Glucose control: Non-insulin therapies

This article is a direct extraction from Chapter 9 of The 2012 SEMDSA Guidelines for the Management of Type 2 Diabetes and should be read in conjunction with the SEMDSA 2012 Treatment Algorithm. The full guideline and poster summary is available on www.semdsa.org.za

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Glycaemic control: SEMDSA 2012 algorithm for type 2 diabetes

Use this algorithm only if the patient does NOT have features of severe decompensation.[1] Progress down this algorithm within three months if HbA_{1C} remains above 7% (or individualised target). Choose therapies that are likely to produce the HbA_{1C} reduction required to achieve the target.[2]
Do not proceed with drug therapy without annual serum eGFR measurement.[3]

LIFESTYLE MEASURES PLUS	PREFERRED THERAPIES	ALTERNATIVE THERAPIES FOR SPECIAL CIRCUMSTANCES[4]		
Step 1: Initiate at least one oral drug at diagnosis	Metformin	SU	DPP-4 inhibitor	Acarbose
Step 2: Combine any two drugs[4]	Metformin + SU	Incretin	Acarbose	Basal insulin
Step 3: Combine three drugs	Metformin + SU + basal insulin (or metformin + pre-mix insulin)	Metformin + SU + incretin	Metformin + SU + acarbose	
Step 4: More advanced therapies	Refer for basal bolus insulin ± additional therapies	Metformin + pre-mix insulin (if not used yet)		

SU: sulphonylurea, but not glibenclamide, DPP-4 inhibitor = dipeptidyl peptidase-4 inhibitor
[1:] Severe decompensation includes any of: FPG > 15 mmol/l, HbA_{1c} > 11%, marked polyuria and polydipsia, weight loss > 5% or ketoacidosis. Refer this patient for specialist care (Step 4).
[2,3:] Refer to full-text guideline (www.semdsa.org.za)
[4:] If at diagnosis, the patient's HbA_{1c} is > 9% without features of severe decompensation, consider initiating therapy at Step 2.

Pharmacotherapy for hyperglycaemia

Initiate drug therapy with metformin (unless contraindicated) at diagnosis. Consider initial therapy with two oral agents when the HbA_{1c} > 9%. Initiate insulin therapy at diagnosis for decompensated hyperglycaemia.

Metformin optimum dose is 2 000 mg/d (1g BID), maximum dose should not exceed 2 550 mg/day (850 mg TID). Do not exceed 1 000 mg/day when eGFR < 45 ml/minute. Discontinue metformin when eGFR < 30 ml/minute. Gastrointestinal side-effects are common, but often transient. The extended-release formulation should be used for intolerable gastrointestinal side-effects. Lactic acidosis is uncommon in the absence of metformin contraindications. Be aware that vitamin B12 deficiency may occur.

Sulphonylureas (SUs) are the preferred second-line oral agent. Glibenclamide should not be used because of the increased risk of severe and prolonged hypoglycaemia. The preferred SUs are gliclazide and its modified release formulation, glimepiride and glipizide. Be aware of the greater hypoglycaemia risk and dose adjustments with renal impairment. Modest weight gain may occur with SUs.

Incretin-based therapies: DPP-4 and glucagon-like peptide-1 (GLP-1) agonist therapy carry a low risk of hypoglycaemia. DPP-4 inhibitors are weight-neutral, while injectable GLP-1 agonists can cause weight loss. However, they lack outcomes data and are more expensive than SUs. They are preferred in situations where the risk of potential hypoglycaemia or weight gain with other therapies is significant, or when insulin therapy is not feasible. Therapy beyond six months should only continue if there has been an adequate therapeutic response.

Insulin therapy may be indicated at any stage when glycaemic control is suboptimal. Basal (intermediate or long-acting) insulin can be initiated at a dose of 10U at bedtime, and up-titrated by 2U every 3-7 days until the target fasting glucose is attained. Insulin therapy must always be accompanied by adequate education, self-blood glucose monitoring and titration algorithms. Weight gain and hypoglycaemia can be significant complications of insulin therapy.

Glitazones (thiazolidenediones) are not recommended therapies.

Specialist referral is appropriate at any stage if glycaemic targets are not met.

Refer to full text guideline (www.semdsa.org.za) for more details.

