NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 9 **August 2009**

What's new this month:

- **This issue of the *Bulletin* summarizes the key changes in the new NICE Clinical Guideline on the management of type 2 diabetes.**
- **As a result of this Guideline, sitagliptin (Januvia) has been re-classified as GREEN subject to NICE initiation criteria (see page 5).**
- **Both pioglitazone (Actos) and rosiglitazone (Avandia) remain GREEN, although it is recommended that new patients requiring glitazone therapy should be initiated on pioglitazone (see page 6).**
- **Exenatide (Byetta) remains GREEN and is now indicated for a wider range of patients (see page 8).**

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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 Lincolnshire website (www.lpct.nhs.uk).

SUMMARY OF PACEF DECISIONS: JUNE 2009 UPDATE

Drug	Indication(s)	Traffic Light Status
Exenatide 5microgram and 10microgram injection (Byetta)	Licensed for use with metformin and/or sulfonylureas in type 2 diabetes in patients inadequately controlled on maximally tolerated doses of these oral therapies	GREEN. N.B. **Treatment should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes** (GPSI), although the GREEN status allows for broader GP initiation. Exenatide initiation should only be considered at Step Three within the context of the NICE initiation criteria as detailed in the text.
Metformin sustained release tablets 500mg, 750mg and 1000mg (Glucophage SR)	Type 2 diabetes , particularly in overweight patients, when diet and exercise provide inadequate control	GREEN N.B. Can be used second line in those unable to tolerate standard release generic metformin tablets
Metformin powder for oral solution 500mg and 1000mg (Glucophage Powder)	Type 2 diabetes , particularly in overweight patients, when diet and exercise provide inadequate control	GREEN N.B. Can be used second line in those unable to swallow standard release generic metformin tablets or sustained release metformin tablets. Should be used in preference to the more costly metformin oral solution
Sitagliptin tablets 100mg	Licensed for dual therapy with	GREEN

(Januvia)	metformin or a glitazone for type 2 diabetes inadequately controlled by diet, exercise and either metformin or a glitazone alone; or with a sulfonylurea in patients with an intolerance or contraindication to metformin, inadequately controlled by maximal tolerated doses of sulfonylurea alone. Also licensed for triple therapy with metformin and a sulfonylurea for type 2 diabetes inadequately controlled by dual therapy.	N.B. Can be considered at step two in combination with either metformin or a sulfonylurea. Can also be considered at step three in combination with metformin and a sulfonylurea (see text for details).
Vildagliptin tablets 50mg (Galvus)	Licensed for the treatment of type 2 diabetes in combination with: (1) metformin, in patients inadequately controlled by maximal tolerated dose of metformin alone; (2) a sulfonylurea, in patients with an intolerance or contraindication to metformin inadequately controlled by maximal tolerated dose of sulfonylurea; (3) a glitazone, in patients with insufficient glycaemic control and for whom the use of glitazone is appropriate	RED-RED
Vildagliptin/metformin tablets 50mg/850mg and 50mg/1000mg (Eucreas)	Licensed for the treatment of type 2 diabetes in patients inadequately controlled by maximal tolerated dose of metformin alone or who are already treated with the combination of vildagliptin and metformin prescribed separately	RED-RED

RED-RED: This signifies that a product is **not recommended** for prescribing in **either** primary or secondary care. All new products are classified as RED-RED pending assessment by PACEF.
RED: This signifies that a product has been approved for use within secondary care, tertiary care or a primary care hosted specialist service only and **should not be routinely prescribed in primary care**. RED drugs may be used within ULHT or LPFT subject to approval for use within each Trust. ULHT/LPFT reserve the right to determine whether or not RED drugs will be used within their Trusts. RED classification does not automatically signify that a drug will be available within secondary/tertiary care.
AMBER: This signifies that a drug has been approved for use in primary care **subject to specialist initiation; a shared care guideline (SCG) may also be required**. The main purpose of the SCG will be to clearly define both specialist and GP responsibilities. Not all AMBER drugs that require SCGs are currently covered by formal documents; PACEF are working to rectify this.
GREEN: This signifies a product that is **approved for initiation in either primary or secondary care**. Specialist initiation and shared care guidelines are not considered necessary.

