by the enzyme DPP-4. Substantial differences in the safety profiles of GLP-1 receptor agonists and DPP-4 inhibitors are likely, as the enzyme DPP-4 is widely expressed in many human tissues, and DPP-4 inhibition thus has a theoretical potential to induce numerous adverse effects [9]. Given the physiologic differences between GLP-1 receptor agonism and DPP-4 inhibition, and the fact that the efficacy and safety of DPP-4 inhibitors have been reviewed recently [21], this paper will focus solely on GLP-1 receptor agonists. ¶

Deleted: pharmacologic mechanisms of GLP-1 receptor agonists also suggest a positive safety and tolerability profile relative to other type 2 diabetes therapies

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2 Before assessing the incidence of hypoglycaemia in clinical trials, it is important to understand
3 the definitions used. In clinical trials, “minor” hypoglycaemia is generally an event of
4 hypoglycaemia with a blood glucose reading of <3.1 mmol/L — with the patient being able to
5 treat the event him- or herself. “Major” hypoglycaemia usually denotes requiring the patient to
6 seek the assistance of another individual to treat the event. In most cases, it is a family member
7 who provides a glass of fruit juice or another rapidly absorbed carbohydrate-rich source [40]. In
8 some studies of exenatide reviewed here, instead of “major” events, more restrictive categories
9 designated as “severe” hypoglycaemia were used, which included criteria such as need for
10 assistance from another person, blood glucose below a certain level (eg, <2.8 mmol/L) and/or
11 loss of consciousness. (Table 3) [22, 26–28]

22 *Compared to sulphonylureas*

23
24 Two phase 3 trials indicate that liraglutide has a reduced potential to induce hypoglycaemia
25 relative to sulphonylurea therapy (Table 3) . The proportion of patients who experienced minor
26 hypoglycaemic events (*i.e.*, episodes that did not require assistance from another person) was
27 substantially lower with liraglutide 1.2–1.8 mg/day monotherapy (8–12%) compared to
28 glimepiride 8 mg/day monotherapy (24%) [30]. In a clinical trial in which liraglutide 0.6–1.8
29 mg/day was added to metformin, the rate of minor hypoglycaemic events was ~3%, which is
30 equivalent to the incidence with placebo added to metformin. Another arm of this study
31 evaluated glimepiride 4 mg/day added to metformin, a combination which was associated with a
32 17% rate of minor hypoglycaemia [32]. No major hypoglycaemic events (*i.e.*, episodes
33 necessitating assistance from another person) occurred in either trial. A phase 2 study of
34 liraglutide 0.65–1.90 mg/day as monotherapy in 165 patients with type 2 diabetes also reported
35 no major or minor hypoglycaemic episodes [42].

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2 No clinical trial data are available from a direct comparison of exenatide with a sulphonylurea.
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4 A monotherapy study yielded a 4–5% hypoglycaemia incidence for exenatide 5–10 μg twice
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6 daily and a 1% incidence for placebo, with no severe episodes [22]. Exenatide 5–10 μg twice
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8 daily added to metformin was associated with a 5% incidence of minor hypoglycaemia and no
9
10 severe hypoglycaemia [24].

11 12 *Added to sulphonylureas*

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15 Consistent with the known ability of sulphonylureas to induce hypoglycaemic episodes, the
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17 percentage of patients who experienced hypoglycaemia was generally higher in studies of GLP-
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19 1 receptor agonists added to a sulphonylurea. In one study, mild-to-moderate hypoglycaemia
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21 occurred in 14–36% of patients with type 2 diabetes who received exenatide 5–10 μg twice
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23 daily in addition to a sulphonylurea, and in another study, minor hypoglycaemia occurred in 5–
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25 9% of patients who were given liraglutide 0.6–1.8 mg/day in addition to a sulphonylurea. Major
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27 hypoglycaemia was not observed in the exenatide trial and occurred in a single patient who
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29 received the highest dose (1.8 mg/day) of liraglutide [23,31]. When added to metformin plus a
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31 sulphonylurea, exenatide 5–10 μg twice daily was associated with an overall hypoglycaemia
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33 rate of 19–28%, which included 1 case of severe hypoglycaemia [25]. Liraglutide 1.8 mg/day
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35 added to metformin plus a sulphonylurea produced a minor hypoglycaemia incidence of 27%.
36
37 Major hypoglycaemia was noted in 5 subjects, but in only one of these cases was medical
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39 assistance required [33].

