Greater East Midlands
Commissioning Support Unit

Prescribing and Clinical Effectiveness Bulletin

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GUIDANCE ON THE CHOICE OF INSULIN REGIMENS FOR PEOPLE WITH TYPE 2 DIABETES MELLITUS

- **This guidance has been developed by PACEF in conjunction with United Lincolnshire Hospitals Specialist Diabetes Services and is intended to aid patient assessment and appropriate insulin selection in patients with type 2 diabetes mellitus (DM) requiring insulin for the first time. This guidance is not intended for patients with type 1 DM where a wider role for insulin analogues is acknowledged.**
- **Local figures suggest that first line use of insulin analogues in preference to human insulin is gaining ground in Lincolnshire even in those patients with type 2 DM for whom human insulin would have been an appropriate first line choice.**
- **Assessment criteria are provided that can be used to determine whether a patient should be managed on a human insulin regimen or a regimen using insulin analogues.**
- **First line use of twice daily human pre-mixed (biphasic) insulin should be considered, particularly when HbA1c is greater than 75mmol/mol. Alternatively, intermediate insulin (isophane, NPH) once or twice daily should be considered if HbA1c is modestly elevated above 58mmol/mol.**
- **Once daily long-acting insulin analogues (i.e. insulin glargine, insulin determir) should be considered if:**
  (1) the person requires help from a carer or healthcare professional to inject insulin and use of a long-acting insulin analogue would reduce the frequency of injections from twice to once daily or:
  (2) the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or is vulnerable to symptomatic hypoglycaemia.
  (3) twice-daily NPH insulin injections plus oral glucose-lowering medications would otherwise be needed or:
  (4) the person cannot use the device to inject NPH insulin.

New Drug Assessment: Insulin degludec 100units/ml and 200units/ml (*Tresiba*)

- **Insulin degludec (*Tresiba*) is designated AMBER (1) for patients with type 1 DM who have recurrent admissions with diabetic ketoacidosis due to poor adherance (2) for patients with type 1 DM with problematic or recurrent nocturnal hypoglycaemia on other long-acting analogues who are not suitable for insulin pump therapy and (3) for a small number of patients with type 2 DM with significant insulin resistance who might otherwise need large doses of *Humulin R* U500 insulin. Insulin degludec (*Tresiba*) should only be initiated by a consultant diabetologist.**
- **Prescribers should also be mindful of the drug safety advice issued by the MHRA in April 2013. Insulin degludec (*Tresiba*) is available in a pre-filled pen device (known as *Flex Touch*) in two strengths: 100units/ml and 200units/ml. The pre-filled pen devices have a dose-counter window that shows the number**

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of units of insulin degludec that will be injected, irrespective of strength. No dose conversion is needed when transferring a patient from one strength of insulin degludec to another. It is crucial that patients are trained in the correct use of *Tresiba* products, in particular how to check the dose-counter window on the pre-filled pen device. Patients should also be aware that two different strengths of the product are available.

- **Prescribers should ensure that the required strength of insulin degludec is always specified on the prescription. Pharmacists and dispensers should ensure that that strength is specified on the dispensed label.**

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SUMMARY OF PACEF DECISIONS: *APRIL2013 UPDATE*

Drug	Indication(s)	Traffic Light and Joint Formulary Status
Insulin degludec 100units/ml and 200units/ml (*Tresiba*)	For the treatment of adults with type 1 or type 2 DM.	AMBER Should only be initiated by a consultant diabetologist within defined criteria.

This bulletin has been created specifically to convey details of decisions taken at the Prescribing and Clinical Effectiveness Forum (PACEF) to all stakeholders across the Lincolnshire Healthcare Community in both primary and secondary care. Back issues of the *PACE Bulletin* and other PACEF publications are available through the NHS in Lincolnshire website (www.lincolnshire.nhs.uk). Follow the commissioning'link to PACEF.

