Prescribing pearls: A guide to sulfonylureas

What is a sulfonylurea?

Sulfonylureas (SUs), structural variants of the earlier sulfonamide antibacterial drugs found to induce hypoglycaemia, have been used since the 1960s.[1] First-generation SUs (e.g. tolbutamide) have been superseded by more potent second-generation SUs (e.g. gliclazide, glipizide and glimepiride).

Historically, SUs have been common add-on therapy to metformin, owing to effectiveness and low cost.[2] Although practice now favours earlier use of newer agents shown to have cardiorenal benefits, SUs are still used extensively across the UK, despite causing weight gain and hypoglycaemia.[3]

Mechanisms of action

SUs act directly on the beta-cells of the islets of Langerhans to stimulate insulin secretion, stimulating insulin release even when glucose concentrations are below the normal threshold for insulin release (<5 mmol/L), which is why they can cause hypoglycaemia.[4] The insulin release also leads to insulin-induced suppression of hepatic glucose production.[5]

SUs vary in their pharmacokinetic properties; consider duration of action when individualising treatment.

Glycaemic effects

SUs reduce fasting glucose by 2–4 mmol/L, decreasing HbA_{1c} by 11–22 mmol/mol when added to lifestyle measures.[9]

The glucose-lowering effect is immediate, provided there are functioning beta-cells. Beta-cell mass in type 2 diabetes declines over time, so the dose may need to be increased and, in a proportion of people, there may be more rapid progression to "treatment failure".[9]

Indications

- First-line treatment as "rescue therapy" for patients with symptomatic hyperglycaemia; review once better glycaemic control achieved.
- First-line treatment in steroid-induced diabetes.[3]
- Add-on therapy in type 2 diabetes.
- First-line treatment of HNF1-alpha MODY (maturity-onset diabetes of the young).[6]

Positioning in guidelines

In NICE's guideline on the management of type 2 diabetes in adults (NG28), SUs may be used first-line for rescue therapy in symptomatic hyperglycaemia, or if low cardiovascular risk and metformin intolerance/contraindication.[7] They are also recommended as the first line for steroid-induced diabetes.[8]

Otherwise, SUs are a third-line option alongside DPP-4 inhibitors and pioglitazone. Drug choice should be based on patient preferences; the individual's clinical, social and occupational circumstances; safety; and, where possible, cost (in terms of person outcomes and NHS costs).[7]

Adverse effects

Weight gain

The anabolic effects of increased insulin production and reduced glucose excretion can lead to 1–4 kg weight gain, with stabilisation at around 6 months.[9]

However, in the ADVANCE study, minimal weight gain was seen with gliclazide modified-release (MR) over a 5-year period.[10]

Hypoglycaemia

Due to the increased risk of hypoglycaemia, glucose monitoring is recommended. Hypoglycaemia occurs annually in ~20% of people treated with SUs[8] and severe hypoglycaemia in ~1%. **This can be life-threatening.** This may not be caused directly by the SU, but may be a marker of severity of comorbidity.[10,11] The risk of hypoglycaemia increases with age, severity of comorbidity, in people with high cardiovascular risk or established CVD, and in people with significantly impaired renal function (stage 3 CKD or above).[12] Use a shorter-acting SU at a lower dose, or avoid SU use.

SU-induced hypoglycaemia may need to be treated in hospital owing to the recurrence of hypoglycaemia, particularly for the longer-acting SUs. Glucagon in type 2 diabetes can be less effective, as it is an insulin secretagogue itself.

Sensitivity reactions and rarer side-effects

Transient cutaneous rashes and, rarely, erythema multiforme, fevers, jaundice, acute porphyria, photosensitivity and blood dyscrasias.

Contraindications

- All SUs contraindicated in those with a history of ketoacidosis or severe hepatic impairment.
- Avoid gliclazide and tolbutamide in acute porphyria.

