Prescribing pearls: A guide to DPP-4 inhibitors (gliptins)

What is a DPP-4 inhibitor?

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as gliptins, are used in the management of type 2 diabetes. They inhibit the enzyme DPP-4, thus impairing the rapid degradation of two key incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[1] DPP-4 plays a role in glucose homoeostasis by increasing nutrient-stimulated insulin synthesis and by reducing glucagon secretion. DPP-4 inhibitors double the circulating concentrations of both GLP-1 and GIP.[2]

The effects of the DPP-4 inhibitors are glucose-dependent and so there is a low risk of hypoglycaemia. The increased concentration of GLP-1 produced leads to reductions in prandial glucose excursions.

Table 1. Licensed indications.

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Monotherapy when metformin is not tolerated or contraindicated	No	Yes	Yes	Yes	Yes
Dual oral therapy	Yes	Yes	Yes	With metformin, sulfonylurea or pioglitazone	Yes
Triple oral therapy	Yes	Yes	Yes	With metformin + pioglitazone or metformin + sulfonylurea	Yes
With insulin	Yes	Yes	Yes	Yes (with or without metformin)	Yes

Positioning in guidelines

In the NICE NG28 guideline,[3] the DPP-4 inhibitors may be used first-line when metformin is contraindicated or not tolerated. DPP-4 inhibitors can also be used in dual therapy or in triple therapy with metformin when blood glucose is not adequately controlled to individualised targets.

The ADA/EASD consensus report[4] highlights the use of DDP-4 inhibitors when intermediate efficacy for glucose lowering is required and where weight management goals would prefer a weight-neutral approach. DPP-4 inhibitors are not recommended for cardiorenal risk reduction in high-risk individuals.

Glycaemic effects

The DPP-4 inhibitors appear to have similar in-class glycaemic efficacy. They result in modest improvement in HbA_{1c}, with a reduction of around 0.5–1.0% when used as monotherapy and around 0.6–1.1% when used in combination with metformin, depending on the agent, dose of therapy and starting HbA_{1c}.[2,5]

DPP-4 inhibitors reduce post-prandial glucose excursions by around 3 mmol/L and basal glycaemia by around 1.0–1.5 mmol/L.

Effects on body weight

DPP-4 inhibitors are weight-neutral, and thus they may be an attractive option for some patients if other options would likely cause additional weight gain.

Cardiovascular safety

DPP-4 inhibitors provide no benefits above the standard of care for people with established or high risk of atherosclerotic cardiovascular disease, heart failure or chronic kidney disease; however, they have mostly demonstrated cardiovascular safety.

In the SAVOR TIMI 53 trial, saxagliptin had no significant difference compared to placebo in the rate of ischemic events; however, the rate of hospitalisation for heart failure was increased.[6]

In the EXAMINE trial, a safety signal for increased risk of hospitalisation for heart failure was identified with alogliptin, particularly in people with a history of heart failure.[7]

A meta-analysis of outcomes data from completed cardiovascular outcome trials suggests that, apart from saxagliptin, DPP-4 inhibitors have a neutral effect on the risk of cardiovascular death, myocardial infarction, stroke and hospitalisation for heart failure.[8]

Side effects

Common: Headache, cough, nasopharyngitis, abdominal pain, dizziness, fatigue, increased infection risk, gastro-oesophageal reflux, skin reactions, vomiting.

Uncommon: Constipation, skin reactions, arthralgia, hypoglycaemia, peripheral oedema.

Frequency unknown: Angioedema, back pain, cutaneous vasculitis, interstitial lung disease, joint disorders, myalgia, pancreatitis, renal impairment, Stevens–Johnson syndrome, hepatic function abnormalities.

Contraindications

- Any sign of acute pancreatitis (e.g. persistent, severe abdominal pain)
- Hypersensitivity to DPP-4 inhibitors in the past
- Pregnancy/breastfeeding
- Some DPP-4 inhibitors are contraindicated at certain thresholds of renal impairment (see *Table 2*)
- Some DPP-4 inhibitors are contraindicated in hepatic impairment (see *Table 3*)
- Type 1 diabetes
- Diabetic ketoacidosis

Cautions

- History of pancreatitis
- Moderate heart failure (saxagliptin only, due to limited experience)
- Severe heart failure (saxagliptin and vildagliptin, due to limited experience)
- Some DPP-4 inhibitors are cautioned at certain thresholds of renal impairment, and dose reductions may be required (see *Table 2*)

Drug interactions

No significant interactions have been reported between DPP-4 inhibitors and any other drugs. The gliptins do not significantly modify the pharmacokinetic profile and exposure of other medicines, and vice versa. Therefore, no dosage adjustment is usually recommended when gliptins are combined with other pharmacological agents. The notable exception to this is saxagliptin.

