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GUIDELINES

Chapter 10: Glucose control: insulin therapy*

*The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. *Chapter 10. Glucose control: insulin therapy in 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S49-50.*

Drug Summary – Insulins

(**Refer to** Appendix 10.1 for a detailed review of insulin therapy)

Mode of action	Insulin and its analogues lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin inhibits lipolysis and proteolysis, and enhances protein synthesis.
Glycaemic efficacy and indications	Efficacy is theoretically unlimited but in practice may be limited by inadequate education and support, or by side effects (weight gain and hypoglycaemia). Insulin should be used in patients with features of metabolic decompensation (catabolic features, severe hyperglycaemia (fasting glucose > 14 mmol/L, random glucose > 16.5 mmol/L or a HbA_{1c} > 10%) or persistent ketosis at any stage of the disease. Insulin should be considered as one of the therapeutic options in patients not achieving adequate glycaemic control on 2 or 3 oral glucose lowering drugs.
Cardiovascular outcome trials	• UKPDS 10-year observational extension showed a decrease in myocardial infarction in the group where treatment had been intensified using insulin or a sulphonylurea • The ORIGIN trial did not show cardiovascular benefit when using a basal insulin analogue in patients with diabetes or intermediate dysglycaemia; it was neutral. • Multiple studies and meta-analyses suggest that insulin may be associated with adverse cardiovascular outcomes when compared to comparators (metformin and sulphonylureas).
Hypoglycaemia	When used as monotherapy, dual therapy or triple therapy most studies show that the addition of insulin increases the risk of hypoglycaemia. The rates of overall and nocturnal hypoglycaemia are lower with long-acting basal insulin analogues when compared to intermediate human insulins (NPH). Analogue basal insulins are preferred when hypoglycaemia is a limiting factor to achieving glycaemic control.
Weight	When used as monotherapy or as add on to oral hypoglycaemic agents most studies show that insulin causes weight gain. Weight gain over three years in the 4T study was 3.6 kg for basal and 5.7 kg for premix insulin. Insulin detemir, however, has been shown in a few studies to either be weight neutral or result in some weight loss in those patients that are overweight or obese.
Non-glycaemic benefits	Insulin also promotes protein synthesis, lipogenesis and increases the permeability of cells to potassium, magnesium and phosphate ions.
Side Effects and Precautions	• Fluid retention, oedema • Lipodystrophy • Local allergy • Systemic allergy • Existing cardiovascular disease: there is no evidence for the cardiovascular safety of insulin in patients with established cardiovascular disease, and some studies suggest a possible harmful effect. Avoiding hypoglycaemia takes precedence over intensive glycemic control in these patients.
Dosing and prescribing	Starting doses: • Basal insulin: Start 10 u at bedtime; monitor fasting glucose; educate the patient to titrate the dose using one of the titration algorithms to achieve fasting glucose targets (refer to Chapter 11, figure 2). • Premix insulin: When escalating from a basal insulin regimen to a premix regimen, administer two-thirds of the total basal insulin dose in the morning, and one-third in the evening. Educate the patient to titrate the doses using one of the titration algorithms to achieve pre-prandial glucose targets (refer to Chapter 11, figure 2). • Prescription for insulin must be accompanied with education about handling, storage, injection technique, injection sites, monitoring, titrating and the detection and management of hypoglycaemia.
Renal dosing	All insulin preparations are metabolised by the kidneys and will therefore require a dose reduction in patients with renal impairment.
Cost	Cost is variable depending on insulin type and dose, and is generally more expensive than oral agents. Refer to Appendix 10.2 for a complete list of insulins and prices.

