Switching from analogue insulin in type 2 diabetes

Key messages

- In type 2 diabetes, long acting analogue insulins have little or no advantage over human isophane (NPH)insulin in most people.
- **NICE** recommends human isophane (NPH)insulin in type 2 diabetes.
- **Start:** Patients with type 2 diabetes starting on insulin should commence with human isophane (NPH) insulin.
- **Switch:** People with type 2 diabetes already on long acting analogue insulin should be reviewed and those with poor glycaemic control switched to human isophane (NPH) insulin.
- **Simple:** Changing from analogue to human isophane insulin is usually simple dose for dose. The same pen can be used in most cases.

Aim of the guideline

Long acting analogue insulins are now the major cost of diabetes care. This does not represent good value for money. Human isophane (NPH) insulin has the same utility at considerably lower cost.

This guidance aims to reduce the use of long acting analogue insulin in patients with type 2 diabetes. Monies saved would be better spent on more cost-effective diabetes services.

What this guidance covers

The guidance concerns the choice of long acting insulin as part of the basal or basal-bolus regimes.

It covers the choice of insulin in type 2 diabetes once the decision to start has been made or patients already on long acting analogue insulin.

It does not include when or whether to start insulin nor does it include detailed insulin management.
Aim

Long acting analogue insulin; insulin detemir (Levemir), insulin glargine (Lantus) and the new insulin degludec (Tresiba) are used either singly or in combination with other insulins. They are an alternative to human isophane (NPH) insulin.

There are also biphasic analogue regimes which mix short acting and long acting analogues but these make up a smaller proportion of insulin use.

Our first priority is to reduce the use of long acting analogue insulin in basal or basal bolus regimens.

Why we are switching

For people with type 2 diabetes there is evidence that long acting analogue insulins confer little or no advantage over human insulin in the vast majority of people requiring insulin. They are very expensive and by any reasonable standard, their general use does not represent good value for money at current prices.

Long acting analogues now account for the major cost in the diabetes prescribing budget and switching half the current patients on long acting analogues to isophane insulin would save £180,000 every year in each CCG.

Despite clear NICE guidance to the contrary, analogue insulins have become the main preferred insulin used by hospitals and GPs in type 2 diabetes. Although east London has below average use of insulin in general, it has one of the highest proportions of people on analogue insulins. The bulk of analogue prescribing is for the long acting analogues, insulin detemir and glargine, which cost 2-4x as much as equivalent human insulin and reduction in their use is the main focus of this document.

The incremental cost-effectiveness ratios (ICERs) of analogue insulins are far outside accepted limits of cost effectiveness, with ICERs ranging from about £100,000 to £400,000 per quality-adjusted life year (QALY). These are vastly greater than the £20,000 to £30,000 per QALY threshold usually considered in NICE’s cost-effectiveness evaluation.

The current routine use of analogue insulins as first line insulin therapy is unjustifiable on cost-effectiveness grounds. They have little if any advantage over human isophane insulin for the vast majority of people and their long term safety is unknown. The money saved would be better spent on effective clinical services for preventing diabetes and reducing cardiovascular risk in diabetes.

At a local diabetes stakeholder meeting it was decided to support NICE guidance (p7) recommending that in type 2 diabetes:

- Patients starting on insulin should be started on human isophane (NPH) insulin, not on analogue insulin.
- Patients currently on long acting analogue insulin as a basal or basal bolus regime should be reviewed with a view to switching to human isophane insulin if HbA1c control is suboptimal.

Analogue insulins

Genetically engineered human insulin (NPH) was introduced in the 1980s to obtain smoother absorption by adding a protamine retarding agent, as in isophane insulin (also known as human NPH insulin – neutral protamine Hagedorn insulin). More recent analogue insulins also aimed to smooth delivery.

Insulin glargine forms an amorphous precipitate when exposed to tissue pH at the injection site, whereas insulin detemir has a fatty acid tail, which binds to albumin and buffers release of insulin.