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41 Sulphonylurea dose reduction appears to be a feasible strategy to reduce the risk of
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43 hypoglycaemia during co-therapy with GLP-1 receptor agonists. In the study of exenatide added
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45 to metformin plus sulphonylurea therapy, the incidence of hypoglycaemia was lower in a
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47 subgroup of the exenatide treatment arm randomized to a minimally effective dose of a
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2 sulphonylurea (16–21%) compared to the subgroup randomized to the maximum recommended
3 dose (22–35%). The impact of dose reduction on glucose-lowering efficacy was minimal [25].
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7 *Added to thiazolidinediones*

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9 Compared to sulphonylureas, there is a decreased risk of minor and major hypoglycaemic
10 episodes with thiazolidinediones [43]. The incidence of hypoglycaemia with GLP-1 receptor
11 agonists added to thiazolidinediones is correspondingly low. Exenatide 10 µg twice daily in
12 combination with a thiazolidinedione, with or without metformin, resulted in an overall
13 hypoglycaemia rate of 11%, with no severe episodes reported [27]. Liraglutide 1.2–1.8 mg/day
14 added to a thiazolidinedione plus metformin was associated with an 8–9% incidence of minor
15 hypoglycaemia, which was comparable to placebo; no major episodes of hypoglycaemia were
16 reported [34].
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25 *Compared to insulin*

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27 Liraglutide and exenatide have each been compared to insulin glargine in head-to-head trials.
28 An open-label comparison of exenatide and insulin glargine yielded similar overall rates of
29 hypoglycaemia (7.3 events/patient year with exenatide 10 µg twice daily and 6.3 events/patient
30 year with insulin glargine), with 4 patients in each group experiencing a severe episode [26]. In
31 a phase 3 study comparing liraglutide and insulin glargine, minor hypoglycaemia occurred at a
32 rate of 1.2 events/patient-year in liraglutide-treated patients and 1.3 events/patient-year in those
33 receiving insulin glargine. Major hypoglycaemic events occurred in 5 patients in the liraglutide
34 group and no patient in the insulin glargine group [33].
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44 The data comparing GLP-1 receptor agonists to insulin glargine should be interpreted with
45 caution, given that patients in both the exenatide and liraglutide trials were receiving
46 concomitant sulphonylurea therapy, which is known to increase hypoglycaemia. The apparent
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2 similarity to insulin glargine is nevertheless a potential advantage for GLP-1 receptor agonists,
3 as insulin analogues are associated with a reduced risk of hypoglycaemic episodes relative to
4 Neutral Protamine Hagedorn insulin [44].
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8 *GLP-1 agents head-to-head*

9
10 Results from a 30-week clinical study of exenatide LAR 2 mg once weekly vs exenatide twice
11 daily, either agent used as monotherapy or added to 1 or 2 oral agents, have been published
12 [28]. Minor hypoglycaemia occurred in 5.4% of patients treated with exenatide LAR, compared
13 to 6.1% of patients treated with exenatide twice daily. In the exenatide LAR group, minor
14 episodes occurred only in patients whose background regimens included a sulphonylurea,
15 yielding an incidence of 14.5% in that subgroup vs 0% in the subgroup not taking
16 sulphonylureas. No major episodes of hypoglycaemia were reported in any patient treated with
17 exenatide LAR or exenatide twice daily [28].
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27 A recent head-to-head, open-label study comparing liraglutide 1.8 mg once daily to exenatide
28 10 µg twice daily, each in combination with metformin and/or a sulphonylurea, found that
29 liraglutide was associated with a significantly lower rate of minor hypoglycaemia (1.9 vs 2.6
30 events/subject year; $P = 0.0131$) despite achieving a significantly greater reduction in glycated
31 hemoglobin (HbA_{1c} ; -1.12% vs. -0.79% ; $P < 0.0001$) vs exenatide [29].
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37 *Renal, hepatic, and cardiac safety*

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39 Animal studies have demonstrated that native human GLP-1 is extracted from the body at
40 multiple sites, including the liver, kidneys, lungs, and peripheral tissues [45,46]. Liraglutide,
41 which shares a 97% structural homology with human GLP-1, has a longer half-life than the
42 native hormone, but is eliminated in a similar manner, with no single organ responsible as the
43 major route of removal [47]. The pharmacokinetics of liraglutide are therefore not substantially
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2 affected by hepatic insufficiency [48] or renal impairment [49], and no dosage adjustment is
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4 required for mild renal impairment in the EU Summary of Product Characteristics. EU labelling
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6 further states that, due to a lack of therapeutic experience in patients with hepatic impairment or
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8 moderate or greater renal dysfunction, use of liraglutide is not recommended for these
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10 populations [50].

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12 Exenatide is a synthetic version of a protein expressed in the saliva of the Gila monster, and has
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14 only a 53% amino acid sequence homology with human GLP-1. The pharmacokinetics of
15
16 exenatide differ substantially from those of the native molecule; exenatide is cleared exclusively
17
18 by glomerular filtration, as demonstrated in a porcine model [46]. Clearance of exenatide was
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20 significantly reduced (by 84%) in patients with end-stage renal disease, and a single 5- μ g dose
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22 was poorly tolerated in this patient group [51]. Accordingly, exenatide is not recommended for
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24 use in patients with severe renal impairment or end-stage renal disease in US or EU labelling
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26 [20,52].

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28 In response to postmarketing reports of altered renal function in patients taking exenatide, the
29
30 US Food and Drug Administration (FDA) has requested an addition to the prescribing
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32 information, whereby healthcare providers should monitor patients taking exenatide for the
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34 development of renal dysfunction [53]. The US drug label notes that, as exenatide is cleared
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36 renally, it is unlikely that hepatic dysfunction would affect its pharmacokinetics [20].