SEMDSA 2017 Recommendations

Consider insulin as first-line therapy at diagnosis, and at any other point in the course of the disease, in the setting of metabolic decompensation with any of the following features: a. Catabolism (marked weight loss) b. Fasting plasma glucose levels >14 mmol/l c. Random glucose levels consistently >16.5 mmol/l d. HbA_{1c} > 10% e. Presence presence of persistent ketogenesis, ketoacidosis or or hyperosmolar non-ketotic state.	C
If insulin is needed at diagnosis, use either pre-mixed insulin twice daily or basal bolus intensive insulin therapy (specialist referral is recommended)	A
Initial insulin therapy at diagnosis is usually temporary, and most patients can be weaned off their insulin with the addition of oral agents. If the patient is not able to transition from insulin to oral therapy reconsider the diagnosis of type 2 diabetes, and refer to a specialist if in doubt.	C
Consider adding basal insulin as the third glucose lowering drug in patients not achieving or maintaining their glycaemic targets on a two-drug oral regimen, especially if targets are unlikely to be achieved with other third line options, and there are adequate resources to support insulin initiation and titration.	B
Insulin therapy must be accompanied with intensive patient education and support, which includes (but is not limited to) SMBG and titration instructions, as well as education about the risk of hypoglycaemia.	B
Analogue insulins offer some advantages over human insulins and are therefore preferred when the acquisition cost is similar.	C
If nocturnal hypoglycaemia is a limiting factor to achieving optimal glycaemic control, consider switching from a human basal insulin to an analogue basal insulin, such as insulin glargine or insulin detemir.	B
If glycaemic targets are not being met despite adequate titration of basal insulin, consider combination injectable therapies using a premix, a basal-plus (prandial insulin) or a basal insulin plus GLP-1 receptor agonist combination. Consider the advantages and disadvantages of each option for each individual patient.	B
Be aware that insulin therapy is associated with the highest rates of hypoglycaemia and weight gain when compared to other glucose lowering drugs. However this is not a reason to delay or withhold insulin therapy when it is needed.	A
Consider referring a patient to an endocrinologist or specialist physician when: • Glycaemic targets are unmet with basal insulin doses > 0.8 u/kg or > 60 u daily. • Glycaemic targets are unmet after 6 months of treatment • There is a need for a basal bolus insulin regimen • Glycaemic targets are unmet with premix insulin doses > 60 u twice daily.	C
• Choice of insulins: insulins with the lowest acquisition cost within each class are preferred. In each insulin class an insulin analogue is the preferred option if the acquisition cost is similar to that of a human insulin. Registered biosimilar preparations are safe and effective. The newer insulins, such as ultra-long acting premixes and U300 concentrated insulins, are not recommended for use at primary care level.	C

Do not persist with any chosen treatment if the HbA_{1c} has not decreased by > 0.5% after six months

Appendix 10.2: Insulin Preparations in South Africa

Basal Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Basal Analogue Insulins	Basaglar	Insulin Glargine	3x5 ml Cartridge	R523.57
	Basaglar	Insulin Glargine	3x5 ml Pen	R598.36
	Optisulin	Insulin Glargine	INJ	R623.30
	Levemir	Insulin Detemir	3x5 ml Cartridge	R678.14
	Lantus	Insulin Glargine	3x5 ml Pen	R688.84
	Levemir	Insulin Detemir	3x5 ml Pen	R800.88
Basal Human Insulins	Biosulin L	Lente Human Insulin	3x5 ml Cartridge	R346.24
	Biosulin N	Isophane Human Insulins	3x5 ml Cartridge	R346.24
	Humulin N		3x5 ml Cartridge	R450.54
	Humulin N		3x5 ml Pen	R450.55
	Protaphane HM		3x5 ml Pen	R627.47

Premix Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Premix Analogue Insulins	Humalog Mix25	Insulin Lispro + Insulin Lispro Protamine	3x5 ml Cartridge	R466.17
	Humalog Mix50		3x5 ml Cartridge	R466.17
	Humalog Mix25		3x5 ml Pen	R553.14
	Humalog Mix50		3x5 ml Pen	R553.15
	Humalog Mix 25		3x5 ml Pen	R595.66
	NovoMix 30	Biphasic Insulin Aspart	3x5 ml Pen	R603.37
	NovoMix 30		3x5 ml Cartridge	R643.76
	Ryzodeg®	Insulin Degludec+Aspart	3x5 ml Pen	R978.64
Premix Human Insulins	Biosulin 30-70	Biosynthetic Human Insulin: 30% Regular Insulin 70% Isophane Insulin	3x5 ml Cartridge	R346.24
	Humulin 30/70		3x5 ml Pen	R450.54
	Humulin 30/70		3x5 ml Cartridge	R450.54
	Actraphane HM		3x5 ml Pen	R593.07
	Actraphane HM		3x5 ml Pen	R627.47

Short/Rapid Acting Insulins

Insulin Type	Medicine Proprietary Name	Active Ingredients	Dosage Form	SEP (R)
Rapid Analogue Insulins	Humalog	Insulin Lispro	3x5 ml Pen	R432.82
	Humalog	Insulin Lispro	3x5 ml Cartridge	R432.82
	NovoRapid	Insulin Aspart	3x5 ml Cartridge	R487.62
	Apidra	Insulin Glulisine	3x5 ml Pen	R510.68
	NovoRapid	Insulin Aspart	3x5 ml Pen	R542.72
	Humalog	Insulin Lispro	3x5 ml Pen	R596.70
Short-Acting Human Insulins	Biosulin R	Regular Human Insulin (rDNA)	3x5 ml Cartridge	R346.24
	Humulin R		3x5 ml Pen	R370.59
	Humulin R		3x5 ml Cartridge	R430.83
	Actrapid HM (ge)		3x5 ml Pen	R491.94

Reference

South African Medicine Price Registery. Database Of Medicine Prices 14th March 2017. http://www.mpr.gov.za/Publish/ViewDocument.aspx?DocumentPublicationId=3285. [Accessed March 20, 2017.]