# GLP-1 RAs:
## Real-World Patient-Care Strategies for Type 2 Diabetes

## Clinical Companion Guide

### Summary

| Medication FDA Approval | Dose | Weight loss | HbA1c | Dosing Frequency | Route of administration |
|---|---|---|---|---|---|
| Exenatide 2005 | 5-10 µg | -1.67 kg | -0.70% | Twice daily with meals | Multiuse pen (SQ) |
| Liraglutide 2010 | 0.6-1.8 mg | -2.3 kg | -1.15% | Daily | Multiuse pen (SQ) |
| Exenatide weekly 2012 | 2 mg | -1.27% | -1.08% | Weekly | Single use pen (SQ) |
| Dulaglutide 2014 | 0.75-4.5 mg | -4.6 kg | -1.8% | Weekly | Single use pen (SQ) |
| Semaglutide 2017 | 0.25-2 mg | -6.4 kg | -2.1% | Weekly | Multiuse pen (SQ) |
| Semaglutide 2019 | 3, 7, 14 mg | -3.4 kg | -0.70% | Daily (empty stomach first in the morning) | Oral |

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## Pharmacokinetic Properties

| Drug<br>(FDA approval date)<br>Labeled indication | Administration \| Device \| Dosing*<br>Bioavailability (F) \| Time to peak concentration ($T_{max}$) \| Half-life ($t½$) \| Elimination \| Renal considerations | |
|---|---|---|
| Dulaglutide<br>(2014)<br>T2D<br>Adult and peds<br>CVRR in people with CVD and in those with high risk | subQ, Pen<br>*T2D, adults:* 0.75 mg once weekly x4 to 8 weeks → 1.5 mg once weekly if needed for glycemic control for at least 4 weeks → 3 mg weekly x at least 4 weeks → 4.5 mg maximum maintenance dose if need for glycemic control<br>*T2D, children/adolescents ≥ 10 to < 18 years:* 0.75 mg once weekly x4 to 8 weeks → 1.5 mg once weekly if needed for glycemic control | |
| | *F*: 47-65%<br>$T_{max}$: 24-72 h<br>$t½$: 5 d | Elimination: Proteolytic degradation by DPP-4, endopeptidases<br>No dose adjustment for altered renal function<br>Use caution when initiating/escalating doses<br>Unlikely to be dialyzable. No supplemental dose necessary. |
| Exenatide<br>(2005)<br>T2D | subQ, Pen<br>*T2D, adults:* 5 µg BID before breakfast and dinner, or within 60 min of 2 main meals ≥ 6 hours apart | |
| | *F*: 55%<br>$T_{max}$: 2-3 h<br>$t½$: 3.5 h | Elimination: Proteolytic degradation by DPP-4, endopeptidases<br>Glomerular filtration<br>Renal function < 30 mL/min, ESRD use not recommended |
| Exenatide ER<br>(2012)<br>T2D<br>Adults and peds | subQ, Pen<br>*T2D, adults, children ≥ 10 years; adolescents:* 2 mg once weekly without regard to meals | |
| | Gradually released from microspheres with $T_{max}$ at week 6-7<br>Plasma concentration generally falls below detectable levels about 10 weeks after discontinuation | |
| Semaglutide<br>(2017/2021)<br>T2D<br>Weight management, chronic | subQ, Pen<br>*T2D, adults:* Once weekly dosing x4 weeks, then may increase dose every 4 weeks as tolerated<br>0.25 → 0.5 → 1.0 → to maximum 2.0 mg<br>*Weight management, adults and children/adolescents ≥ 12 to < 18 years:*<br>As above to 2.4 mg once weekly maintenance dose | |