Deleted: The authors of a recent case report stated that exenatide 5 μ g twice daily worsened kidney function parameters in a patient with pre-existing moderate renal impairment. Although additional potential contributory factors in this case were noted, such as polypharmacy and the off-label use of exenatide with insulin, the authors concluded that exenatide should be used cautiously in patients with even mild-to-moderate renal impairment [50].

Deleted: Given that renal dysfunction is common in patients with type 2 diabetes, prescribers should be aware of this potential risk.

37
38 There are few data available on the cardiovascular safety of GLP-1 receptor agonists. A
39
40 congress abstract indicates that liraglutide does not prolong QTc interval [54]. A study in mice
41
42 demonstrated beneficial effects of liraglutide on coronary function, including enhanced
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44 cardiomyocyte survival, reduced infarct size, and improved survival following induced coronary
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46 artery occlusion [55]. Data published in a letter in *Diabetic Medicine* suggests that liraglutide
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48 improves certain biomarkers associated with increased cardiovascular risk [56]. Exenatide has
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2 exhibited the ability to attenuate ischemia-reperfusion injury in the rat heart and prolong
3 survival in mice with artificially induced dilated cardiomyopathy [57,58]. Liraglutide has met
4 recently updated FDA approval criteria regarding cardiovascular risks in antidiabetes therapies.
5
6 Given the low rates of cardiovascular events observed in liraglutide clinical trials, the agency
7
8 has required an additional clinical cardiovascular safety study post approval [59].
9
10

11 *Drug interactions*

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13 Clinical studies have demonstrated consistently favourable drug-interaction profiles for GLP-1
14
15 receptor agonists. This is an important consideration for patients with type 2 diabetes, who
16
17 frequently have comorbid conditions and require complex pharmaceutical regimens. Of
18
19 particular note, GLP-1 receptor agonists do not appear to substantially affect the
20
21 pharmacokinetics of many cardiovascular drugs, which play a critical role in reducing the risk
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23 of microvascular and macrovascular complications in type 2 diabetes [8].
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26 Exenatide

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28 An open-label pharmacokinetic study demonstrated that exenatide 10 μg twice daily
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30 significantly decreased the bioavailability of concomitantly administered lovastatin in healthy
31
32 subjects. However, a retrospective analysis of data from three phase 3 clinical trials found no
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34 significant difference between exenatide and placebo in patient cholesterol levels or statin
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36 dosages. The authors concluded that co-administration of exenatide does not require adjustment
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38 of statin dosage [60].
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42 Exenatide exerted no significant effect on warfarin plasma concentration-time profiles in a study
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44 of healthy Asian individuals, although a minor decrease in warfarin anticoagulant effect was
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46 noted [61]. An open-label study in healthy subjects, which evaluated the effects of exenatide on
47
48 digoxin pharmacokinetics, found that the maximum plasma concentration of digoxin was
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2 significantly decreased by 17% after exenatide co-administration, but concentrations remained
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4 in the therapeutic range. Digoxin dosage adjustment was not considered warranted [62].
5

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7 In a randomised, placebo-controlled study in healthy subjects, exenatide slowed the rate of
8
9 paracetamol absorption, but had little effect on the extent of absorption [63].
10

11 Liraglutide

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14 Liraglutide was administered to healthy subjects to evaluate its effects on the pharmacokinetics
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16 of 4 representative drug classes (atorvastatin, lisinopril, digoxin, and griseofulvin) with different
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18 solubility and permeability properties. The absorption kinetics of the oral drugs were altered
19
20 slightly in the presence of liraglutide, as would be expected from its effects on gastric emptying.
21
22 However, in all cases, the effects were minor and did not require dose adjustment [64].
23

24
25 Compared to placebo, liraglutide lowered the maximum plasma concentration of
26
27 ethinylestradiol (by 12%) and levonorgestrel (13%) in healthy postmenopausal women after oral
28
29 contraceptive dosing, and delayed time to maximum plasma concentration of both agents by
30
31 approximately 1.5 hours. No clinically relevant change in overall exposure was observed,
32
33 however, and thus liraglutide is not expected to impact contraceptive efficacy [65].
34

35
36 Liraglutide, relative to placebo, lowered the maximum plasma concentration of paracetamol and
37
38 slightly delayed the time to maximum concentration. However, overall exposure was equivalent
39
40 [66].
41

42 *Antibodies*

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44 Protein-based therapies, including insulin, have the potential to induce antibody formation if the
45
46 molecules differ from the native human protein. Liraglutide shares high (97%) amino-acid
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48 sequence homology to native human GLP-1; homology is lower for exenatide (53%). The
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2 immune response can be problematic from a clinical standpoint — particularly if the antibodies
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4 neutralize the efficacy of the biotherapeutic agent or cause a general immune reaction (*e.g.*,
5
6 allergy, anaphylaxis) [67].
7