“The insulin analogues are designed to modify the delivery of insulin to its target tissues, but not its action, and controversy revolves around the clinical utility of such pharmacokinetic differences” Gale E. Newer insulins in type 2 diabetes BMJ 2012 doi: 10.11.1136.
Starting and switching

If an insulin is to be started, this should be with human isophane (NPH) insulin.

All patients on long acting analogue insulins should be reviewed by their responsible clinician at the next appropriate review.

Patients on long acting analogue insulin should be changed to human isophane insulin if glycaemic control is suboptimal* and in particular if HbA1c is 75 mmol/mol (9%) or more - unless there are compelling reasons otherwise.

*What is considered optimal glycaemia may differ between individual patients particularly in regard to duration of diabetes.

How to switch insulin

In general the change from analogue to human insulin can be simply made dose for dose, with the type but not the dose of insulin changed. Patients can continue their usual blood glucose monitoring during the changeover.

Long acting insulin is usually given once daily in the evening prior to the evening meal but may alternatively be given in the morning. For specific advice, please consult you network diabetes nurse specialist.

The table below ensures there is a simple switch generally using the same insulin dose with the same pens, the only exception is the switch from Levemir FlexPen to Humulin I KwikPen.

<table>
<thead>
<tr>
<th>ANALOGUE</th>
<th>HUMAN ISOPHANE</th>
<th>SAME PEN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lantus cartridges</td>
<td>Inuman Basal cartridges</td>
<td>ClickStar pen</td>
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<tr>
<td>LantusSolostar</td>
<td>Inuman Basal Solostar</td>
<td>Prefilled Solostar pen</td>
</tr>
<tr>
<td>Levemir cartidges -</td>
<td>Insulatard cartridges</td>
<td>NovoPen4</td>
</tr>
<tr>
<td>Levemir Innolet</td>
<td>Insulatard Innolet</td>
<td>Prefilled clockdial disposable</td>
</tr>
<tr>
<td>Levemir FlexPen</td>
<td>Human I KwikPen</td>
<td>CHANGE OF PEN</td>
</tr>
<tr>
<td>Other vials and syringes (v few)</td>
<td>Any of the Human NPH insulins</td>
<td>FlexPen to KwikPen</td>
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Special consideration

HGV and PSV drivers already on a long acting analogue should remain on it unless there are clinical grounds for changing therapy.

Drivers of HGV or PSV vehicles are able to start on human isophane NPH insulin. If hypoglycaemia has been an issue on insulin, consideration should be given to the reasons for this and likely impact of treatment changes.

Human isophane NPH insulin is the preferred therapy for all other drivers starting or switching.

Housebound patients are often given their long acting insulin in the morning. Where there are problems delivering night time injections, day time injection is an option. Human isophane insulin confers similar flexibility in dose timing as analogue insulin.

Hypoglycaemia

Hypoglycaemia including nocturnal hypoglycaemia is an issue relevant to all types of insulin.

Hypoglycaemia is rarely due to the type of insulin used – it usually has a clear trigger related to insulin dose or environmental factors - timing of meals, missing meals, alcohol use, illness or other factors.

If hypoglycaemia is an issue then it should be confirmed and the causes addressed. Changing to analogue insulins will not rectify non-concordance with dietary advice and should not be used in this circumstance. Hypoglycaemia unawareness is very uncommon and can be dealt with depending on the specific clinical circumstance.

Analogue insulin and hypoglycaemia

The claimed benefits of the LA analogues relate entirely to their lower rates of hypoglycaemia.

A meta-analysis found statistically significantly lower rates of nocturnal hypoglycaemia and any hypoglycaemia with the LA analogues compared with human isophane insulin. There was no difference in severe hypoglycaemia.

Many of the studies were small, of short duration and some failed to report the data on which claims were made. Some of the studies exaggerated nocturnal hypoglycaemia by treating to low glucose targets.

The authors of the NHS Health Technology Assessment concluded “… even the effect on nocturnal hypoglycaemias was only minor”. Waugh et al Health Technol Assess. 2010 doi: 10.3310/hta14360.