9.1 Metformin

Metformin was isolated from *Galega officinalis* (goats rue), which was used to treat symptoms characteristic of diabetes mellitus in medieval times. The plant extract, however, was found to be toxic in studies carried out in the early 1920s. Metformin, as we know it, was developed in the 1950s, together with the other biguanides, phenformin and buformin. However, owing to the common occurrence of lactic acidosis with the others, metformin is now the only biguanide that is commercially available.

9.1.1 Mechanism of action

Metformin exerts its effect by activating adenosine monophosphate (AMP) kinase, resulting in reduction of hepatic glucose production via multiple intracellular pathways. Additional effects that have been described include improved peripheral glucose utilisation, reductions in gastrointestinal glucose absorption, enhanced incretin responses, improvements in free fatty acid metabolism, lipid profiles, vascular and endothelial function and a reduction in cancer mortality.

9.1.2 Efficacy

Metformin is now well established as the primary "anchor" oral anti-diabetic agent in the management of type 2 diabetes. It is the only drug with proven efficacy in reducing cardiovascular outcomes and mortality as a primary endpoint in a randomised controlled trial (UKPDS 34). In this study, patients assigned to intensive blood glucose control with metformin had a significant 32% lower risk of developing any diabetes-related endpoint than patients assigned to conventional diet treatment. The metformin group also had significantly greater risk reduction than the group assigned to intensive therapy with a sulphonylurea or insulin. It is not widely known, though, that metformin did not demonstrate any significant microvascular benefits compared to conventional diet treatment, and this remained so in the post-trial monitoring follow-up study.

When used as monotherapy, metformin can reduce HbA_{1c} by 1-2%.

9.1.3 Dosing

The minimum effective dose of metformin is 500 mg once daily, and the optimal dose is about 2 000 mg per day in two or three divided doses, although some patients derive additional benefit from doses up to 2 550 mg per day.

Table I: Traditional contraindications to metformin use

Renal dysfunction
Severe liver disease
Use of intravenous contrast media
Major surgical procedures
Congestive heart failure
Acute myocardial infarction
History of lactic acidosis
History of alcohol abuse

9.1.4 Adverse effects and contraindications

About 30% of users will report gastrointestinal side-effects (e.g. diarrhoea, cramping, bloating and flatulence). These can be minimised by titrating the dose gradually over one or two months, or by temporarily discontinuing the drug before reintroducing it. Fewer than 10% of patients will need to discontinue the drug permanently because of gastrointestinal intolerance. In this circumstance, because it is desirable to retain the metformin molecule, the extended-release formulation of metformin should be prescribed instead of switching to another class of drug.

Lactic acidosis with metformin is now known to be rare (0.05 cases/1 000 patient years), and most of these cases occur in the context of inappropriate usage.

However, widespread usage and experience have shown that metformin is a useful drug, even in conditions where it is supposedly contraindicated. So, despite the contraindication in liver disease, metformin can actually improve liver function in patients with non-alcoholic fatty liver disease. Also, the Food and Drug Administration (FDA) in the United States has withdrawn the heart failure contraindication based on publications of improved outcomes in heart failure patients on metformin. And metformin has shown some benefit compared to insulin and sulphonylureas in the aftermath of acute myocardial infarction (DIGAMI-2) study.

Not surprisingly, then, many surveys have shown that metformin remains in use at the time of contraindications confirming a lack of respect for the current licensing guidance. This has been most obvious in patients with renal impairment, where its continued use has reassuringly not been associated with adverse outcomes. Accumulated data on metformin usage in renal impairment has led to a relaxation of the guideline here (Table II). Notwithstanding the better than expected adverse event profile with metformin, It remains important to follow prescribing recommendations and to remain vigilant against a too casual approach to using metformin.

Table II: Metformin use in renal disease

Estimated glomerular filtration rate (eGFR)	Action
> 60 ml/minute/1.73 m^2	- No renal contraindication to metformin - Monitor renal function annually
45-60 ml/minute/1.73 m^2	- Continue use - Increase monitoring of renal function (every three to six months)
30-45 ml/minute/1.73 m^2	- Prescribe metformin with caution - Do not exceed 1 000 mg total daily dose - Closely monitor renal function (every three months)
< 30 ml/minute/1.73 m^2	- **Stop metformin**

9.1.5 Metformin in the 2012 SEMDSA treatment algorithm

At step 1, as monotherapy, metformin is the initial therapy of choice and should be started at the time of diagnosis in all patients (overweight and normal weight), unless specifically contraindicated. It is recommended that metformin therapy continue even when other classes of (including insulin) are added subsequently.