8
9 Antibodies developed in 41–49% of patients treated with exenatide in phase 3 studies. The
10
11 presence of antibodies did not affect therapeutic efficacy or increase adverse events [23–25].
12
13 The exenatide labelling does note, however, that efficacy was attenuated in the small percentage
14
15 of patients who developed high-titre antibodies in these trials. In all, 6% of patients treated with
16
17 exenatide developed high-titre antibodies, of whom half (3% of total patients) had a reduced
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19 treatment response [20]. A recent study found anti-exenatide antibodies in 27–28% of patients
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21 who received exenatide 5–10 μg twice daily as monotherapy, but with no apparent effects on
22
23 glucose-lowering efficacy or safety [22].
24

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26 A single case report has disclosed the occurrence of anaphylaxis in a patient treated with
27
28 exenatide. The patient, who had a history of allergy and asthma, required epinephrine and
29
30 corticosteroids [68].
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33 The likelihood of an immune response appears to be greater with exenatide LAR than with
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35 twice-daily exenatide. A 15-week clinical trial of exenatide LAR ($n = 45$ subjects) yielded an
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37 antibody formation rate of 67%. Analysis of individual subjects did not reveal a correlation
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39 between antibody generation and either efficacy or safety [69]. A subsequent 30-week, large-
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41 scale clinical trial ($n = 295$ subjects) found anti-exenatide antibodies in 74% of patients
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43 receiving exenatide LAR, and high-titre anti-exenatide antibodies in 24% of patients who
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45 received this agent. Reduction in $\text{HbA}_{1\text{C}}$ appeared to be attenuated in the group with high-titre
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47 antibodies (–1.4%) compared to patients with low-titre (–2.0%) or no (–1.9%) antibodies,
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49 although no statistical analysis was provided [28]. Additional data are expected from phase 3
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2 studies that have been completed; the results of these trials are not yet available as journal
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4 publications [70].
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7 Compared to rates observed in exenatide trials, antibody formation was lower in phase 3
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9 liraglutide trials, ranging from 9–13%, due to liraglutide's higher homology to native human
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11 GLP-1. There was no association between antibody generation and efficacy [31,33].
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14 Immunogenicity thus does not appear to be a major safety concern for GLP-1 receptor agonists,
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16 and antibody generation does not impact glucose-lowering efficacy, except in the small
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18 proportion of patients who develop high antibody titres with exenatide. There has so far been
19
20 only a single published case of allergy or anaphylaxis, which was reported with exenatide.
21

22 *Pancreatitis*

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24 Reliable epidemiologic data on the incidence of acute pancreatitis in patients with type 2
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26 diabetes are scarce. Even studies of the general population show substantially different
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28 incidence rates. A systematic review of data from European epidemiologic studies, for example,
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30 found that the annual incidence of first pancreatitis attack ranged from 4.21 to 24.2 per 100,000
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32 persons in the United Kingdom and from 15.9 to 45.33 per 100,000 persons in European
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34 countries other than the United Kingdom. Reasons for the apparently higher incidence outside
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36 the United Kingdom were uncertain [71].
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39 A retrospective epidemiologic study from the United States showed a threefold increase in
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41 pancreatitis cases in type 2 diabetic patients compared to the general population [72]. Known
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43 pancreatitis risk factors — such as biliary disease, hypertriglyceridemia [73], obesity, and use of
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45 sulphonylureas [74] — are more common in patients with type 2 diabetes than the population as
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47 a whole.
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2 Cases of acute pancreatitis have been reported in patients with type 2 diabetes treated with
3 exenatide. Based on 30 reports from use outside clinical trials, submitted from April 2005
4 through December 2006, the FDA requested that a warning be added to the exenatide product
5 label cautioning prescribers to be vigilant for the possibility of pancreatitis [75,76]. As of
6 December 2007, the postmarketing incidence of pancreatitis in patients receiving exenatide was
7 27 events per 100,000 patient-years [77]. As this incidence is within the range for the general
8 population, and would hardly justify a label warning, the FDA based its decision on an apparent
9 temporal association between exenatide use and pancreatitis in the reported cases [75]. A more
10 recent claims-based safety surveillance system reported no difference in risk for acute
11 pancreatitis between exenatide and sitagliptin and the comparators metformin and glyburide, a
12 sulphonylurea. The estimated risk of acute pancreatitis among exenatide patients was calculated
13 at 0.13% [78]. In the period since it requested the label change, the FDA has disclosed 6 cases
14 of necrotizing or haemorrhagic pancreatitis in association with the use of exenatide, 2 of which
15 were fatal [79].
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29 The incidence of pancreatitis in patients treated with exenatide was higher during clinical
30 development: 170 cases per 100,000 patient-years. Yet this rate was lower than that observed
31 for placebo-treated patients (300 cases per 100,000 patient-years) or insulin-treated patients
32 (200 cases per 100,000 patient-years) in the same clinical trials [76]. It therefore seems likely
33 that the increased incidence of pancreatitis in the patients receiving exenatide, placebo, or
34 insulin is attributable to a pre-existing elevation in risk among patients with type 2 diabetes.
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41 Analysis of individual pancreatitis cases in patients treated with exenatide supports this view.
42 Of the first 30 pancreatitis cases from spontaneous use reported to the FDA, 90% involved
43 known contributory factors, including obesity, gallstones, alcohol use, and hypertriglyceridemia
44 [75]. A published case report of pancreatitis following exenatide initiation also cited pre-
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existing risk factors, *i.e.*, obesity and use of medication known to have an association with pancreatitis [80].