GUIDANCE ON THE CHOICE OF INSULIN REGIMENS FOR PEOPLE WITH TYPE 2 DIABETES MELLITUS

Introduction

NICE Clinical Guideline 87 *Type 2 diabetes – The management of type 2 diabetes* (May 2009) (currently under review) recommends that insulin therapy in type 2 DM should be commenced with isophane insulin (human NPH) injected at bedtime or twice daily according to need with once daily long-acting insulin analogues to be considered as alternatives in specifically defined circumstances. Despite this, Lincolnshire performance against the national indicator designed to reflect insulin preference clearly indicates that insulin analogues are widely and increasingly being prescribed first line. The table below compares the performance of all four Lincolnshire CCGs against county and national averages:

	Percentage of intermediate and long-acting insulins prescribed as insulin analogues (insulin glargine or insulin determir)(Items)(December 2012 Qtr)
Lincolnshire East CCG	91.75%
Lincolnshire West CCG	89.01%
South Lincolnshire CCG	91.97%
South West Lincolnshire CCG	88.81%
Lincolnshire	90.63%
National	83.13%

In terms of change against time, national performance against this indicator is improving (i.e the percentage is declining), while Lincolnshire preference for insulin analogues continues to grow (i.e. the percentage is increasing).

It is the purpose of this special edition of the *PACE Bulletin* to clearly define the role of both isophane insulin (human NPH) and the once daily long-acting insulin analogues (i.e. insulin glargine, insulin determir). This guidance has been developed in conjunction United Lincolnshire Hospitals Trust Specialist Diabetes Services.

This guidance applies to type 2 DM only and for those commencing insulin, not for those for whom their existing regimen of insulin is satisfactory.

Assessment

Prior to initiation of insulin, every patient should be assessed and due consideration given to:

- Physical abilities (e.g. manual dexterity, tremor etc) - device suitability may influence insulin choice.
- Cognitive abilities (e.g. memory) - this may compromise the patient's ability to manage their own therapy or may lead to a specific device or regimen being chosen.
- Lifestyle (e.g. working practices, irregular working hours, irregular meal breaks, active hobbies etc) - this may influence dosage frequency and insulin choice.
- Medical needs (e.g. steroid use) - this may change the blood glucose profile resulting in elevation during the day and steep decline overnight.
- Dependence (e.g. needing a carer or support from a healthcare professional) - less frequent once daily administration may be more practical in this group.
- Vulnerability to hypoglycaemia (e.g. length of time having diabetes, vulnerability to falls, severe cardiovascular complications etc) – this may influence insulin choice.
- HbA1c - the level of HbA1c at the time of introducing insulin may influence regimen choice.

Assessment can be undertaken by suitably trained and experienced staff in general practice. Alternatively, the patient can be referred to the community diabetes specialist nursing team.

Regimen recommendations (see separate formulary section for product details)

First Line

- Consider a twice daily pre-mixed (biphasic) human insulin (particularly where HbA_{1C} > 75mmol/mol). Examples of biphasic pre-mixed human insulins include: *Humulin M3* and *Insuman Comb 15, 25* and *50*. Continue metformin if tolerated and not contra-indicated.
- Alternatively, consider once or twice daily intermediate insulin (isophane) with or without oral hypoglycaemic agents. This regimen is particularly useful for people with an HbA1c modestly elevated above 58mmol/mol who only require some initial background insulin in addition to pre-existing oral agents. Brands of human isophane insulin include *Insulatard*, *Humulin I* and *Insuman Basal*.

Alternatives

- Consider pre-mixed preparations that include short-acting insulin analogues rather than pre-mixed preparations that include short-acting human insulin preparations if:
    - injecting insulin immediately before a meal is required or
    - hypoglycaemia is a problem or
    - there are marked postprandial blood glucose excursions

  NovoMix 30 and *Humalog Mix 25* and *50* are available in biphasic formulations
- Consider using a long-acting insulin analogue (insulin glargine or insulin determir) if:
    - the person needs assistance from a carer or healthcare professional to inject insulin and the use of a long-acting analogue would reduce the frequency of injections from twice to once daily **or**
    - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or is vulnerable to symptomatic hypoglycaemia **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.
- Consider switching to a long-acting insulin analogue (detemir or glargine) from NPH in people:
    - who do not reach their target HbA1c because of significant hypoglycaemia **or**
    - who experience significant hypoglycaemia on NPH insulin irrespective of the level of HbA1c reached **or**
    - who cannot use the device needed to inject NPH insulin but who could administer their own insulin safely and accurately if a switch to a long-acting analogue were made **or**
    - who need help from a carer or healthcare professional to administer insulin injections and for whom switching to a long-acting insulin analogue would reduce the number of daily injections.

