

Guideline for Insulin Therapeutic Review in patients with Type 2 Diabetes

1. Introduction

This guideline has been developed in order to support practices to undertake insulin therapeutic reviews as part of the annual review, opportunistically, or as part of the Enhanced Management of Diabetes (EMD) service. The drivers for this process are firstly clinical, to improve care for our diabetic patients; and secondly economic since there are considerable variations in the cost of insulin therapy.

The aim is to provide simple, straightforward information about different insulins available. It is not a replacement for detailed information about insulin initiation or continuing care of patients on insulin therapy.

The guideline describes various clinical scenarios which demonstrate how patients uncontrolled on their present insulin regimes, may be considered for alternative human insulin regimes.

The guideline is for **Type 2 diabetics only**.

Support for implementation of this guideline will be available from the West Berkshire Stakeholder Network ('Diabetes Sans Frontières'), CCG leads and Community DSNs.

2. Clinical care and economics

Analogue insulins (eg. Lantus (glargine), Levemir (detemir), NovoMix 30, NovoRapid, Humalog, Apidra) are more expensive than the older human insulins (eg. Insulatard, Insuman, Humulin) – in some cases more than double the cost (see Appendix for price comparisons). However, in Type 2 diabetes there is no evidence they improve control and NICE recommends the use of human insulins first-line. **Many Type 2 diabetics currently using analogue insulins can safely be switched to human insulins without difficulty and with no prejudice to their care. This will result in considerable cost savings.**

(ref: **Newer insulins in type 2 diabetes Edwin AM Gale, *BMJ* 2012; 345**
<http://dx.doi.org/10.1136/bmj.e4611> (Published 11 September 2012))

3. Commonly used Insulins (See Appendix for complete list including price comparison)

Analogue insulins

Once daily 'basal' insulins

Insulin Glargine (Lantus, Sanofi)

Insulin Detemir (Levemir, Novo Nordisk)

Twice daily Biphasic insulin 'mixtures'

NovoMix 30 (Novo Nordisk)

Humalog Mix 25 or 50 (Lilly)

Rapid acting insulins

Novorapid (Novo Nordisk)

Humalog (Lilly)

Apidra (Sanofi)

DSF preferred human insulins

Intermediate acting Isophane (NPH) insulins (once or twice daily)

Insuman Basal (Sanofi)

Humulin I (Lilly)

Insulatard (Novo)

Biphasic insulins (mixtures)

Insuman Comb 15, 25, 50 (Sanofi)

Humulin M3 (Lilly)

4. Patient Selection

In general, patients for review will be uncontrolled on present regime, ie. HbA1c >58mmol/mol (7.5%). In certain circumstances a higher HbA1c may be acceptable eg. elderly housebound where a once-daily insulin injection is all that is feasible.

5. Preliminary considerations

- **Is metformin dose maximised?** If not, and it is tolerated, increase to 1g twice daily after food. If possible, we should aim to get every Type 2 diabetic onto metformin. If standard metformin is not tolerated, then try using slow-release metformin (metformin mr, Glucophage SR) taken once daily after the evening meal, up to 2g.
- **Continue SU** if initiating insulin, at least to begin with.
- **How, where and when do they inject?** Some diabetics always inject into the same place in which case there will be fibrosis which reduces absorption. Encourage rotation of sites. Ask about timing in relation to eating and exercise.
- **What size needles do they use?** 4 or 5mm length are preferred since they are less painful and absorption will be steadier since they will not penetrate muscle.
- **Lifestyle factors:** diet and exercise
- **Consider GLP-1 analogues** (Exenatide, Liraglutide) if the BMI is >35 (beyond the scope of this review)