At step 2, metformin can be added as a second-line agent in patients where treatment has been initiated with any other class of drug.

9.2 Sulphonylureas

Sulphonylurea drugs have been used in the treatment of type 2 diabetes mellitus (diabetes) since the 1950s.

9.2.1 Mechanisms of action

These drugs induce insulin release by binding to specific receptors on the pancreatic beta cell-K_{ATP} channel. The beta cell-K_{ATP} channel is a hetero-octamer, comprising a potassium channel (Kir6.2) and a sulphonylurea receptor (SUR1). The binding of sulphonylureas to SUR1 leads to glucose-independent closure of the potassium channel, membrane depolarisation, the opening of calcium channels, and the release of stored insulin. Sulphonylureas may have additional effects, including decreasing growth-hormone secretion, and there is experimental evidence of increased lipogenesis and glycogen synthesis.

Sulphonylurea drugs available in South Africa include glibenclamide, gliclazide, glipizide, glimepiride and chlorpropamide (no longer in clinical use). These drugs are compared in Table III.

9.2.2 Efficacy

The clinical efficacy of sulphonylurea drugs has been demonstrated in many studies, including the United Kingdom Prospective Diabetes Study (UKPDS). The reduction in glycated haemoglobin A_{1c} (HbA_{1c}) ranges from 1.5 to 2.0%, with similar efficacy amongst the different sulphonylureas. Furthermore, the UKPDS showed significant reduction in microvascular complications of diabetes with sulphonylurea therapy. More recently, ADVANCE study showed that modified-release gliclazide significantly reduced microvascular complications in a large cohort of subjects with type 2 diabetes and risk factors for vascular disease. By contrast, macrovascular disease was neither reduced nor worsened in the ADVANCE study.

9.2.3 Dosing

- Glibenclamide: Starting dose 2.5 mg once daily; maximal dose 15 mg daily. Doses exceeding 10 mg per day to be given in two divided doses.
- Gliclazide: Starting dose 40 mg once daily; maximal dose 320 mg daily. Doses exceeding 80 mg per day to be given in two divided doses.
- Gliclazide modified-release: Starting dose 30 mg once daily; maximal dose 120 mg once daily.
- Glimepiride: Starting dose 1 mg daily; maximal dose 6 mg once daily.
- Glipizide: Starting dose 2.5 mg once daily; maximal dose 40 mg daily. Doses exceeding 15 mg per day to be given in two divided doses.

9.2.4 Adverse effects and contraindications

Concern that sulphonylurea drugs may worsen cardiovascular outcome derives from the University Group Diabetes Program, in which tolbutamide was used. Subsequent studies have examined the role of sulphonylurea drugs binding to cardiac SUR receptors and the possibility of reduction in ischaemic pre-conditioning as an explanation for varied cardiac outcomes with different agents. There is evidence that glipizide, gliclazide and glimepiride bind the cardiac SUR less avidly than glibenclamide. A French study showed that prior treatment with glibenclamide was associated with increased mortality and increased rate of complications in subjects with type 2 diabetes after acute myocardial infarction, as compared to prior treatment with gliclazide or glimepiride.

The major adverse effects of sulphonylureas include weight gain and hypoglycaemia. Weight gain has been demonstrated in numerous studies. The UKPDS reported a mean weight gain of 5.3 kg over the first six years of the study, with most of the weight gain occurring in the first year of treatment. Lesser degrees of weight gain have been reported with gliclazide and glimepiride.

Hypoglycaemia is the most serious adverse effect of therapy with sulphonylurea drugs. The incidence of sulphonylurea drug-induced hypoglycaemia in South Africa is unknown. In the first 10 years of the UKPDS, hypoglycaemia (of any severity) occurred in 11% of patients per year treated with chlorpropamide, 17.7% treated with glibenclamide, and 36.5% treated with insulin. A number of studies have