REPORTING INCIDENTS TO THE NATIONAL PATIENT SAFETY AGENCY (NPSA)
The NPSA are keen to encourage the anonymous reporting of patient safety errors and systems failures both from healthcare professionals and patients. The National Reporting and Learning System (NRLS) has been set up to facilitate this process. Healthcare professionals

can either report patient safety incidents through their local risk management scheme or directly into the NRLS using the eForm on the NPSA website. Please access www.npsa.nhs.uk for more information. **All healthcare professionals are encouraged to report incidents, errors and systems failures; the aim is to help the NHS to learn from things that go wrong.**

NICE CLINICAL GUIDELINE 87: *TYPE 2 DIABETES – THE MANAGEMENT OF TYPE 2 DIABETES* (PARTIAL UPDATE OF CG66) (MAY 2009)

This issue of the *PACE Bulletin* is designed specifically to reflect the key points of the recently updated NICE Clinical Guideline on the management of type 2 diabetes mellitus (CG87). There are some significant changes from the previous guideline (CG66) that are highlighted in the text.

The key points are as follows:

Glycated haemoglobin (HbA1c)

When setting a target glycated haemoglobin (HbA1c):

- Involve the person in decisions about their individual HbA1c target, which may be above the 6.5% set for people with type 2 DM in general.
- Encourage the person to maintain their individual target unless the resulting side effects (including hypoglycaemia) or their efforts to achieve this impair their quality of life.
- Offer therapy (lifestyle and medication) to help achieve and maintain the HbA1c target level.
- Inform a person with a higher HbA1c that any reduction in HbA1c towards the agreed target is advantageous to their future health.
- Avoid pursuing highly intensive management to levels of less than 6.5%.

Measure HbA1c levels at:

- 2-6 monthly intervals (tailored to individual needs) until the blood glucose level is stable on unchanging therapy
- 6 monthly intervals once the blood glucose level and blood glucose lowering therapy are stable.

PACEF Observations:
Large observational studies show a strong link between hyperglycaemia (as measured by HbA1c) and both macrovascular and microvascular complications; such complications are observed to show a marked reduction with tighter blood glucose control. Traditionally, observational data has been used to support the hypothesis that the lower the HbA1c the better. On the other hand, randomised controlled trials largely report no significant reductions in cardiovascular adverse outcomes associated with more intensive hypoglycaemic therapy compared to standard therapy. PACEF are continuing to monitor the emerging evidence in this complex area and are likely to issue additional guidance shortly. Local diabetologists advise that tight blood glucose control has lasting benefits in relation to both microvascular and macrovascular disease, particularly when pursued in younger newly diagnosed patients. For older patients, HbA1c targets may need to be less strict and should be tailored to the needs of the individual.

Self-monitoring of plasma glucose

- Self-monitoring of plasma glucose should be available:(1) to those on insulin treatment; (2) to those on oral glucose-lowering medications to provide information on hypoglycaemia; (3) to assess changes in glucose control

resulting from medications and lifestyle changes; (4) to monitor changes during intercurrent illness; (5) to ensure safety during activities, including driving.

- SMBG should be offered to newly diagnosed type 2 diabetics only as an integral part of his/her self-management education. The person should understand the purpose of self-monitoring and how to interpret and act on results.
- The person should be assessed at least annually to establish how self-monitoring skills are maintained, the quality and appropriate frequency of testing, how results are used, the impact on the person's quality of life, whether there is continued benefit and the equipment being used.
- If SMBG is appropriate but blood glucose monitoring is unacceptable to the individual discuss the use of urine glucose monitoring.

PACEF Recommendation:
Standard PACEF advice is that SMBG is recommended in type 1 DM, but is not recommended as standard for all type 2 diabetics. In type 2 DM, it should be used if the patient is on insulin or is experiencing hypoglycaemia, hyperglycaemia or other symptoms of poor diabetic control; it can also be a useful addition to education on diet and lifestyle and for patients with inter-current illness. It is unlikely to be necessary in patients controlled on diet and exercise alone. A typical frequency of testing for a type 2 diabetic not on insulin is once or twice a week. Patients drawing regular prescriptions for large quantities of blood glucose testing strips need to be identified and reviewed.