6. Analogue to human insulin conversion guidance for uncontrolled patients with type 2 diabetes

Analogue insulin regime	Suggested human insulin replacement regime
Basal analogue insulin (eg. once daily Glargine or Levemir)	Possibilities: a) Twice daily isophane (Insuman Basal Insulatard, Humulin I,) or mixture (Insuman 15/25/50, Humulin M3) where twice-daily dosing is feasible. Divide the original dose into equal parts to inject twice daily, then titrate up as necessary. Control may be better with mixtures than isophane. b) Some elderly housebound patients should probably remain on once-daily analogues, especially if given by DN, even if control is not so good. Once daily isophane can be considered.
Twice daily analogue mixture (eg. NovoMix 30, Humalog mix)	Twice daily mixture or isophane, SAME DOSE initially but then titrate up
Basal-bolus regime	Usually these patients can be conveniently switched to a twice-daily mixture to improve control, or onto twice daily isophane with the same total dose. Basal bolus is rarely necessary in Type 2 patients.

7. Injection devices

In order to keep costs as low as possible, consider changing injection devices from prefilled, disposable pens to cartridges loaded into permanent, re-usable pens. Most human insulin cartridges are significantly cheaper than the prefilled pens. In addition, there is less wastage and the 'permanent' pens are better made, easier to use and last for years. However, for some patients disposable pens are preferable since they are easier to use.

The ClikSTAR, NovoPen and Humapen Luxura reusable pens are quite similar and easy to use. The Autopen is a more complicated device and is not recommended unless the patient is already familiar with it and is competent in its use.

7.1 Reusable insulin pens

Injection device	Products which fit
ClikSTAR (<i>Sanofi</i>)	Sanofi cartridges (<i>Insuman, Lantus, Apidra</i>)
NovoPen (<i>Novo</i>)	NovoNordisk cartridges (<i>Insulatard, NovoMix, NovoRapid, Levemir</i>)
Humapen Luxura (<i>Lilly</i>)	Lilly cartridges (<i>Humulin, Humalog</i>)
(Autopen 24)	Sanofi cartridges (<i>Insuman, Lantus, Apidra</i>)
(Autopen Classic)	Lilly cartridges (<i>Humulin, Humalog</i>)

7.2 Disposable insulin pens

Injection device	Products for which available
SoloStar (<i>Sanofi</i>)	Sanofi insulins (<i>Insuman, Lantus, Apidra</i>)
FlexPen (<i>Novo</i>)	NovoNordisk insulins (<i>NovoMix, NovoRapid, Levemir</i>)
KwikPen (<i>Lilly</i>)	Lilly insulins (<i>Humulin, Humalog</i>)
InnoLet (<i>Novo</i>)*	NovoNordisk insulins (<i>Insulatard, Levemir</i>)

*The InnoLet is a disposable insulin pen made by Novo, available loaded with Insulatard or Levemir. It is a large, easy-to-use device and particularly suitable for elderly patients who have difficulty seeing or manipulating the smaller pens, or for others with poor sight or arthritis affecting the hands.

8. Other considerations

Dietary considerations possibly contributing to poor glycaemic control

In all overweight patients consider weight reduction and reducing carbohydrate portion size to improve glycaemic control (make use of carbohydrate portion size book as part of EMD service), enquire about alcohol intake, consider referral to Barometer or Weight No Longer.

Bariatric Surgery

Consider referring patients for an opinion regarding bariatric surgery particularly if on very high insulin doses and if BMI >45. NICE recommends bariatric surgery as treatment of choice for obese patients with BMI >50

9. New insulin starts

DSF recommends the use of human insulins for initiation of therapy in type 2 diabetics.

10. Isophane or Mixture?

Many patients will do well with isophane and this would probably be the insulin to start with.

Consider switching to a mixture if control is not satisfactory with Isophane; but the patient will need to understand that s/he will need to eat 30-45 minutes after injecting or there will be a risk of hypo.