Cautions

Use with caution in:

- G6PD deficiency.
- Older people (prescribe lower doses and shorter-acting SUs to avoid prolonged hypoglycaemia).
- Renal or mild/moderate hepatic dysfunction (dose reductions and shorter-acting SUs may be indicated).
- Obesity (these medications contribute to weight gain).

Drug interactions

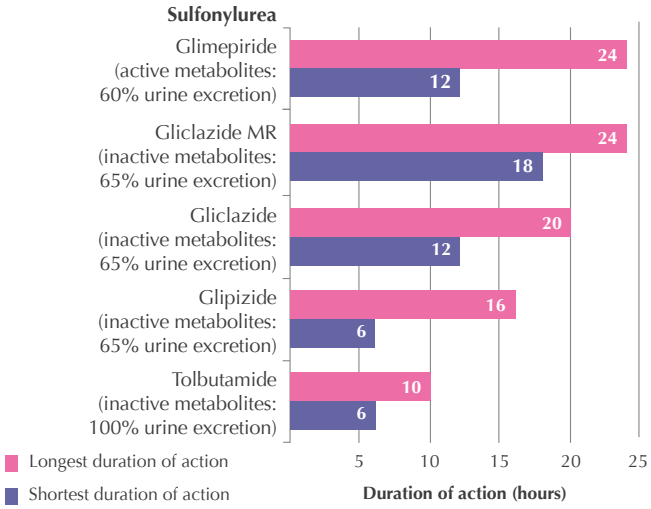
SUs are hepatically metabolised, highly plasma protein-bound drugs. This can lead to interactions with drugs that inhibit hepatic metabolism (e.g. amiodarone, chloramphenicol, clarithromycin, azole antifungal agents and monoamine oxidase inhibitors), drugs that induce hepatic metabolism (e.g. rifampicin) and other protein-bound drugs (e.g. sulfonamides, warfarin and NSAIDs). Displacement from proteins by competing drugs increases hypoglycaemia risk.

To reduce the risk of hypoglycaemia, reduce doses of SU and insulin initially when adding any other glucose-lowering drugs. Beta-blockers can reduce the warning signs of hypoglycaemia and should be used with caution alongside SUs.[13]

Available sulfonylureas[14]

SU	Strengths	Dosing
Gliclazide (immediate release)	40 mg, 80 mg, 160 mg	Initially 40–80 mg daily; increased, if necessary, up to 160 mg once daily, with breakfast. Divide doses higher than 160 mg; max. 320 mg/day
Gliclazide (modified release)	30 mg, 60 mg	Initially 30 mg daily with breakfast. Adjust dose every 4 weeks (after 2 weeks, if no decrease in blood glucose); max. 120 mg/day
Glimepiride	1 mg, 2 mg, 3 mg, 4 mg	Once daily with first main meal
Glipizide	5 mg	Initially 2.5–5 mg daily, take shortly before breakfast or lunch, up to 15 mg may be given as a single dose, higher doses divided; max. 20 mg/day
Tolbutamide	500 mg	0.5–1.5 g daily in divided doses, dose to be taken with or immediately after meals; alternatively 0.5–1.5 g once daily, dose to be taken with or immediately after breakfast; maximum 2 g per day

Duration of action of SUs[15]



Glibenclamide is not readily available in the UK, but can be imported (some patients stabilised on this for HNF1-alpha MODY may need it).

Initiating and monitoring gliclazide

- Consider the level of risk of hypoglycaemia and its consequences (e.g. age, frailty status, comorbidities including renal impairment, does the person drive (see **Resources**) or operate machinery as part of their job?
- To reduce risk of hypoglycaemia, start at low dose and titrate up, as indicated below.
- Ensure the person with diabetes and/or carers know what hypoglycaemia is, how to recognise it and how to treat it effectively (see **Resources**).
- Agree an individual blood glucose (BG) target, with particular attention to the person's risk of hypoglycaemia (as above).
- Ensure drivers understand the DVLA requirement to test their glucose levels at times relevant to driving and follow DVLA guidance.