Blood-glucose-lowering therapy

Step One: If $HbA_{1C} \geq 6.5\%$ after trial of lifestyle interventions - initiate **metformin**.

Metformin

- **Start metformin in a person who is overweight or obese and whose BG is inadequately controlled by lifestyle intervention (nutrition and exercise) alone. Consider as a first line option even for those who are not overweight.**
- **Continue metformin even if BG control remains or becomes inadequate and another oral glucose-lowering medication (usually a sulfonylurea) is added.**
- Titrate up gradually over several weeks to minimise gastrointestinal (GI) side effects. Consider modified release metformin (Glucophage SR) if GI tolerability prevents the person continuing with metformin.
- Review metformin dose if serum creatinine >130umol/litre or estimated GFR is <45ml/min/1.73m^2.
- Stop metformin if serum creatinine > 150umol/litre or eGFR < 30ml/min/1.73m^2.
- Prescribe metformin with caution for those at risk of sudden deterioration in kidney function and those at risk of eGFR falling to <45ml/min/1.73m^2.

PACEF Recommendation: Metformin
The United Kingdom Prospective Diabetes Study (UKPDS) established metformin as the first line drug of choice for the treatment type 2 diabetes. In the study, metformin was shown to reduce the rates of myocardial infarction, diabetes related death and all-cause mortality. Standard release generic metformin tablets should be prescribed first line. Modified release metformin (Glucophage SR) is more costly, but may be an option in those experiencing

gastric intolerance with standard release metformin; it is a once daily formulation available in 500mg, 750mg and 1000mg strengths. Where a daily dose of 1500mg is indicated, the 750mg strength should be prescribed both to reduce the patient's tablet burden and to minimize the cost of treatment. Glucophage Powder for oral solution is comparably priced to Glucophage SR tablets and offers an alternative for patients with swallowing difficulties. It should be used in preference to the more costly metformin oral solution wherever possible. Prescribers are urged to utilize the range of alternative metformin formulations to enable as many people to benefit from metformin as possible.

Consider a sulfonylurea first line if:

- the person is not overweight.
- metformin is not tolerated or is contra-indicated.
- a rapid therapeutic response is required because of hyperglycaemic symptoms.

Step Two: If HbA_{1c} remains ≥ 6.5% - use **metformin and sulfonylurea combination therapy.**

Metformin and sulfonylurea

Insulin secretagogues: Sulfonylureas

- **A sulfonylurea should be added as second line therapy when BG control remains or becomes inadequate with metformin.**
- **Continue with a sulfonylurea even if BG control remains or becomes inadequate and another oral glucose-lowering medication is added.**
- Agents with a low acquisition cost should be prescribed.
- Once-daily sulfonylureas are preferred, particularly where concordance is a problem.
- Patients should be informed of the risk of hypoglycaemia.

PACEF Recommendation: Sulfonylureas
The once daily sulfonylurea of lowest acquisition cost is generic gliclazide (with generic glipizide as an alternative). Branded prescribing of any of these agents or use of Diamicron MR is not recommended.

Second Line Role of Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitaglitin and vildagliptin)

Consider adding a DPP-4 inhibitor instead of a sulfonylurea as second-line therapy to first-line metformin when control of BG remains or becomes inadequate (HbA_{1C} ≥ 6.5% or other higher level agreed with the individual) **if**:

- **The person is at significant risk of hypoglycaemia** or its consequences (e.g. older people, those working in certain jobs [i.e. working at heights or with heavy machinery] or **people in certain social circumstances** [i.e. those living alone] **or**
- **The person does not tolerate a sulfonylurea or a sulfonylurea is contra-indicated.**

Consider adding a DPP-4 inhibitor as second-line therapy to first-line sulfonylurea monotherapy when control of BG remains or becomes inadequate (HbA_{1C} ≥ 6.5% or other higher level agreed with the individual) **if**:

- **The person does not tolerate metformin or metformin is contra-indicated.**

Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1C} in six months).