Table III: Comparison of the pharmacokinetic profiles of sulphonylurea drugs

	Glibenclamide	Gliclazide	Glimepiride	Glipizide
Protein binding	99%	96%	>99%	>90%
Peak concentration (hours)	3-4	3-4	2-3	2.5
Elimination $t_{½}$ (hours)	10	10-12	5-8	2-4
Metabolism	CYP2C9	CYP2C9	CYP2C9	CYP2C9
Excretion of metabolites	50% renal 50% GIT	60-70% renal 10-20% GIT	60% renal 40% GIT	-
Duration of hypoglycaemic effect (hours)	16-24	24	16-24	12-24

shown higher rates of hypoglycaemia with glibenclamide than with other second-generation sulphonylureas. This observation is possibly related to the long duration of action of glibenclamide, as well as the hypoglycaemic activity of both primary metabolites (4-trans-hydroxy-glibenclamide and 3-cis-hydroxy-glibenclamide). One study showed the incidence of severe hypoglycaemia with glibenclamide to be 5.6/1 000 person years, compared to 0.86/1 000 person years in subjects treated with glimepiride. Gliclazide has also been shown to be associated with less hypoglycaemia than glibenclamide. Glimepiride and glipizide appear to have similar hypoglycaemic-potential. The GUIDE study compared gliclazide-modified release with glimepiride and showed that both drugs were equally efficacious but gliclazide-modified release had a significantly lower rate of hypoglycaemia. Significant risk factors for severe sulphonylurea-induced hypoglycaemia include renal impairment, advanced age and polypharmacy.

9.2.4.1 Contraindications to sulphonylurea use

- Brittle or unstable diabetes.
- Type 1 diabetes.
- Renal impairment: Glibenclamide is absolutely contraindicated if eGFR has not been measured in the preceding year, or if it is < 60 ml/minute/1.73m^2. Doses of gliclazide, glimepiride and glipizide may need to be reduced in renal impairment. No dose adjustments are recommended for gliclazide modified-release with renal impairment.
- Severe liver dysfunction.
- Allergy to sulphonamides or sulphur.
- Caution in elderly subjects.
- Caution in porphyria.
- Caution in lactation.

9.2.5 Sulphonylurea drugs in the 2012 SEMDSA treatment algorithm

Sulphonylureas are retained as a therapeutic option. The use of glibenclamide is strongly discouraged, other than in gestational diabetes, if the decision is taken to treat this condition with a sulphonylurea.[22] In all other instances, preference should be given to other second-generation sulphonylurea drugs. In making this recommendation the Guideline Committee and other experts considered their collective experience with regards to glibenclamide-induced severe hypoglycaemia, as well as the lack of renal function testing for a significant (if not the majority) of South Africans with diabetes. Notwithstanding the lack of formal studies, the committee felt that there are too many patients who present to hospitals with undiagnosed renal failure and inappropriate glibenclamide therapy in both the public and private health care sectors. We therefore propose that glibenclamide therapy be phased out in favour of the other second generation sulphonylureas. We recommend that in the meantime, pharmacists should not dispense glibenclamide without the patient having record of a valid estimated glomerular filtration measurement > 60ml/min/1.73m^2 from the preceding 12 months.

9.2.5.1 Indications for second-generation sulphonylureas (glibenclamide not preferred)

- Step 1: Monotherapy at diagnosis in persons intolerant of metformin, or in normal-weight individuals or those with marked symptoms of hyperglycaemia.
- Step 2: Added to metformin, basal insulin, a glucagon-like peptide-1 (GLP-1) agonist, or a dipeptidyl peptidase-4 (DPP-4) inhibitor.
- Step 3: Triple therapy with metformin and basal insulin, or metformin and an incretin.
- In gestational diabetes, glibenclamide is the sulphonylurea of choice (for specialist use only).

9.3 Alpha glucosidase inhibitors

9.3.1 Mechanism of action

Acarbose is an oligosaccaride that competitively inhibits alpha glucosidase on the brush border of the small intestine. This inhibits the conversion of complex carbohydrates into monosaccharides, and results in a reduction and delay in the absorption of glucose.

9.3.2 Efficacy

In a meta-analysis of 30 randomised, controlled trials, acarbose monotherapy reduced HbA_{1C} by 0.8% without causing hypoglycaemia or weight gain. The dose of 100 mg three times daily was not more effective than addition to metformin, sulphonylurea and insulin, which result in HbA_{1c} reductions of 0.8%, 0.9% and 0.5%, respectively.

In all studies, acarbose significantly reduced postprandial glucose (2.3-3.5mmol/l), and caused statistically significant weight loss or was weight neutral.