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| Drug<br>(FDA approval date)<br>Labeled indication | Administration \| Device \| Dosing*<br>Bioavailability (F) \| Time to peak concentration ($T_{max}$) \| Half-life ($t_{½}$) \| Elimination \| Renal considerations | |
|---|---|---|
| | *F*: 89%<br>$T_{max}$: 1-3 d<br>$t_{½}$: 5.7-6.7 d | Proteolytic cleavage of peptide backbone; sequential oxidation of fatty acid side chain<br>No dose adjustment for altered renal function<br>Use caution when initiating/escalating doses<br>Unlikely to be dialyzable. No supplemental dose necessary. |
| Semaglutide, oral<br>(2019) | Oral tablet<br>T2D, adults: Initial 3 mg daily x30 day → 7 mg daily x 30 days → 14 mg maximum daily maintenance dose | |
| | *F*: 0.4% to 1.0%<br>$T_{max}$: 1 h<br>$t_{½}$: 5.7-6.7 d | Elimination as for semaglutide injection |
| Tirzepatide<br>GIP/GLP-1 RA<br>(2022)<br>T2D | subQ, Pen<br>T2D, adults: 2.5 mg once weekly x4 weeks → increase by 2.5 mg once weekly every 4 weeks → to maximum 15 mg/week maintenance dose | |
| | *F*: 80%<br>$T_{max}$: 8-72 h<br>$t_{½}$: 5 d | Proteolytic cleavage of peptide backbone; sequential oxidation of fatty acid side chain, amid hydrolysis<br>No dose adjustment for altered renal function<br>Use caution when initiating/escalating doses<br>Unlikely to be dialyzable. No supplemental dose necessary. |
| *Dose escalation recommendations: Start with low (subtherapeutic) dose and gradually increase as tolerated to maintenance dose<br>GLP-1 RAs and the GIP/GLP-1 dual agonist are recommended adjuncts to diet and exercise | | |
| Liraglutide<br>(2010); T2D<br>Adults and peds<br>Weight management, chronic<br>Adults and peds | subQ, Pen<br>*T2D, adults, children ≥ 10 years, adolescents:* 0.6 mg once daily x1 week → increase by 0.6 mg daily in weekly increments → to maximum 1.2 mg daily maintenance dose<br>*Weight management, adults, children ≥ 12 years, adolescents:* as above → increase to maximum 3 mg once daily as tolerated if goal weight not achieved | |
| | F: 55%<br>$T_{max}$: 10-14 h<br>$t_{½}$: 1-3 d | Elimination:<br>Proteolytic degradation by DPP-4, endopeptidases<br>No dose adjustment for altered renal function<br>Use caution when initiating/escalating doses<br>Unlikely to be dialyzable. No supplemental dose necessary. |

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| Drug (FDA approval date) Labeled indication | Administration \| Device \| Dosing* Bioavailability (F) \| Time to peak concentration ($T_{max}$) \| Half-life ($t_{½}$) \| Elimination \| Renal considerations | |
|---|---|---|
| Insulin degludec - Liraglutide (iDegLira) (2016) T2D | subQ, Pen<br>T2D, adults: Patient-specific initial dosing and dose titration | |
| | $T_{max}$: iDeg no pronounced peak<br>$t_{½}$: iDeg 25 h<br>$t_{½}$: Lira 13 h | Proteolytic degradation<br>No dose adjustment for altered renal function<br>Use caution when initiating/escalating doses<br>Unlikely to be dialyzable. No supplemental dose necessary. |

## GLP-1 RAs Class Effects

| Effects | Comments |
|---|---|
| Adverse drug reactions (ADRs) | • Most common (≥ 5%): nausea, abdominal pain, diarrhea, dyspepsia, decreased appetite, vomiting, and constipation<br>• Dermatologic reactions: Skin rash, urticaria<br>• Local injection site reactions<br>• Serious, reported:<br>– Pancreatitis (including hemorrhagic pancreatitis and necrotizing pancreatitis), gall bladder disease (cholelithiasis, cholecystitis, cholestasis, cholangitis), and acute kidney injury from dehydration associated with GI ADRs<br>• Immediate hypersensitivity reactions, including anaphylaxis and angioedema<br>• Neutralizing anti-drug antibodies may develop |
| Drug-specific ADRs | • Exenatide and exenatide ER: Injection site reactions, including bruising, cellulitis, erythema, hematoma, nodule, pruritus, and necrosis (> 10% of study patients)<br>• Dulaglutide: Diabetic retinopathy complications, including vitreous hemorrhage, onset of diabetes-related blindness, and the need for treatment with an intravitreal agent or retinal photocoagulation<br>• Semaglutide: Diabetic retinopathy complications, as above<br>• Tirzepatide: Diabetic retinopathy complications, as above<br>• Combination GLP-1 RA/basal insulin<br>• Insulin degludec and liraglutide: Hypoglycemia<br>• Insulin glargine and lixisenatide: Hypoglycemia |

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| Effects | Comments |
|---|---|
| **Contraindications** | • Avoid in patients with pre-existing gastroparesis<br>• Patients with a personal or family history of medullary thyroid cancer<br>• Patients with multiple endocrine neoplasia syndrome type 2 (MEN 2)<br>US Boxed Warning:<br>– In male and female rats, GLP-1 RAs caused dose-related and treatment-durations-dependent increase in the incidence of thyroid C-cell tumors after lifetime exposure. It is unknown whether GLP-1 RAs cause thyroid C-cell tumors, including medullary thyroid carcinoma, in humans.<br>• Hypersensitivity to drug or any component of formulation |
| **Pregnancy** | GLP-1 RAs and dual-acting GIP/GLP-1 RA are not recommended during pregnancy or in patients planning to become pregnant |
| **Drug interactions** | • GLP-1 RAs cause a delay in gastric emptying, which has the potential to impact the absorption of concomitantly administered oral medications<br>• Consider reducing the dose of concomitantly administered insulin secretagogues (sulfonylureas, meglitinides) or insulin to reduce the risk of hypoglycemia<br>• Drugs associated with hypo- or hyperglycemia may alter the therapeutic effects of antidiabetic agents<br>• Avoid concomitant DPP-4 inhibitor due to lack of additive glycemic benefit<br>• GLP-1 RAs may alter the effects of warfarin. Monitor therapy. |