- **A DPP-4 inhibitor may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if: (1) further weight gain would cause or exacerbate significant problems associated with high body weight; (2) a thiazolidinedione is contraindicated; or (3) the person has previously had a poor response to a thiazolidinedione.** Where either sitagliptin or a thiazolidinedione is suitable, the choice of treatment should be based on patient preference.

PACEF Recommendations: DPP-4 inhibitors

DPP-4 inhibitors are advocated by NICE at both steps 2 and 3 of the updated Clinical Guideline for type 2 diabetes. At step 2 they should be considered in combination with first line metformin in patients at significant risk of hypoglycaemia (where a sulfonylurea might be problematic), people living alone or in those for whom a sulfonylurea is contraindicated or not tolerated. Alternatively, they should be considered in combination with sulfonylurea monotherapy in patients unable to tolerate metformin or for whom metformin is contraindicated. At step 3 sitagliptin can be considered as part of triple therapy with metformin and a sulfonylurea when control of BG remains or becomes inadequate and insulin is unacceptable or inappropriate.

There are currently two DPP-4 inhibitors available in the UK, sitagliptin (Januvia) and vildagliptin (Galvus); vildagliptin is also available in combination with metformin (Eucreas). PACEF assessed all of these drugs and formulations shortly after launch and all were designated RED-RED. In response to this Clinical Guideline, all of these decisions have been reviewed. The NICE Guideline Development Group (GDG) reviewed all clinically relevant trials and concluded that DPP-4 inhibitors were non-inferior to sulfonylureas (specifically glipizide) and glitazones (pioglitazone and rosiglitazone) in terms of reduction in HbA1c. Sitagliptin and vildagliptin emerged as well tolerated with little difference in tolerability between the two in terms of discontinuation rates in trials. A recent Cochrane review highlighted headache as a problem, especially with vildagliptin. No cases of severe hypoglycaemia were reported in any of the trials for either drug; this is the basis for the recommendation that DPP-4 inhibitors should be considered in people at risk of hypoglycaemia. DPP-4 inhibitors were also found not to have caused weight gain in most cases, although the lack of long-term safety and outcomes data remains a concern. In the same Cochrane review an increase in all-cause infections was reported with DPP-4 inhibitors and it was recommended that their use should be avoided in patients with a history of recurrent urinary tract infections. DPP-4 inhibitors also contribute to T-cell activation which can compromise immune function. PACEF reviewed the full text guideline and concluded that it was justified to reclassify sitagliptin (Januvia) as GREEN subject to NICE initiation criteria. NICE have supported a role for DPP-4 inhibitors in both dual and triple therapy (see Step 3). At present, sitagliptin is the only DPP-4 inhibitor licensed for both of these indications. In addition, vildagliptin is contra-indicated in congestive heart failure (NYHA class III-IV) and should only be prescribed with caution in CHF NYHA class I-II; this renders the use of vildagliptin as a possible alternative to the glitazones potentially problematic. As a result of this, PACEF have re-classified sitagliptin (Januvia) as GREEN subject to NICE initiation criteria; vildagliptin (Galvus) and vildagliptin/metformin (Eucreas) retain their RED-RED classification.

Second Line role of Thiazolidinediones (pioglitazone, rosiglitazone)

- **Consider adding a thiazolidinedione instead of a sulfonylurea as a second line therapy to first-line metformin when control of BG remains or becomes inadequate** (HbA1c > 6.5% or other higher level agreed with the individual) **if: the person is at significant risk of hypoglycaemia or its consequences** (e.g. those working at heights or with heavy machinery) **or people in certain social circumstances** (e.g. those living alone) **or a sulfonylurea is contraindicated or not tolerated.**
- **Consider adding a thiazolidinedione as second-line therapy to first-line sulfonylurea monotherapy when control of BG remains or becomes inadequate** (HbA1c > 6.5% or other higher level agreed with the individual) **if: metformin is contraindicated or not tolerated.**
- Do not commence or continue a thiazolidonedione in people who have heart failure or who are at higher risk of fracture.
- If prescribing a glitazone, warn about significant oedema and tell the person what to do if this happens.
- When selecting a thiazolidinedione take into account up-to-date advice from the regulatory bodies (EMA and MHRA), cost, safety and prescribing issues.
- Only continue thiazolidinedione therapy if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1C} in six months).
- **A thiazolidinedione may be preferable to a DPP-4 inhibitor if: (1) the person has marked insulin insensitivity; (2) a DPP-4 inhibitor is contraindicated; or (3) the person has previously had a poor response to a DPP-4 inhibitor.** Where either a DPP-4 inhibitor or a thiazolidinedione is suitable, the choice of treatment should be based on patient preference