APPENDIX A: Price comparison of analogue and human insulins

Biphasic analogue insulins (mixtures)

Manufacturer	Brand name	Cost per 5x3ml
Lilly	Humalog Mix25 (cartridges)	29.46
Lilly	Humalog Mix25 Kwikpen (disposable pens)	30.98
Novo Nordisk	NovoMix 30 Penfill cartridge	28.84
Novo Nordisk	NovoMix 30 FlexPen (disposable pens)	32.00

Once daily basal analogues

Sanofi	Lantus KlikSTAR (cartridge) (glargine)	41.50
Sanofi	Lantus SoloSTAR (disposable pens)	41.50
Novo Nordisk	Levemir cartridge (detemir)	42.00
Novo Nordisk	Levemir FlexPen (detemir)	42.00

Rapid acting analogues

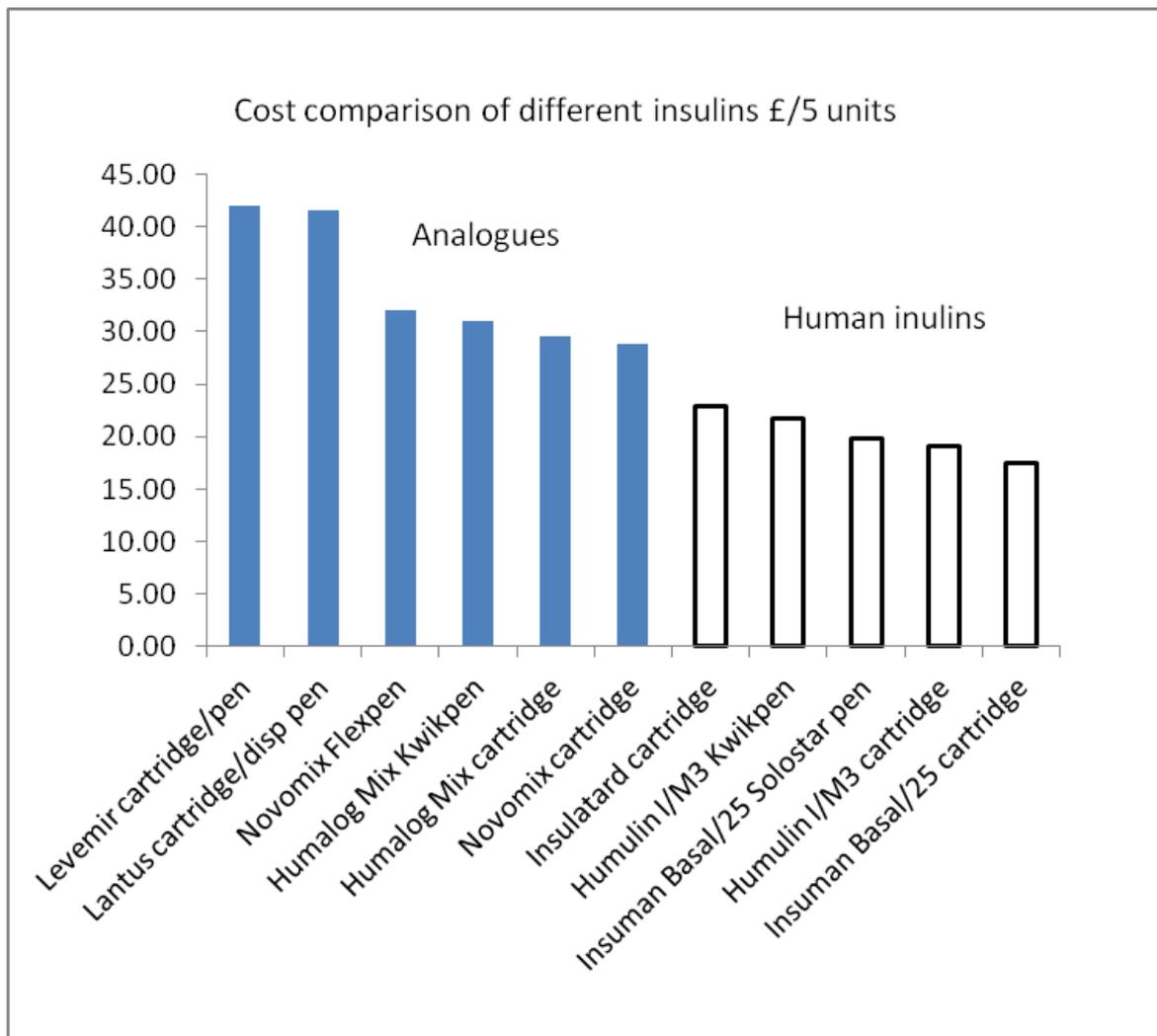
Novo Nordisk	NovoRapid cartridge	28.31
Novo Nordisk	NovoRapid FlexPen	30.60
Lilly	Humalog cartridge	28.31
Lilly	Humalog KwikPen	29.46
Sanofi	Apidra cartridge	28.30
Sanofi	Apidra SoloStar	28.30