9.3.2.1 Cardiovascular effects

The Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial randomly assigned 1 429 patients with impaired glucose tolerance to acarbose 100 mg three times daily or placebo for a mean of 3.3 years. In a pre-planned secondary analysis, acarbose significantly reduced the risk of cardiovascular events by 49%, and the risk of developing hypertension was decreased by 34%. The magnitude of the effect is unexpected and may be related to the fact that acarbose targets postprandial hyperglycaemia (an independent risk factor for cardiovascular disease), but it needs verification. However, positive cardiovascular outcomes trials have been difficult to achieve, and these results should not be ignored.

9.3.3 Dosing

Start with 50 mg once daily with meals, and increase by 50 mg every two weeks if tolerated. The maximum dose is 100 mg three times daily, although a meta-analysis showed the same glycaemic benefit and better tolerability with 50 mg three times daily.

9.3.4 Adverse effects

Gastrointestinal side-effects (flatulence and diarrhoea) are common when initiating therapy, and are related to fermentation of the high saccharide load in the colon. This has led to discontinuation rates as high as 35% in clinical trials. Side-effects can be minimised by slow dose titration.

Acarbose does not cause hypoglycaemia when used as monotherapy, but may aggravate hypoglycaemia caused by sulphonylureas and insulin.

9.3.5 Acarbose in the 2012 SEMDSA treatment algorithm

The indications for acarbose in the SEMDSA algorithm are identical to those for DPP-4 inhibitors (Table VI).

INCRETINS

Incretins are gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating. One of their many physiological roles is to increase of insulin secretion and suppress glucagon secretion from the beta and alpha cells of the pancreas respectively, after eating. The net effect is to increase insulin-mediated glucose disposal in peripheral tissues and to suppress hepatic glucose production, both of which result in lowering of blood glucose. These effects of incretins have made them suitable targets for pharmacological development.

The incretin effect

According to the incretin effect, oral glucose has a greater stimulatory effect on insulin secretion than intravenous glucose. This is mediated by several gastrointestinal peptides, particularly glucagon-like peptide-1 (GLP-1). GLP-1 also suppresses glucagon production and, in pharmacological doses, can delay gastric emptying and reduce food intake.

GLP-1 levels are abnormally low in patients with type 2 diabetes mellitus (diabetes). Endogenous GLP-1 has a short half-life of one to two minutes, as a result of rapid degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). GLP-1 levels can be raised therapeutically by the use of injectable GLP-1 agonists that are resistant to enzymatic degradation, or by oral DPP-4 inhibitors (DPP4), which inhibit the degradation of endogenous GLP-1. When used alone, incretin mimetics do not cause hypoglycemia, because the effect on insulin and glucagon secretion is glucose dependent.

9.4 Dipeptidyl peptidase-4 inhibitor (gliptins)

9.4.1 Mechanism of action

In animal models, GLP-1 stimulates beta-cell proliferation and differentiation, and reduces apoptosis. However, the potential to positively impact on beta cell survival in humans has not been proven.

9.4.2 Efficacy

The DPP-4 inhibitors appear to have similar efficacy, and will reduce HbA_{1c} modestly, by 0.5-1.1%, when compared to placebo.

9.4.3 Dosing

The DPP-4 inihibitors include linagliptin, saxagliptin, sitagliptin and vildagliptin. These drugs are taken orally most are given once daily. No dose titration is necessary. Table IV provides a summary of the doses of the DPP-4 inhibitors.

9.4.4 Adverse effects and contraindications

DPP-4 inhibitors appear to have a good safety profile in short-term studies (6-24 months), where the majority of monotherapy studies reveal a safety profile comparable to that of placebo. They do not cause weight gain or hypoglycaemia, except when combined with other drugs capable of causing hypoglycaemia. DPP-4 inhibitors can be used in elderly patients without dose adjustments.

Uncommon potential adverse events include:
- Nasopharyngitis
- Urinary tract infections
- Lymphopenia

Table IV: Doses of DPP-4 inhibitors

DPP-4 inhibitor	Recommended dose	Renal impairment	Hepatic impairment
Linagliptin[a,b]	5 mg once daily	No dose adjustment	No dose adjustment
Saxagliptin[c]	5 mg once daily	eGFR < 50 ml/minute: use 2.5 mg once daily	Contraindicated in moderate to severe disease
Sitagliptin[a]	100 mg once daily	eGFR < 50 ml/minute: use 50 mg once daily eGFR < 50 ml/minute: use 25 mg once daily	Contraindicated in severe disease
Vildagliptin	50 mg twice daily (once daily with sulphonylureas)	Contraindicated	Contraindicated in moderate to severe disease

a: No registration in South Africa at time of publication (March 2012)
b: Linagliptin should not be used if the patient is being treated with a P-glycoprotein or cytochrome (CY) P3A4 inducer, e.g. rifampicin
c: The dose of saxagliptin requires adjustment if taken concurrently with a strong CYP3A4/5 inhibitor, e.g. ketoconazole, itraconazole, indinavir, nelfinavir, ritonavir, saquinavir

- Pancreatitis
- Hypersensitivity skin reactions.