Consider using a basal bolus regimen in light of lifestyle (eg shift work or erratic eating pattern). Insulin analogues are more appropriate for this flexible regimen.

Self-monitoring of blood glucose should be available to all patients on insulin treatment. The person should understand the purpose of self-monitoring and how to interpret and act on results.

Monitoring and re-assessment of patients

If adequate glycaemic control is not achieved through the use of the regimens detailed above, assess the patient for:

- signs of lipodystrophy;
- evidence of poor injection technique;
- prevention and management of hypoglycaemia;
- signs of nocturnal hypoglycaemia;
- ability to self-adjust doses;
- erratic lifestyle or change in routine;
- engagement with regular exercise;
- weight loss plan (if appropriate).

Consider intensifying therapy by changing the insulin regimen if the agreed level of control if not achieved.

Refer to community diabetes specialist nurses as appropriate.

Reference:

NICE Clinical Guideline 87 *Type 2 diabetes – The management of type 2 diabetes* (May 2009)

NEW DRUG ASSESSMENT: *INSULIN DEGLUDEC 100 UNITS/ML AND 200 UNITS/ML (TRESIBA)*

Insulin degludec (*Tresiba*) is an ultra-long acting insulin analogue licensed for the treatment of adults with type 1 or type 2 DM. It has a half-life of longer than 25 hours and a duration of action that exceeds 40 hours. It is available as a 100units/ml *Penfill* cartridge for use in the *NovoPen 4/Novopen Echo* device or as a 100 units/ml or 200units/ml pre-filled *FlexTouch* pen.

The main supporting evidence for the use of insulin degludec in type 1 DM comes from an open-label randomised controlled trial (RCT) in 629 adults which compares insulin degludec with insulin glargine. The results show insulin degludec to be non-inferior to insulin glargine in terms of glycaemic control with both insulins reducing glycated haemoglobin (HbA1c) levels to a similar degree. In an analysis of secondary end points, insulin degludec was also shown to reduce the rate of nocturnal hypoglycaemia compared with insulin glargine. However, the absolute difference in this rate was small and the trial failed to find a difference in the rates of overall, daytime or severe hypoglycaemia. Further evidence submitted to the Scottish Medicines Consortium (SMC) has also shown that insulin degludec is non-inferior to insulin determir in terms of glycaemic control. There are no published studies comparing insulin degludec with isophane insulin (human NPH) and no long-term patient-oriented outcome or safety data.

The evidence base for use in type 2 DM comes from an open-label RCT in 1006 adults which compares insulin degludec with insulin glargine. Again, the results show insulin degludec to be non-inferior to insulin glargine in terms of glycaemic control. In an analysis of secondary end points, insulin degludec was also shown to reduce the overall rate of hypoglycaemia, nocturnal hypoglycaemia and (in a post-hoc analysis) daytime hypoglycaemia, compared with insulin glargine. Again, the absolute difference in these rates was small and the trial failed to find a difference in the rate of severe hypoglycaemia.

There are no published studies comparing insulin degludec with isophane insulin (human NPH) in either type 1 or type 2 DM and no long-term patient-oriented outcome or safety data.

Insulin degludec (*Tresiba*) is the first insulin approved in Europe at a higher strength than 100units/ml; a 200units/ml strength is also available. This has resulted in the MHRA issuing specific drug safety advice to minimise risks arising from patient confusion over strengths and doses (see below).