A total of 7 pancreatitis cases occurred in 4257 liraglutide-treated patients in the liraglutide development program, compared to 1 case among 2381 patients in comparator groups. Given the small number of cases, it is difficult to draw conclusions about possible causation, and the FDA has required additional postmarketing mechanistic studies in animals and epidemiologic evaluation [59].

Deleted: Initial reports from the liraglutide phase 3 development program suggest that the incidence of acute pancreatitis with liraglutide and comparator agents is consistent with the expected incidence for a type 2 diabetes population.

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Deleted: cannot scientifically be determined whether treatment with liraglutide may or may not have a weak association with the development of pancreatitis [30–32]

Effects on the thyroid

C-cells present in the thyroid produce the hormone calcitonin, which regulates bone resorption [81]. In studies of mice and rats, liraglutide induced hyperplasia and adenomas of the C-cell.

Carcinoma of the C-cell was observed at the highest liraglutide dose in female mice and at several doses in male and female rats. These abnormalities were preceded by acute and chronic increases in calcitonin, which can be regarded as a biomarker of C-cell activation and C-cell mass. Similar findings did not occur in nonhuman primates at high liraglutide doses [82].

In vitro experiments suggest that C-cell neoplasia are mediated through the GLP-1 receptor. Rats appear to have a much higher density of GLP-1 receptors on their C-cells than humans.

Preclinical data also demonstrate that the GLP-1 receptor of the C-cell is a functional receptor in rodents, whereas this is not the case in primates or humans [82].

To assess the potential role of GLP-1 agonists like liraglutide on human C-cell function, calcitonin screening was performed in individuals included in the liraglutide development program. At up to 2 years of liraglutide exposure, calcitonin levels were similar between patients receiving liraglutide and comparator treatments [59]. These findings and the preclinical data suggest that, unlike in rodents, GLP-1 receptor agonists do not activate the human C-cell, and that

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2 the GLP-1 receptor is not a functional receptor in the human thyroid [82]. The US prescribing
3 information for liraglutide lists a history of medullary thyroid carcinoma or Multiple Endocrine
4 Neoplasia syndrome type 2 as contraindications to use [83]
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8 **Tolerability**

9 *Gastrointestinal adverse events*

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12 Like other type 2 diabetes therapies, GLP-1 receptor agonists have been associated with
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14 gastrointestinal adverse effects, such as nausea, vomiting, and diarrhoea. Clinical trial data on
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16 exenatide and liraglutide can enable prescribers to assess the impact of gastrointestinal
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18 symptoms on the potential role of these agents in treatment.
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22 Exenatide 5–10 μg twice daily as monotherapy was associated with incidences of 3–13% for
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24 nausea, 4% for vomiting, and 0–3% for diarrhoea (Table 4) [22]. Nausea incidence was 36–
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26 57%, vomiting occurred in 10–17% of patients, and diarrhoea was reported in 8–17% of
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28 patients enrolled in clinical trials of exenatide 5–10 μg twice daily added to metformin and/or a
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30 sulphonylurea [23–26]. Nausea incidence correlated with the dosage of exenatide. These data
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32 are consistent with rates from a study of exenatide 10 μg twice daily added to a
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34 thiazolidinedione, with or without metformin (nausea, 40%; vomiting, 13%; diarrhoea, 6%)
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36 [27]. Gastrointestinal symptoms were short-lived, however. Across studies, nausea was most
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38 frequent during the first 8 weeks of therapy and then declined [23–27].
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41 A comparative clinical trial of exenatide LAR and exenatide twice daily indicated that exenatide
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43 LAR was associated with incidences of 26.4% for nausea, 10.8% for vomiting, and 13.5% for
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45 diarrhoea. The incidence of nausea for exenatide twice daily (34.5%) significantly exceeded that
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47 observed with exenatide LAR. Nausea with both treatments was predominantly mild in intensity
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49 [28].
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2 Liraglutide has demonstrated a similar profile of transient gastrointestinal adverse effects [29–
3 34]. In phase 3 studies (as monotherapy or in combination with oral agents), liraglutide 0.6–1.8
4 mg once daily was associated with an incidence of 10–40% for nausea, 4–17% for vomiting,
5 and 8–19% for diarrhoea [30–34]. Across studies, nausea occurred early during treatment, and
6 the percentage of patients experiencing symptoms decreased by week 4 [30–34]. A head-to-
7 head comparative study yielded nausea incidences of 28% for exenatide 10 µg twice daily and
8 26% for liraglutide 1.8 mg once daily. The incidence rate of nausea reported in the liraglutide
9 group declined after a few weeks, in contrast to a relatively sustained rate reported with
10 exenatide throughout the trial duration of 26 weeks [29].