9.4.5 DPP-4 inhibitors in the 2012 SEMDSA treatment algorithm

The clinical use of DPP-4 inhibitors is summarised in Table V.

9.5 GLP-1 agonists

9.5.1 Mechanism of action

Refer to the section on "the incretin effect" above.

9.5.2 Efficacy

The GLP-1 agonists are associated with a reduction in HbA_{1c} that is similar to introducing another oral agent or insulin (Table VI). Liraglutide appears to be slightly more potent than exenatide, especially where fasting glucose is concerned. This effect results from the longer activity profile of liruglutide. The main advantage is that unlike most other diabetes drugs, the GLP-1 agonists promote weight loss. In the LEAD-6 study which compared liraglutide 1.8mg with exenatide 10 µg twice daily in patients inadequately

Table V: Acarbose and DPP-4 inhibitors in the 2012 SEMDSA treatment algorithm

Absolute contraindications
- There is a compelling indication for insulin therapy - History of a serious hypersensitivity reaction to DPP-4 inhibitors. - Patients with a history of acute pancreatitis, chronic or recurring pancreatitis and those with pancreatic cancer.
Indications for DPP-4 inhibitors or acarbose
At Step 3: Add-on therapy as part of an oral three-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control with combination therapy with maximally tolerated doses of metformin and sulphonylureas, **and** ☐ Patient is a poor candidate for insulin therapy (See Table IX), **and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
At Step 2: Add-on therapy as part of an oral two-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control on monotherapy with metformin (at maximally tolerated dose) or a sulphonylurea (at least at half of maximal dose or highest tolerated dose), **and** ☐ Unable to tolerate or has contraindications to addition of the second, as yet unused agent, from the above mentioned (metformin or sulphonylurea)**, and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
At Step 1: Use as monotherapy (must meet all criteria) ☐ Candidate for oral therapy and is intolerant of or has contraindications to use of both metformin and sulphonylureas**, and** ☐ Reduction in HbA_{1c} < 1% required in order to reach patient-specific goal.
Dose:
Refer to product labeling for dosing information.
Discontinuation:
Discontinue if HbA_{1c} reduction < 0.5% after three to six months of therapy.

Table VI: Mean expected reduction in HbA1c levels for the GLP-1 agonists

	Exenatide	Liraglutide 1.2mg
Monotherapy	0.9%	1.1%
Added to existing metformin	Up to 1.4%; mean 1.0%	1.0%
Added to existing sulphonylurea	Up to 1.4%; mean 1.0%	1.1%
Added to existing metformin plus a sulphonylurea	1.1%	1.3%

Table VII: Dosing information of GLP-1 agonists

	Exenatide	Liraglutide
Recommended daily dose	Initial dose: 5 µg per dose, twice daily. If initial dose is tolerated and a dosage increase is indicated, increase the dose to 10 µg twice daily after one month of therapy.	Initial dose: 0.6 mg per day for one week. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycaemic control, the dose can be increased to 1.8 mg.
Dosing frequency	Twice daily, any time within the 60-minute period before the morning and evening meals. Should not be administered after a meal. If a dose is missed, the treatment regimen should be resumed with the next scheduled dose.	Once daily, any time of day, independently of meals
Renal impairment	Contraindicated if eGFR < 30 ml/minute	No adjustment
Use with sulphonylureas	A lower dose of the sulphonylurea may be required, as hypoglycaemia has been reported more often in those treated with this combination	
Injection sites	Thighs, abdomen or upper arms	