Saxagliptin is metabolised to an active metabolite by CYP3A4/5 enzymes.[9] Exposure to saxagliptin and its primary metabolite is reported to be significantly altered when saxagliptin is co-administered with specific strong inhibitors (e.g. ketoconazole, diltiazem) or inducers (e.g. rifampicin, dexamethasone) of CYP3A4/5. **Glycaemic control should be carefully assessed when saxagliptin is used concomitantly with a potent CYP3A4/5 inducer.**

There is an additive effect of using a DPP-4 inhibitor alongside other agents that decrease blood glucose; thus, a dose reduction of agents that act independently of glucose levels (e.g. sulfonylureas) may be indicated to avoid hypoglycaemia.[9]

Table 2. Dosage of DPP-4 inhibitors at different renal thresholds.

Creatinine clearance	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
>50 mL/min	25 mg	5 mg	5 mg	100 mg	50 mg twice daily (50 mg once daily if in dual therapy with a sulfonylurea)
45–50 mL/min	12.5 mg	5 mg	5 mg	100 mg	50 mg once daily
30–44 mL/min	12.5 mg	5 mg	2.5 mg	50 mg	50 mg once daily
<30 mL/min	6.25 mg	5 mg	2.5 mg (avoid if end-stage renal disease on dialysis)	50 mg	50 mg once daily

Table 3. Hepatic impairment thresholds for DPP-4 inhibitor use.

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin	Vildagliptin
Mild hepatic impairment	Continue	Continue	Continue	Continue	Avoid
Moderate hepatic impairment	Continue	Continue	Caution	Continue	Avoid
Severe hepatic impairment	Avoid	Continue	Avoid	Continue	Avoid

Use of DPP4-inhibitors in older frail populations

Oral DPP-4 inhibitors have few notable side effects and are associated with a minimal risk of hypoglycaemia. DPP-4 inhibitors have been formally evaluated in frail older adults, demonstrating efficacy and safety profiles similar to those in younger adults.

DPP-4 inhibitors are one of the few oral agents that are useful in patients with significant renal impairment.

Caution should be taken with saxagliptin in adults with a history of heart failure or in those at risk of heart failure.[6] Care should also be taken with alogliptin.[7]

Initiating and monitoring

If adding a DPP-4 inhibitor to sulfonylurea, meglitinide or insulin therapy, consider whether a dose reduction of the sulfonylurea/meglitinide/insulin is needed to reduce hypoglycaemia risk.

Prior to initiating saxagliptin, vildagliptin or alogliptin:

- Check liver and kidney function

During treatment:

- **Vildagliptin:** Monitor liver function tests (LFTs) at 3-monthly intervals post-initiation for the first year and periodically thereafter. If transaminase levels increase, repeat the LFTs and monitor until these normalise
- **Saxagliptin:** Monitor renal function periodically
- **Alogliptin:** Monitor renal function periodically

Key summary table

Glycaemic efficacy	Low
Hypoglycaemia risk	Low
Weight gain	Neutral
CV effects: ASCVD/CV mortality	Neutral
CV effects: Heart failure	Use saxagliptin and alogliptin with caution if moderate-to-severe heart failure
Cost	Sitagliptin: Low (now generic). Other DPP-4is: High
Formulations	Oral
Renal effects: progression to DKD	Neutral
Renal effects: need for dosage adjustments	Initiate at appropriate dose after baseline renal function tests; reduce doses in renal function decline
Hepatic effects: need for dosage adjustments	Use saxagliptin with caution in moderate hepatic impairment

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; DKD=diabetic kidney disease.

Available drugs, doses, brands and dosing schedules

Drug	Brand	Doses	Notes
Alogliptin	Vipidia	25 mg, 12.5 mg and 6.25 mg	Recommended dose 25 mg once daily
Linagliptin	Trajenta	5 mg	Recommended dose 5 mg once daily; can be taken with or without food
Saxagliptin	Onglyza	2.5 mg, 5 mg	Recommended dose 5 mg once daily; reduce dose to 2.5 mg if eGFR <45
Sitagliptin	Januvia	25 mg, 50 mg and 100 mg	Can be taken with or without food
Vildagliptin	Galvus	50 mg	Recommended dose 50 mg twice daily (50 mg once daily if eGFR <45) Not recommended in hepatic dysfunction; perform LFTs before initiating
Saxagliptin + metformin	Komboglyze	2.5/1000 mg, 5/1000 mg or 5/2000 mg	2.5/1000 mg, 5/1000 mg or 5/2000 mg once daily with evening meal
Sitagliptin + metformin	Janumet	50/500 mg and 50/1000 mg	50/500 mg twice daily, with meals Can increase to 50/1000 mg twice daily (maximum dose), with meals

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