A cost comparison reveals that insulin degludec is almost double the cost of established long acting insulin analogues which, in turn, are significantly more costly than standard isophane (NPH) insulin (see Appendix 1). The annual cost of therapy with each type of insulin is estimated as follows:

	Annual Treatment Cost (assuming a dose of 30-60 units per day)
Insulin degludec (*Tresiba*) (Novo Nordisk)	£525 -£1,049
Insulin determir (*Levemir*) (Novo Nordisk)	£306 - £612
Insulin glargine (*Lantus*) (Sanofi)	£303 - £605
Isophane (NPH) insulin	£82 -164

PACEF Recommendation:
PACEF are supportive of the use of insulin analogues in both type 1 and type 2 DM within the context of NICE clinical guidelines. A review of published clinical trial data in both type 1 and type 2 DM reveals that insulin degludec (*Tresiba*) is non-inferior to insulin glargine and may have some benefits in terms of reduced nocturnal hypoglycaemia in type 1 DM and reduced nocturnal and daytime hypoglycaemia in type 2 DM. Further evidence submitted to the SMC suggests that insulin degludec may also be non-inferior to insulin determir. However, PACEF were concerned about the lack of comparative data against isophane insulin (human NPH) as well as a lack of patient orientated outcomes data and long-term safety data. Direct cost comparison also revealed that insulin degludec is almost double the cost of insulin determir and insulin glargine. Within this context, NICE have already expressed concern over the cost-effectiveness of existing insulin analogues. Published reviews of the trials have suggested that due to its limited benefits in comparison with insulin glargine, and its increased cost, insulin degludec should be reserved for those who struggle with glycaemic control overnight. As a result of this, insulin degludec (*Tresiba*) is designated AMBER (1) for patients with type 1 DM who have recurrent admissions with diabetic ketoacidosis due to poor adherance (2) for patients with type 1 DM with problematic or recurrent nocturnal hypoglycaemia on other long-acting analogues and are not suitable for insulin pump therapy and (3) for a small number of patients with type 2 DM with significant insulin resistance who might otherwise need large doses of *Humulin R* U500 insulin. Insulin degludec (*Tresiba*) should only be initiated by a consultant diabetologist. Prescribers should also be mindful of the drug safety advice issued by the MHRA in April 2013 and summarized below.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (APRIL 2013)

Insulin degludec (Tresiba): available in additional higher strengths than existing insulins – care needed to minimise risk of error

Insulin degludec (*Tresiba*) is available in a pre-filled pen device (known as *Flex Touch*) in two strengths:100units/ml and 200units/ml. The pre-filled pen devices have a dose-counter window that shows the number of units of insulin degludec that will be injected, irrespective of strength. No dose conversion is needed when transferring a patient from one strength of insulin degludec to another. It is crucial that patients are trained in the correct use of *Tresiba* products, in particular how to check the dose-counter window on the pre-filled pen device. Patients should also be aware that two different strengths of the product are available.

Prescribers should ensure that the required strength of insulin degludec is always specified on the prescription. Pharmacists and dispensers should ensure that that strength is specified on the dispensed label.

Reference:
MHRA, *Drug Safety Update* (April 2013)

Appendix 1 Formulary Products

Bi-Phasic Human (pre-mix neutral insulin/ isophane insulin)			
Product	**Device**	Price	**Company**
Humulin M3 30%/70%	**10ml vial** **5 x 3ml cartridges (for *Autopen Classic* , *Humapen Luxura and Savvio*)** **5 x 3ml *Kwikpen* prefilled device**	**£15.68** **£19.08** **£21.70**	**Lilly**
Insuman Comb 15 15%/85%	**5 x 3ml cartridge (for *Autopen 24* and *ClikSTAR*)**	**£17.50**	**Sanofi-Aventis**
Insuman Comb 25 25%/75%	**5ml vial** **5 x 3ml *SoloSTAR* prefilled device** **5 x 3ml cartridge (for *Autopen 24* and *ClikSTAR*)**	**£5.61** **£19.80** **£17.50**	**Sanofi-Aventis**
Insuman Comb 50 50%/50%	**5 x 3ml cartridge (for *Autopen 24* and *ClikSTAR*)**	**£17.50**	**Sanofi-Aventis**
Bi-Phasic Analogue (pre-mix)			
Novomix 30 Soluble (insulin aspart 30% + protamine insuin aspart 70%)	**5 x 3ml *Penfill* cartridges (for *Novopen 4* or *NovoPen Echo*)** **5 x 3ml *Flexpen* prefilled device**	**£28.79** **£29.89**	**Novo Nordisk**
Humalog Mix 25 (Insulin lispro 25% + insulin lispro protamine 75%)	**10ml vial** **5 x 3ml cartridges (for *Autopen Classic* or *Humapen*)** **5 x 3ml *Kwikpen* prefilled device**	**£16.61** **£29.46** **£30.98**	**Lilly**
Humalog Mix 50 (Insulin lispro 50% + protamine insulin aspart 50%)	**5 x 3ml cartridge (for Autopen Classic or Humapen)** **5 x 3ml *Kwikpen* prefilled device**	**£29.46** **£30.98**	**Lilly**
Intermediate Human Insulin (Isophane)			
Insulatard	**10ml vial** **5 x 3ml Penfill cartridges (for *Novopen 4* and**	**£7.48** **£22.90**	**Novo Nordisk**