11
12 The development of nausea during use of exenatide or liraglutide is likely due to the inhibition
13 of gastric emptying associated with these agents [84,85]. Deceleration of gastric transit and
14 resultant increased feelings of satiety may also contribute to the beneficial weight loss that
15 occurs with use of GLP-1 receptor agonists. The occurrence of gastrointestinal adverse effects
16 and weight loss do not appear to be related, however, as the nausea associated with GLP-1
17 receptor agonists is transient, whereas the weight effects appear to be sustained. In three phase 3
18 studies of exenatide, a weight reduction from baseline to week 30 in the range of 0.9 to 2.8 kg
19 was observed. No correlation between weight loss and the presence of nausea was found [23–
20 25]. Similarly, a weight loss of 1.0–3.2 kg from baseline to endpoint occurred in five phase 3
21 liraglutide studies, which were 26 to 52 weeks in duration [29,30,32–34]. Patients treated with
22 liraglutide 0.6–1.2 mg/day in another phase 3 study experienced a slight (<1 kg) weight gain,
23 most likely due to the use of sulphonylurea background therapy [31]. As with exenatide, no
24 correlation between weight loss and the occurrence of nausea was found [30,32].

25
26 Gastrointestinal symptoms are therefore a frequent but transient adverse effect of treatment with
27 GLP-1 receptor agonists, and do not present a major obstacle to the use of these agents. Nausea
28 is the most common symptom, whereas more inconvenient effects such as vomiting and
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2 diarrhoea occur less frequently. Titration of exenatide has been found to reduce gastrointestinal
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4 complaints following treatment initiation [86], and exenatide prescribing information
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6 accordingly recommends starting treatment at a 5- μ g twice daily dose and increasing to 10- μ g
7
8 twice daily based on clinical response [20].
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10 Unlike GLP-1 receptor agonists, DPP-4 inhibitors are not associated with gastrointestinal
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12 complaints, but neither are they associated with weight loss. These class differences may be
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14 attributable to the greater degree of GLP-1 receptor stimulation with GLP-1 receptor agonists
15
16 than with DPP-4 inhibitors [9]
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18 *Injection-site reactions*

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21 Few data are available on the incidence of injection-site reactions with GLP-1 receptor agonists,
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23 but existing information does not suggest that this is a significant tolerability concern. Phase 3
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25 studies of exenatide or liraglutide do not report local reactions in discussions of common
26
27 adverse events [23–25,30–32]. A study that assessed different dosing regimens of exenatide ($n =$
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29 123 subjects) reported that mild-to-moderate bruising occurred in 7.3% of patients treated with
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31 the drug [85]. Exenatide LAR, which consists of microspheres composed of exenatide and a
32
33 biodegradable medical polymer, was associated with more frequent injection-site bruising (7%
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35 at the 2.0-mg dose and 13% at the 0.8-mg dose) compared to placebo injection (0%) [71]. A
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37 trial that compared the two exenatide formulations found injection-site bruising in 4.7% of
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39 patients receiving exenatide LAR and 10.3% of those who received exenatide twice daily.
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41 Injection-site pruritus, typically mild in intensity, occurred in 17.6% of subjects in the exenatide
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43 LAR group and 1.4% of those in the exenatide twice-daily group [28].
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45 **Conclusions**

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2 The novel, incretin-based, mechanism of action of GLP-1 receptor agonists mitigates common
3 adverse effects associated with other type 2 diabetes therapies. GLP-1 receptor agonists have
4 been shown to increase endogenous insulin secretion, but unlike sulphonylureas, the newer
5 agents exert this effect only in the presence of hyperglycaemia. Furthermore, GLP-1 receptor
6 agonists do not interfere with the natural physiologic response to low blood glucose levels (*i.e.*,
7 glucagon secretion). Taken together, these observations explain the low propensity of exenatide
8 and liraglutide induction of hypoglycaemic episodes.
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16 GLP-1 receptor agonists have also been shown to achieve weight loss, in contrast to the weight
17 increase associated with other therapeutic classes. The weight-reducing effect of GLP-1 receptor
18 agonists may be related to their inhibition of gastric emptying, which increases feelings of
19 satiety. The gastric effects of GLP-1 receptor agonists are also likely to be the cause of the
20 gastrointestinal symptoms associated with these therapies. Whereas weight loss has been
21 sustained to at least a year in clinical trials, the gastrointestinal adverse effects subside after
22 several weeks of treatment. Prescribers may mitigate these symptoms by gradually titrating
23 GLP-1 receptor agonists in patients initiating therapy.
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32 GLP-1 receptor agonists appear to be safe for use in type 2 diabetes patients with hepatic
33 impairment. With respect to renal impairment, exenatide is excreted via the kidneys and should
34 be used with caution in patients with renal insufficiency. Liraglutide, which more closely
35 resembles native human GLP-1 in structure and pharmacokinetics, does not have a single major
36 route of elimination and appears to be safe for use in patients with decreased renal function.
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40 Both GLP-1 receptor agonists have a benign drug-interaction profile, an important consideration
41 for type 2 diabetes patients, who must often manage complex pharmaceutical regimens.
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Antibody induction by exenatide twice daily and liraglutide once daily has shown little impact on efficacy or safety. Antibody generation rates with exenatide once weekly seem somewhat higher, but the implications of these observations for clinical use remain to be established.