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### GLP-1 RAs Outcomes

| Drug | A1C lowering at max dose | Weight loss at max dose | Cardiovascular outcomes ASCVD/Heart Failure (Studies were carried out on very high-risk patients) |
|---|---|---|---|
| Exenatide (2005) | -0.89% | -1.9 kg | Retrospective study (Best JH, et.al., 2010)<br>Exenatide twice-daily treatment was associated with lower risk of CVD events and hospitalizations than treatment with other glucose-lowering therapies |
| Exenatide ER (2012) | -1.4% | -1.4 kg | EXSCEL (Holman RR, et.al., 2017)<br>In patients with T2D with or without previous CV disease, incidence of major cardiac adverse events did not differ significantly between once weekly exenatide group and placebo group |
| Dulaglutide (2014) | -1.5% (at 1.5 mg) | -2.9 kg (at 1.5 mg) | REWIND (Gerstein HC, et.al., 2019)<br>Dulaglutide was added to existing therapies in T2D patients at high CV risk<br>All-cause mortality did not differ between groups |
| Liraglutide (2010) | -1.5% | -3.3 kg | LEADER (Marso SP, et.al., 2016)<br>In patients with T2D, the rate of the first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo |
| Semaglutide (2017/2021) | -1.9% | -5.6 kg | SUSTAIN 6 (Marso SP, et.al., 2016)<br>In patients with T2D with high CV risk, the rate of CV death, nonfatal MI, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo<br>Semaglutide subcutaneous injection and oral are approved for risk reduction of major CV events in adults with T2D and established cardiovascular disease |
| Semaglutide oral (2019) | -1.3% | -3.8 kg | PIONEER 6 (Husain M, et.al., 2019)<br>In patients with T2D, the CV profile of oral semaglutide was not inferior to placebo |
| Tirzepatide dual-acting GIP/GLP-1 RA (2022) | -2.5% | -12.9 kg | Ongoing studies:<br>SUMMIT, SURMOUNT-MMO, SURMOUNT-5, SURPASS-CVOT |
| Insulin degludec and Liraglutide (iDegLira) (2016) | -1.6% | Potential for insulin-induced weight gain | n/a |
| Insulin glargine and Lixisenatide (iGlarLix) (2016) | -1.3% to -1.9% | Potential for insulin-induced weight gain | n/a |

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Inclusion: 27 trials; combined total of 56,004 participants

## Counseling About the Management of Common Side Effects

**General recommendations:**

- Address baseline GI disorders prior to starting GLP-1 therapy
- Gradual, individualized dose escalation may help reduce GI side effects
- Listen to your hunger and satiety signals on this class of medication

**If GI symptoms are persistent:**

- Pause GLP-1 RA dose escalation and identify any underlying disorders
- Consider lower doses for those unable to tolerate standard maintenance dose
- Stop GLP-1 RA. After symptoms resolve, consider initiating a different GLP-1 RA or alternative therapy, if appropriate.

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### NAUSEA

Nausea is mild to moderate in most patients and usually subsides after dose escalation

Advise patients to:

- Reduce meal size
- Be mindful about being full and stop eating when full
- Avoid high-fat or spicy foods
- Moderate consumption of alcohol and fizzy beverages

### DIARRHEA

- Increase dietary fiber or OTC soluble fiber supplement (ie, psyllium)
- Bismuth, loperamide, or other OTC antidiarrheal (short-term management)

### CONSTIPATION

- Counsel on healthy bowel habits
- Increase dietary fiber and water intake
- PEG 3350 or other fiber supplement
- Stool softeners

## Standards of Care in Diabetes and Algorithms 2023

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Samson SL, Vellanki P, Blonde L, et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm - 2023 Update. *Endocr Pract*. 2023;29(5):305-340.

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## Prescribing Information


Dulaglutide: V47. December 2022. Accessed June 2, 2023. https://uspl.lilly.com/trulicity/trulicity.html#pi

Exenatide: https://www.ema.europa.eu/en/documents/product-information/byetta-epar-product-information_en.pdf

Exenatide ER prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/209210s017lbl.pdf. Accessed July 3, 2023

Liraglutide prescribing information: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022341s027lbl.pdf Accessed July 3, 2023

Liraglutide/insulin degludec (IDegLira Semaglutide oral: Jan 2023. https://www.novo-pi.com/rybelsus.pdf Accessed June 2, 2023.

Lixisenatide/insulin glargine (IGlarLixi) prescribing information: https://www.novo-pi.com/xultophy10036.pdf. Accessed July 3, 2023

Semaglutide prescribing information: https://www.novo-pi.com/ozempic.pdf. Accessed July 3, 2023

Semaglutide, oral, prescribing information: https://www.novo-pi.com/rybelsus.pdf. Accessed July 3, 2023

Tirzepatide: May 2022. FDA Labeling (package insert). Accessed June 30, 2023 https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215866s000lbl.pdf



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