In patients with clear environmental causes for hypoglycaemia, education and support is more likely to improve matters than analogue insulin.

Analogue insulin: other issues

In terms of overall HbA1c lowering, there is no difference between LA analogues and human isophane (NPH) insulin.

Like all other insulins, analogues cause weight gain averaging 5.7kg over 3 years in one recent trial. Adverse reactions are similar to other insulins with local reactions.

None of the trials provided data on effects of LA analogues on cardiovascular morbidity or mortality, long-term safety data or quality of life.

Alternative regimens

On reviewing insulin use it may be felt that basal insulin is no longer appropriate, in which case consideration can be given to alternative regimens using isophane insulin basal-bolus or biphasic.

It is practical to change one insulin at a time.

Patients experiencing recurrent severe hypoglycaemia should be managed in conjunction with specialist clinicians.

Training and education

A number of different people may administer insulin including district nurses, practice nurses and family members.

This guidance and educational events should be made available to the wider group of stakeholders and will be accompanied by a patient information leaflet.
NICE guidance

NICE guidance (May 2009 CG66 updated) states "The long-acting insulin analogues (glargine and detemir) did not appear to be cost-effective options when compared with NPH insulin.

NPH insulin should be used as the initial insulin.

The use of insulin glargine or insulin detemir could be recommended only after a trial of NPH insulin; recommendations were made on their use in subgroups with the greatest potential to benefit, based on clinical judgement."

Although there are a small number of circumstances identified by NICE where analogues might be beneficial, these are a matter of judgement and not mandatory. The current widespread use of analogue insulins outside these circumstances is contrary to NICE guidance.

NICE lists some possible circumstances where analogue insulin may be appropriate instead of NPH insulin:

• the person needs assistance from a carer or healthcare professional to inject insulin, and use of a long-acting insulin analogue (insulin detemir, insulin glargine) would reduce the frequency of injections from twice to once daily, or
• the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes, or
• the person would otherwise need twice-daily NPH insulin injections in combination with oral glucose-lowering drugs, or
• the person cannot use the device to inject NPH insulin.

Where patients have been started on analogue insulins without justification above, or the use of analogues have conferred no advantage, switching to NPH insulin is a more cost-effective option.

Long acting insulins

<table>
<thead>
<tr>
<th>ANALOGUE</th>
<th>ISOPHANE</th>
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<tbody>
<tr>
<td>Lantus - Insulin glargine</td>
<td>Insuman Basal</td>
</tr>
<tr>
<td>Leveimir - Insulin detemir</td>
<td>Insulatard</td>
</tr>
<tr>
<td>Tresiba - Insulin degludec</td>
<td>Humulin I</td>
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Long acting insulin are used in basal and basal-bolus regimens.

Basal

• Long-acting insulin or intermediate-acting insulin usually given once at bedtime or twice daily; usually with oral hypoglycaemic agents.
• District nurses often give housebound patients their insulin in the morning.
• Used when starting insulin in type 2 diabetes.

Basal-bolus

• Long acting or intermediate insulin usually given at bedtime or twice daily.
• Combined with rapid- or short-acting insulin injections to cover mealtimes.
• Offers greater flexibility and is the usual method to intensify insulin to control glycaemia.

Other insulins

Biphasic insulin

<table>
<thead>
<tr>
<th>ANALOGUE</th>
<th>ISOPHANE</th>
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<tbody>
<tr>
<td>NovoMix 30</td>
<td>Humulin M3</td>
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<tr>
<td>Humalog Mix25 or 50</td>
<td>Insuman Comb 15, 25 or 50</td>
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• Biphasic insulin usually twice but sometimes three times a day, before meals.

Short acting insulin

<table>
<thead>
<tr>
<th>ANALOGUE</th>
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<tbody>
<tr>
<td>Insulin aspart - NovoRapid</td>
<td>Actrapid</td>
</tr>
<tr>
<td>Insulin lispro - Humalog</td>
<td>Humulin S</td>
</tr>
<tr>
<td>Insulin glulisine – Apridra</td>
<td>Insuman Rapid</td>
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