Isophane insulins (once or twice daily)

Lilly	Humulin I cartridge	19.08
Lilly	Humulin I KwikPen (disposable pens)	21.70
Novo Nordisk	Insulatard Penfill cartridge	22.90
Novo Nordisk	Insulatard InnoLet disposable injection device	20.40
Sanofi	Insuman Basal KlikSTAR (cartridge)	17.50
Sanofi	Insuman Basal SoloSTAR (disposable pen)	19.80

Biphasic human insulins (mixtures)

Lilly	Humulin M3 (cartridge)	19.08
Lilly	Humulin M3 KwikPen (disposable pen)	21.70
Sanofi	Insuman Comb 15/25/50 KlikSTAR (cartridge)	17.50
Sanofi	Insuman Comb 15/25/50 SoloSTAR (prefilled pen)	19.80



APPENDIX B. Case Scenarios (For illustrative purposes only)

Scenario one

78 years old, BMI 28, HbA1c 8.8% (73mmol/mol). Uncontrolled on basal analogue insulin, Levemir 40U once daily.

Patient either underinsulinised with existing basal regime or needs conversion to a BD regime to cover post prandial glucose excursions

Consider dividing the total analogue insulin daily dose in two and changing to isophane insulin (eg. Humulin I, Insulatard, Insuman Basal 20 units twice daily) or an insulin mixture (eg. Humulin M3 or Insuman Comb 25, 20 units twice daily) and titrating the dose to achieve acceptable control. Both isophane and human mixtures should be given 30 minutes before main meals.

Scenario two

74 years old, BMI 23, HbA1c 8.4% (68 mmol/mol). Uncontrolled on basal insulin Glargine 24 units/day.

*As he is low weight, likely to be insulin sensitive and therefore may be considered at risk of hypo. It may be necessary to simply titrate the existing basal **analogue** regime. If unable to control, consider converting to BD human mixture (eg Humulin M3/Insuman Comb 25 twice daily, starting at 12units twice daily 30 minutes before food and titrating up).*

Basal-bolus regime may be considered inappropriate.

Scenario three

54 years, BMI 28, HbA1c 9.2% (77mmol/mol). Uncontrolled on NovoMix 30, 40 units twice daily)

Consider direct conversion to a human BD mixture eg Humulin M3, 40 units twice daily and titrate up.

Scenario four

48 years old, High BMI 37, HbA1c 10.3% (89mmol/mol). Uncontrolled on basal bolus regime: Glargine 60 units daily and NovoRapid 20 units TDS (total dose 120 units/day)

Despite a large dose of insulin, control is poor and an expensive and complex basal bolus regime is not justified - it does not work!

*Consider **reducing** insulin dose as this patient might be over-insulinised but resistant to the effects of insulin, hence poor control. Try halving insulin dose and monitor for any deterioration in blood glucose.. May benefit from weight loss as a result of insulin dose reduction. May be preferable to improve control via helping patient to reduce carbohydrate portion size.*

In addition to insulin dose reduction and dietary management, you could substitute a human twice daily insulin regime instead of continuing with the basal bolus. For this either isophane or a mixture would be suitable. So, as a first step reduce the basal bolus to half: 30 units of Glargine + 10 units tds of Novorapid; then, assuming no change in control, substitute 30 units bd of human isophane or a mixture.

This patient may also be suitable for a GLP-1 initiation. This could be purely a GLP-1, or a combination of GLP-1 and insulin (unlicensed use)