Starting doses

The starting dose of gliclazide is usually 80 mg with a meal. However, consider starting with 40 mg if there are any particular concerns about hypoglycaemia.

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Encourage self-monitoring of blood glucose (SMBG) at different times of day to gather baseline information, including fasting, pre-meal, 2 hours post-meals and bedtime readings over 7–14 days, and review results. A BG profile will help identify whether to initiate a dose with breakfast and/or the evening meal.

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If given with breakfast, it will potentially lower BG levels up to the evening meal.

If given with evening meal, it will lower BG levels pre-bed and during night.

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Encourage person to continue SMBG before and 2 hours after meals. Review BG readings after 1–2 weeks. **(Remember, HbA_{1c} will not reveal daily variability of glucose levels or identify hypoglycaemia, and should not be used to assess response to an SU)**

Titrating doses

If BG readings are consistently high from breakfast to the evening meal, consider increasing the morning dose.

If BG readings are high after evening meal and on waking, consider increasing the evening dose.

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Increments of 40–80 mg can be made every 1–2 weeks, depending on how high the BG levels are:

- If fasting glucose levels are only just above target (7–9 mmol/L), titrate up by 40 mg.
- If glucose levels are all in double figures, titrating by 80 mg would be more appropriate.

Always consult the **Summary of Product Characteristics** before prescribing any drug. Visit: www.medicines.org.uk/emc

Using gliclazide for steroid-induced hyperglycaemia

If using gliclazide for steroid-related hyperglycaemia, refer to How to diagnose and manage steroid-induced diabetes.

Deprescribing

- Stop gliclazide if "treatment failure" is suspected (see **Glycaemic effects**).
- If using for rescue therapy, monitor SMBG and decrease gliclazide dose as other medication becomes effective (decrease in same way as titration).
- If using for steroid-related hyperglycaemia, decrease the gliclazide dose if steroid dose decreased (see How to guide).
- Stop gliclazide if eGFR <30 mL/min/1.73 m^2.

Prescribing tips and special circumstances

Shorter-acting SUs (e.g. gliclazide, glipizide) reduce the risk of prolonged hypoglycaemia, and are generally preferred to longer-acting glimepiride.

Modified-release gliclazide allows for once-daily dosing and may be associated with the lowest risk of hypoglycaemia.[16]

Always provide access to home glucose testing and be alert to the risk of hypoglycaemia – if hypoglycaemia is suspected, consider a reduction in dose.

Sulfonylureas and fasting

There is a risk of hypoglycaemia with sulfonylureas any time fasting occurs (e.g. for surgery, investigations or during Ramadan). Less risk of hypoglycaemia if on stable SU dose at least 3 months prior to Ramadan, and with glipizide, glimepiride and gliclazide.[17,18] Take once-daily dose at *iftar* (sunset); if twice daily, then usual dose at iftar and consider reduced dose at *suhoor* (sunrise).[19]

See our *How to* series for further guidance:

Surgery | **Ramadan**

Resources

- Diabetes UK:
  - *What is a hypo?*
- Fitness to drive:
  - *How to assess fitness to drive*
  - *Assessing fitness to drive: a guide for medical professionals*

Key summary table

Efficacy	High efficacy
Hypoglycaemia risk	Yes
Weight gain	Yes
CV effects: ASCVD/CV mortality	Neutral in CVOTs/possible increased mortality with studies of older SUs
CV effects: HF	Neutral
Cost	Low
Formulations	Oral
Renal effects: progression to DKD	Neutral
Renal effects: need for dosage adjustments	Initiate at low doses, titrate conservatively in renal impairment (reduce doses in renal decline)
Hepatic effects: need for dosage adjustments	Initiate at low doses and titrate conservatively (reduce doses in hepatic function decline). Manufacturers advise to avoid in severe impairment (increased risk of hypoglycaemia)

ASCVD=atherosclerotic cardiovascular disease; CV=cardiovascular; CVOT=cardiovascular outcome trial; DKD=diabetic kidney disease; HF=heart failure.

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