	Novopen Echo) **5 x 3ml *InnoLet* prefilled device**	**£20.40**	
Humulin I	**10ml vial** **5 x 3ml cartridge (for *Autopen Classic* and *HumaPen* Luxura and Savvio ranges)** **5 x 3ml *Kwikpen* prefilled device**	**£15.68** **£19.08** **£21.70**	**Lilly**
Insuman Basal	**5ml vial** **5 x 3ml cartridges (for *Autopen 24* and *ClikSTAR*)** **5 x 3ml *SoloSTAR* prefilled device**	**£5.61** **£17.50** **£19.80**	**Sanofi-Aventis**
Long-Acting Insulin Analogue			
Insulin glargine LANTUS	**10ml vial** **5 x 3ml cartridges (for *Autopen 24* and *ClikSTAR*)** **5 x 3ml *SoloSTAR* prefilled device**	**£30.68** **£41.50** **£41.50**	**Sanofi-Aventis**
Insulin detemir LEVEMIR	**5 x 3ml *Penfill* cartridge (for *Novopen 4* or *Novopen Echo*)** **5 x 3ml *Flexpen* prefilled device** **5 x 3ml *InnoLet* prefilled device**	**£42.00** **£42.00** **£44.85**	**Novo Nordisk**
Insulin degludec TRESIBA	**5 x 3ml 100 units/ml *Penfill* cartridges (for *NovoPen 4* or *NovoPen Echo*)** **5 x 3ml 100 units/ml *FlexTouch* pre-filled pen** **3 x 3ml 200units/ml *FlexTouch* pre-filled pen**	**£72.00** **£72.00** **£86.40**	**Novo Nordisk**
Short Acting Human (Soluble)			
Humulin S	**10ml vial** **5 x 3ml cartridges (for *Autopen Classic* and *HumaPen* luxura and Savvio ranges)**	**£15.68** **£19.08**	**Lilly**
Insuman Rapid	**5 x 3ml cartridges (for *Autopen 24* and *ClikSTAR*)**	**£17.50**	**Sanofi-Aventis**
Actrapid	**10ml vial**	**£7.48**	**Novo Nordisk**
Rapid Acting Analogue			
Insulin aspart NOVORAPID	**10ml vial** **5x 3ml *Penfill* cartridges (for *Novopen 4* or *NovoPen Echo*)** **5 x 3ml *Flexpen* prefilled device** **5 x 3ml *FlexTouch* prefilled device**	**£14.08** **£28.31** **£30.60** **£32.13**	**Novo Nordisk**
Insulin glulisine APIDRA	**10ml vial** **5 x 3ml cartridges (for *Autopen 24* and *ClikSTAR*)** **5 x 3ml *SoloSTAR* prefilled device**	**£16.00** **£28.30** **£28.30**	**Sanofi-Aventis**
Insulin lispro HUMALOG	**10ml vial** **5 x 3ml cartridges (for *Autopen Classic* and *Humapen Luxura and Savvio ranges*)** **5 x 3ml *Kwikpen* prefilled device**	**£16.61** **£28.31** **£29.46**	**Lilly**

Other insulin products are available: Hypurin porcine and bovine
Other pens are available: Humapen Luxura HD and Humapen Memoir from Lilly; Autopen Classic and Autopen 24 from Owen Mumford; Novopen Echo from Novo Nordisk

Reference:

MIMS (May 2013)

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