PACEF Recommendations: Thiazolidinediones (Glitazones)

Prescribers are reminded that glitazones are advocated by NICE at both steps 2 and 3 of the updated Clinical Guideline for type 2 diabetes. At step 2 they should be considered in combination with first line metformin in patients at significant risk of hypoglycaemia (where a sulfonylurea might be problematic), people living alone or in those for whom a sulfonylurea is contraindicated or not tolerated. Alternatively, they should be considered in combination with sulfonylurea monotherapy in patients unable to tolerate metformin or for whom metformin is contraindicated. At step 3, they can be considered as part of triple therapy with metformin and a sulfonylurea when control of BG remains or becomes inadequate and insulin is unacceptable or inappropriate.

The NICE GDG were concerned about an apparent increased risk of non-fatal myocardial infarction with rosiglitazone, but, despite reservations, were not minded to unequivocally recommend a preference for pioglitazone in all circumstances. Local diabetologist advice is that rosiglitazone should no longer be initiated due to concerns over cardiovascular safety. Where a glitazone is indicated, pioglitazone should be initiated.

All patients currently taking rosiglitazone and pioglitazone should have been reviewed to ensure that they are fully aware of the cardiovascular safety risks and that these risks are minimized. Both pioglitazone and rosiglitazone are contra-indicated in patients with cardiac failure or a history of cardiac failure. The European Medicines Agency (EMEA) has recommended that, in patients with ischaemic heart disease, rosiglitazone should only be used after careful evaluation of each patient's individual risk.

Fluid retention is well documented with glitazones and may exacerbate or precipitate heart failure, particularly in patients at risk (e.g. those with a prior MI or symptomatic coronary artery disease, the elderly, those with mild to moderate renal failure, those on concurrent NSAID or insulin therapy). Patients

should be monitored closely during treatment for signs and symptoms of fluid retention, including weight gain or oedema. Treatment should be stopped if any deterioration in cardiac status occurs. People who are at particular risk of heart failure should start rosiglitazone or pioglitazone at the lowest available dose; any dose increases should be done gradually.
The increased fracture risk with both of the glitazones necessitates the need for caution in those at risk. The FRAX assessment tool is a useful way of assessing fracture risk when considering a glitazone (www.shef.ac.uk/FRAX/tool.jsp)

Rapid-acting insulin secretagogues [e.g. nateglinide (Starlix) and repaglinide(Prandin)]

- Consider a rapid-acting insulin secretagogue in people with erratic lifestyles.

Acarbose (Glucobay)

- Consider acarbose for a person unable to use other glucose lowering medications.

Step Three: If HbA_{1C} remains $\geq$ 7.5%

- **Consider adding sitagliptin or a thiazolidinedione instead of insulin if insulin is unacceptable (because of employment, social, recreational or other personal issues or obesity).**
- **Consider adding exenatide to metformin and a sulfonylurea if criteria are met.**

Third Line Role of Dipeptidyl peptidase-4 (DPP-4) inhibitors (sitaglitin only)

- **Consider adding sitagliptin as a third-line therapy to first-line metformin and a second-line sulfonylurea when control of BG remains or becomes inadequate** (if $HbA_{1C} \geq$ 7.5% or other higher level agreed with the individual) **and insulin is unacceptable or inappropriate.**
- Only continue DPP-4 inhibitor therapy if the person has had a beneficial metabolic response (a reduction of at least 0.5 percentage points in HbA_{1C} in six months).
- **Sitagliptin may be preferable to a thiazolidinedione (pioglitazone, rosiglitazone) if: (1) further weight gain would cause or exacerbate significant problems associated with high body weight; (2) a thiazolidinedione is contraindicated; or (3) the person has previously had a poor response to a thiazolidinedione.** Where either sitagliptin or a thiazolidinedione is suitable, the choice of treatment should be based on patient preference.