Table VIII: GLP-1 agonists in the 2012 SEMDSA treatment algorithm

Contraindications
- There is a compelling indication for insulin therapy. - History of hypersensitivity to GLP-1 agonists. - Renal failure (consult product label to assess suitability). - Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (liraglutide). - Patient has severe gastrointestinal disease, including gastroparesis. - Patient has a history of pancreatitis. - Relative exclusions to use include triglyceride level > 10 mmol/l, gallstones with intact gallbladder, and alcohol abuse. - Planned treatment regimen includes a DPP-4 inhibitor, meglitinide or acarbose (unstudied). - Patient is not obese
Indications for GLP-1 agonist use
At Step 3: Add-on therapy as part of a three-drug regimen (must meet all criteria) ☐ Inadequate glycaemic control on combination therapy with maximally tolerated doses of metformin and sulphonylureas**, and** ☐ Patient is not a candidate for a third oral agent from step 3, **and** ☐ Patient is a poor candidate for insulin therapy (see Table IX), **and** ☐ Reduction in HbA_{1c} < 1,5% required in order to reach patient-specific goal. ***At Step 2: Add-on therapy as part of a two-drug regimen (must meet all criteria)*** ☐ Patient has not achieved desired HbA_{1c} with one oral agent and is not a candidate for any other agent (oral or insulin) available at Step 2; **and** ☐ Reduction in HbA_{1c} < 1.5% required in order to reach patient-specific goal.
Dose
Refer to product labeling for dosing information.
Follow-up
Only continue therapy beyond six months if there has been a good clinical response to therapy: - HbA_{1c} reduction > 0.5% *and* weight loss > 3%, *or* - HbA_{1c} reduction > 1%, *or* - Weight loss > 5%

Table IX: Circumstances where insulin therapy may not be desirable

- Insulin allergy
- Failure or inability to master injections or self-titration
- Frequent or severe hypoglycemia despite multiple dosage adjustments
- Circumstances exist where the risk of severe hypoglycemia and/or its potential consequences are significant and/or catastrophic
- Workers with frequent rotating shifts
- Occupations such as truck or bus drivers / heavy machinery operators)
- Obesity related morbidity which has worsened or is likely to worsen significantly with weight gain from insulin therapy

controlled on metformin and / or a sulphonylurea, the mean weight loss over 26 weeks was about 3kg. The HbA1C reduction with liraglutide was 1.1% versus 0.8% with exenatide.

9.5.3 Dosing

Exenatide and liraglutide are examples of GLP-1 agonists. The GLP-1 agonists are available only as injectables in the form of pen devices. Exenatide is distributed as 5 µg and 10 µg pens; liraglutide, as a single multi-dose pen delivering 0.6–1.8 mg per injection. The dose of liraglutide should not exceed 1.2 mg, as the 1.8 mg is only marginally more effective.

The GLP-1 agonists are approved for combination therapy with metformin and/or sulphonylureas. Liraglutide is also licensed for use as initial monotherapy. There are some promising data on combinations with insulin, but this is not yet an approved indication. There is no data on combinations with acarbose or DPP-4 inhibitors.

Table VII provides a summary of the dosing information of the GLP-1 agonists.

9.5.4 Adverse effects and contraindications

While the GLP-1 agonists do not, by themselves, cause hypoglycaemia, the risk is increased when used with sulphonylureas. It is advisable to reduce the sulphonylurea dose when adding a GLP-1 agonist.

The common side-effect on initiating therapy is nausea and vomiting (approximately 25%), and this can be severe, leading to discontinuation in some. It is usually transient (4-8 weeks), can be minimised by titrating up the dose slowly, and it responds to anti-nausea medication. Both the GLP-1 agonists should probably be avoided in patients with significant gastrointestinal disease, particularly gastroparesis.

Recently, reports of pancreatitis with GLP-1 agonists have emerged. It is not clear whether pancreatitis is directly related to therapy but these drugs are best avoided in patients with a history of or potential for pancreatic disorders. Patients should be warned to report symptoms suggestive of pancreatitis immediately, discontinue the drug immediately on suspicion and not to restart a GLP-1 agonist if the diagnosis of pancreatitis is confirmed.

In animal models, liraglutide was associated with the development of C cell tumours. The possible effect on medullary thyroid carcinoma (MTC) in humans is not known. Nevertheless, liraglutide is contraindicated in patients with a history of MTC or multiple endocrine neoplasia syndrome (MENS) type 2.

Exenatide is cleared by the kidneys, and should not be prescribed in patients with severe renal impairment (i.e. eGFR < 30 ml/minute).

9.5.5 GLP-1 agonists in the 2012 SEMDSA treatment algorithm

The clinical use of GLP-1 agonists is summarised in Table VIII .