Reports of pancreatitis warrant vigilance for signs and symptoms of pancreatic dysfunction in patients treated with GLP-1 receptor agonists. The likelihood of pancreatitis is elevated in patients with type 2 diabetes relative to the general population, however, and the role of GLP-1 receptor agonist therapy versus pre-existing risk factors in the cases reported to date is uncertain. Additional clinical trial and postmarketing data will further clarify the pancreatic safety profile of these agents.

Safety and tolerability data on GLP-1 receptor agonists, together with their documented efficacy in lowering blood glucose, indicate that these agents provide a potentially valuable therapeutic option for type 2 diabetes. The favourable effects of these therapies on weight and risk of hypoglycaemia, relative to older treatments, promise to fill a previously unmet need in the management of type 2 diabetes. As more trial data become available and clinical use increases, the role of GLP-1 receptor agonists in meeting the treatment challenges of type 2 diabetes will be more clearly defined.

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Table 1. Common adverse effects of established diabetes therapies. Adapted from Nathan *et al.* [1,2]

Pharmacotherapy	Common adverse effects
Metformin	Gastrointestinal
Sulphonylureas	Weight gain, hypoglycaemia
Thiazolidinediones	Weight gain, fluid retention
α -Glucosidase inhibitors	Gastrointestinal
Glinides	Weight gain, hypoglycaemia
Pramlintide	Gastrointestinal
Insulin	Weight gain, hypoglycaemia

Table 2. Phase 3 data on the glucose-lowering efficacy of GLP-1 receptor agonists

Drug Dosage ^a	Study length	Baseline HbA _{1c} (%)	HbA _{1c} change from baseline (%)	Weight change from baseline (kg)
Exenatide				
10 µg twice daily (monotherapy) [22]	24 weeks	7.8	-0.9	-3.1
10 µg twice daily (added to sulphonylurea) [23]	30 weeks	8.6	-0.86	-1.6
10 µg twice daily (added to metformin) [24]	30 weeks	8.18	-0.8	-2.8
10 µg twice daily (added to sulphonylurea + metformin) [25]	30 weeks	8.5	-0.77	-1.6
10 µg twice daily (added to sulphonylurea + metformin) [26]	26 weeks	8.2	-1.11	-2.3

10 μ g twice daily (added to thiazolidinedione \pm metformin) [27]	16 weeks	7.89	-0.89	-1.8
10 μ g twice daily (monotherapy or added to 1 or 2 oral agents) [28]	30 weeks	8.3	-1.5	-3.6
10 μ g twice daily (added to metformin and/or sulphonylurea) [29]	26 weeks	8.1	-0.79	-2.9
Exenatide LAR				
2 mg once weekly (monotherapy or added to 1 or 2 oral agents) [28]	30 weeks	8.3	-1.9	-3.7
Liraglutide				
1.8 mg once daily (monotherapy) [30]	52 weeks	8.3	-1.14	-2.4

1.8 mg once daily (added to sulphonylurea) [31]	26 weeks	8.5	-1.1	-0.2
1.8 mg once daily (added to metformin) [32]	26 weeks	8.4	-1.0	-2.8
1.8 mg once daily (added to sulphonylurea + metformin) [33]	26 weeks	8.3	-1.33	-1.8
1.8 mg once daily (added to thiazolidinedione + metformin) [34]	26 weeks	8.6	-1.48	-2.0
1.8 mg once daily (added to metformin and/or sulphonylurea) [29]	26 weeks	8.2	-1.12	-3.2

^aHighest drug dosage used in each study.

Table 3. Incidence of hypoglycaemia in clinical trials of GLP-1 receptor agonists

Monotherapy					
	Liraglutide 1.2–1.8 mg/d	Glimepiride 8 mg/d		Exenatide 5–10 µg bid	Placebo
Minor hypos (% subjects) [30]	8–12	24	All hypos (% subjects) [22]	4–5	1
Major hypos ^a (% subjects) [30]	0	0	Severe hypos ^b (% subjects) [22]	0	0
Added to metformin					
	Liraglutide 0.6–1.8 mg/d	Glimepiride 4 mg/d		Exenatide 5–10 µg bid	Placebo
Minor hypos (% subjects) [32]	~3	17	Mild/moderate hypos (% subjects) [24]	5	5
Major hypos ^a (% subjects)	0	0	Severe hypos ^a (% subjects)	0	0