PACEF Recommendation:
Sitagliptin (Galvus) is the only DPP-4 inhibitor licensed for triple therapy and appropriate for step 3 use. It is also the only DPP-4 inhibitor approved for use by Lincolnshire PACEF.

Third Line role of Thiazolidinediones (pioglitazone, rosiglitazone)

- **Consider adding a thiazolidinedione as third-line therapy to first-line metformin and a second-line sulfonylurea when control of BG remains or becomes inadequate** (HbA1c > 7.5% or other higher level agreed with the individual) **and insulin is unacceptable or inappropriate.**
- **A thiazolidinedione may be preferable to a DPP-4 inhibitor if: (1) the person has marked insulin insensitivity; (2) a DPP-4 inhibitor is**

contraindicated; or (3) the person has previously had a poor response to a DPP-4 inhibitor. Where either a DPP-4 inhibitor or a thiazolidinedione is suitable, the choice of treatment should be based on patient preference.

Glucagon Like Peptide -1 (GLP-1) Mimetic: Exenatide

Consider adding a GLP-1 mimetic (exenatide) as third line therapy to first line metformin and a second line sulfonylurea when control of BG remains or becomes inadequate (HbA1c > 7.5% or other higher level agreed with the individual) **and the person has:**

- **a BMI >35kg/m^2** in those of European descent (with appropriate adjustment for other ethnic groups) and **specific psychological, biochemical or physical problems arising from high body weight** or
- **a BMI < 35kg/m^2 and therapy with insulin would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities.**
- Only continue GLP-1 mimetic (exenatide) therapy if the person has had a beneficial metabolic response (a reduction of at least 1.0 percentage point in HbA_{1c} and a weight loss of at least 3% of initial body weight at 6 months).

PACEF Recommendations:

Prescribers are reminded that exenatide (Byetta) is classified as GREEN. Treatment should primarily be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation. Exenatide initiation should only be considered at Step Three within the context of the NICE initiation criteria as detailed above. These criteria have broadened in comparison to those published in NICE CG66. Patients with a BMI below 35kg/m^2 can now be considered where insulin initiation would have significant occupational implications or weight loss would benefit other significant obesity-related co-morbidities. Ongoing treatment should be reviewed and discontinued if the person is not deemed to be responding sufficiently as defined by the NICE review criteria detailed above.

Prescribers are also reminded of the risk of acute pancreatitis with exenatide. This has resulted in the MHRA issuing the following advice to healthcare professionals:

(1) Patients should be informed of the characteristic symptoms of acute pancreatitis (e.g. persistent severe abdominal pain; back pain may also be present).

(2) If pancreatitis is suspected, exenatide and other potentially suspect medicines should be discontinued.

(3) As with all new medicines, the safety of exenatide remains under close review and all suspected adverse reactions should be reported using the yellow card scheme.

Step Four: If HbA_{1C} remains ≥ 7.5%

Oral agent combination therapy with insulin

When starting basal insulin therapy:

- Continue with metformin and the sulfonylurea (and acarbose if used).
- Review the use of the sulfonylurea if hypoglycaemia occurs.
- When starting pre-mixed insulin therapy (or mealtime plus basal insulin regimens): continue with metformin; continue with sulfonylurea initially, but review and discontinue if hypoglycaemia occurs.

- For a person on dual therapy who is markedly hyperglycaemic, consider starting insulin in preference to adding other drugs to control BG unless there is strong justification not to.