9.6 Thiazolidinediones

Thiazolidinediones are drugs that act as selective ligands for the nuclear transcription factor, peroxisome proliferator-activating receptor gamma (PPARγ), and cause increased insulin sensitivity through multiple mechanisms. These mechanisms include alteration in fatty acid uptake and in adipokine release. Rosiglitazone and pioglitazone belong to this class. These drugs are licensed for the treatment of type 2 diabetes, either alone or in combination with metformin, sulphonylureas and insulin.

Both rosiglitazone and pioglitazone have a modest effect on glycaemic control and, in maximal doses, lower HbA_{1c} by 1-1.5%. Both drugs increase high-density lipoprotein (HDL) cholesterol by approximately 10%. Pioglitazone has a neural effect on low-density lipoprotein (LDL) cholesterol, whereas rosiglitazone increases LDL cholesterol. Variable effects on triglycerides have been reported, and both agents lower blood pressure. Approximately 1-2 kg of weight gain occurs for every 1% reduction in HbA_{1c}.

In A Diabetes Outcome Progression Trial (ADOPT), rosiglitazone demonstrated superior durability in glycaemic control when compared to glibenclamide and metformin. A greater improvement in insulin sensitivity and beta cell function was also noted with rosiglitazone. Rosiglitazone has, however, been associated with an increase in adverse cardiovascular events in a meta-analysis, with and odds ratio for myocardial infarction of 1.43 [95% confidence interval (CI) 1.03-1.98, p=0.03]. A more recent meta-analysis has confirmed these initial findings. The Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Combination Therapy for Type 2 Diabetes (RECORD) trial showed an increased risk of heart failure and bone fractures when rosiglitazone was added to metformin or sulphonylurea drugs, but no increase in cardiovascular morbidity or mortality.

The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) was a secondary prevention study in subjects with type 2 diabetes and pre-existing cardiovascular disease. The addition of pioglitazone 45 mg daily to conventional therapy was inconclusive for the composite primary end-point, but led to a 16% reduction in a composite secondary end-point of death, non-fatal myocardial infarction and stroke (hazard ratio 0.841, 95% CI 0.72-0.98, p=0.0273) when compared to placebo. The Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial showed a reduction in progression of carotid intima media thickness with pioglitazone a compared to glimepiride, and the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE) trial showed a more favourable effect of pioglitazone on coronary atheroma volume, measured with intracoronary ultrasound, as compared to glimepiride.

Both rosiglitazone and pioglitazone cause fluid retention, and may precipitate or exacerbate cardiac failure. Heart failure approximately doubled in the rosiglitazone group in the RECORD trial, when compared to an active control. In the PROactive study, 11% of subjects in the pioglitazone group developed heart failure, compared to 8% in the control group (p<0.0001), although there was no increase in the rate of deaths as a result heart failure.

Fractures have occurred with greater frequency in association with both rosiglitazone and pioglitazone. In the ADOPT study, upper limb and foot fractures occurred significantly more frequently in women (but not men) treated with rosiglitazone, when compared to those treated with either metformin or glibenclamide. In the PERISCOPE trial, fractures occurred in 3% of the group treated with pioglitazone, as opposed to none in the control group, p=0.004.

Concern has been raised regarding a possible increase in neoplasms associated with the use of thiazolidinediones. In the RECORD trial, there was no increase in the incidence of malignancy in the rosiglitazone group. In the PROactive study, more bladder cancers and fewer breast cancers were reported in the pioglitazone group, although the small numbers prevented conclusions from being made. More recently, an interim report of a large managed health organisation study showed an excess of bladder cancers in subjects treated with pioglitazone for longer than 24 months (hazard ratio 1.4, 95% CI 1.03-2.00), but not for those exposed to shorter duration therapy. No increased risk of 10 other common cancers was found in a parallel study. In view of the possibility of an increased risk of bladder cancer, the French medicine regulatory agency (AFSSAPS) suspended the use of pioglitazone in that country in June 2011. In July 2011, the manufacturer of rosiglitazone (GlaxoSmithKline) voluntarily discontinued the supply of rosiglitazone (Avandia) in South Africa.

9.6.1 Thiazolidinediones in the 2012 SEMDSA treatment algorithm

Pioglitazone has been removed from the 2012 treatment algorithm. Rosiglitazone is no longer available in South Africa.

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