[32]			[24]		
Added to sulphonylurea					
	Liraglutide 0.6–1.8 mg/d	Placebo		Exenatide 5–10 µg bid	Placebo
Minor hypos (% of subjects) [31]	5–9	3	Mild/moderate hypos (% of subjects) [23]	14–36	3
Major hypos^a (# of events) [31]	1	0	Severe hypos^a (# of events) [23]	0	0
Added to metformin + sulphonylurea, vs. placebo					
	Liraglutide 1.8 mg/d	Placebo		Exenatide 5–10 µg bid	Placebo
Minor hypos (% subjects) [33]	27	17	Overall hypos (% subjects) [25]	19–28	13
Major hypos^a (# of subjects)	5	0	Severe hypos^a (# of events) [25]	1	0

[33]					
Added to thiazolidinedione ± metformin					
	Liraglutide 1.2–1.8 mg/d	Placebo		Exenatide 10 µg bid	Placebo
Minor hypos (% subjects) [34]	8–9	5	Overall hypos (% subjects) [27]	11	7
Major hypos^a (% subjects) [34]	0	0	Severe hypos^c (% subjects) [27]	0	0
Added to metformin + sulphonylurea, vs. insulin glargine					
	Liraglutide 1.8 mg/d	Insulin Glargine^d		Exenatide 10 µg bid	Insulin Glargine^e
Minor hypos (events/subject year) [33]	1.2	1.3	Overall hypos (events/subject year) [26]	7.3	6.3
Major hypos (# of subjects) ^a [33]	5	0	Severe hypos^c (# of subjects) [26]	4	4
Monotherapy, added to 1 oral agent, or added to 2 oral agents					

Deleted: 27
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			Exenatide 10 µg bid	Exenatide 2 mg/week
		Minor hypos (% subjects) [28]	6	5
		Major hypos^f (% subjects) [28]	0	0
Added to metformin and/or sulphonylurea				
	Liraglutide 1.8 mg/d		Exenatide 10 µg bid	
Minor hypos (events/ subject year) [29]	1.9		Minor hypos (events/subject year) [29]	2.6

Hypos = hypoglycaemic episodes; d = day; bid = twice daily.

^aRequired assistance from a third party, including intravenous glucose or intramuscular glucagon.

^bRequired assistance from a third party and associated with an SMBG <3 mmol/L or prompt recovery after oral carbohydrate, glucagon injection, or glucose.

^cRequired assistance from another person and had a blood glucose measurement <2.8 mmol/L or had promptly recovered after an oral carbohydrate or glucagon injection or intravenous glucose.

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^dInsulin glargine was titrated individually according to a guideline adapted from Davies *et al.*⁴²

^eInsulin glargine was self-titrated by patients to achieve a fasting blood glucose level of <5.6 mmol/L.

^fExperienced loss of consciousness, seizure, or coma which resolved after administration of glucagon or glucose, or required third-party assistance to resolve, and a glucose concentration of <3 mmol/L.

Deleted: Hypoglycaemic events were reported as overall hypoglycaemic events, minor/mild-to-moderate events, or major/severe events. Events were categorized as major/severe if assistance from another person was necessary for treatment of the hypoglycaemia. ¶

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Table 4. Incidence of gastrointestinal adverse events with GLP-1 receptor agonists (% of subjects)

Drug Dosage	Nausea	Vomiting	Diarrhoea
Exenatide 5–10 μg twice daily (monotherapy)	3–13	4	0–3
Placebo [22]	0	0	0
Exenatide 5–10 μg twice daily (added to SU)	39–51	10–13	9–11
Placebo [23]	7	2	4
Exenatide 5–10 μg twice daily (added to MET)	36–45	11–12	12–16
Placebo [24]	23	4	8
Exenatide 5–10 μg twice daily (added to MET + SU)	39–48	14–15	10–17
Placebo [25]	21	4	6
Exenatide 10 μg twice daily (added to MET + SU)	57	17	8
Insulin glargine [26]	9	4	3

Exenatide 10 μ g twice daily (added to TZD \pm MET)	40	13	6
Placebo [27]	15	1	3
Exenatide 2 mg once weekly (monotherapy, or added to 1 or 2 oral agents)	26	11	14
Exenatide 10 μ g twice daily (monotherapy, or added to 1 or 2 oral agents) [28]	34	19	13
Exenatide 10 μ g twice daily (added to MET and/or SU)	28	not reported	not reported
Liraglutide 1.8 mg/day (added to MET and/or SU) [29]	26	not reported	not reported
Liraglutide 1.2–1.8 mg/day (monotherapy)	28–29	9–12	16–19
Glimepiride 8 mg/day [30]	8	4	9
Liraglutide 0.6–1.8 mg/day (added to SU)	10 ^a	4 ^a	8 ^a
Placebo [31]	2	not reported	not reported

Liraglutide 0.6–1.8 mg/day (added to MET)	11–19	5-7	8-15
Placebo [32]	not reported	1	4
Liraglutide 1.8 mg/day (added to MET + SU)	14	6	10
Placebo [33]	4	4	5
Liraglutide 1.2–1.8 mg/day (added to TZD + MET)	29-40	7-17	not reported
Placebo [34]	not reported	not reported	not reported

SU = sulphonylurea; MET = metformin; TZD = thiazolidinedione.

^aData were reported only for the dose group with the highest incidence (liraglutide 1.2 mg/day).