Starting insulin

- When starting insulin, use a structured programme employing active insulin dose titration that encompasses: (1) structured education; (2) telephone support; (3) frequent self-monitoring; (4) dose titration to target; (5) dietary understanding; (6) management of hypoglycaemia; (7) management of acute changes in plasma glucose control; (8) support from an appropriately trained and experienced healthcare professional.
- Preferably, insulin therapy should be commenced with human NPH injected at bedtime or twice daily according to need. [NPH insulin is also known as isophane insulin; brands of human isophane insulin include Insulatard, Humulin I and Insuman Basal].
- Consider, as an alternative, a once daily long-acting insulin analogue (i.e. insulin glargine, insulin determir) if:
  - 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:
  - the person's lifestyle is restricted by recurrent symptomatic hypoglycaemic episodes or.
  - twice-daily NPH insulin injections plus oral glucose-lowering medications would otherwise be needed or
  - the person cannot use the device to inject NPH insulin.
- Consider twice daily biphasic human insulin (pre-mixed) regimens, particularly where HbA_{1C} > 9.0%. A once daily regimen may be an option when starting therapy. [Examples of biphasic human insulin pre-mixed include: Mixtard 30, Humulin M3 and Insuman Comb 15, 25 and 50.
- Consider pre-mixed insulin analogue preparations rather than pre-mixed human insulin preparations when: immediate injection before a meal is preferred or; hypoglycaemia is a problem or; there are marked postprandial blood glucose excursions [Insulin aspart (NovoMix 30) and insulin lispro (Humalog Mix 25 and 50) are available in biphasic formulations]
- Consider switching to a long-acting insulin analogue (insulin determir, insulin glargine) from NPH insulin in people: (1) who do not reach their target HbA1c because of significant hypoglycaemia or (2) who experience significant hypoglycaemia on NPH insulin irrespective of HbA1c reached or (3) 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 insulin analogue were made or (4) 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.

Step Five: If HbA1C remains ≥ 7.5%

- Increase insulin dose and intensify regimen over time.

Combination pioglitazone and insulin therapy

- **Consider combining pioglitazone with insulin therapy if a thiazolidinedione has had a marked glucose-lowering response previously or the person is on high-dose insulin and their BG is inadequately controlled.**

PACEF Recommendation: Glitazones and Insulin
The incidence of heart failure is increased when either rosiglitazone or pioglitazone is combined with insulin. Clinical trials have recorded an increased risk of cardiac ischaemia for rosiglitazone combined with insulin. This combination should only be used in exceptional circumstances and under close supervision.

Blood pressure management

- BP target should be < 140/80mmHg; if there is kidney, eye or cerebrovascular damage the target should be < 130/80mmHg.
- If BP reaches and consistently remains at target, monitor every 4 to 6 months.
- If not hypertensive or not suffering from renal disease, measure BP annually.
- If BP is above 150/90; repeat within one month.
- If BP is above140/80 or 130/80 with kidney, eye or cerebrovascular damage, repeat within 2 months.

If BP remains above target

Step One: Advice on lifestyle changes

If BP remains above target

Step Two: ACE Inhibitor (ACEI)

- For people of African-Caribbean descent use ACEI, plus diuretic or generic calcium channel blocker (CCB).
- If there is a risk of pregnancy, start with a CCB.
- If the patient is intolerant to an ACEI, change to an Angiotensin 2 Receptor Blocker (A2RB).

PACEF Recommendation:
Where an ACEI is indicated, low cost generically available ACEIs such as ramipril capsules (tablets are more expensive) and lisinopril tablets are recommended. Angiotensin 2 Receptor Blockers should only be considered where the patient has proven intolerance to at least one ACEI.

If BP remains above target

Step Three: Add CCB or diuretic (usually bendroflumethiazide 2.5mg daily).

PACEF Recommendation:
Where a CCB is indicated, generic amlodipine tablets are recommended.

If BP remains above target

Step Four: Add another drug (either diuretic or CCB dependent upon what has already been selected).

If BP remains above target

Step Five: Add an alpha blocker, beta blocker or potassium sparing diuretic. Exercise caution with the potassium sparing diuretic if already taking and ACEI or A2RB.

The management of blood lipids in type 2 Diabetes Mellitus

- Review CV risk status should be reviewed annually. Such an assessment should involve an assessment of risk factors (e.g. features of metabolic

syndrome and waist circumference), note changes in personal or family history and include a full lipid profile including HDL-C and TG.

- People should be considered at high premature cardiovascular (CV) risk unless **all** of the following apply: they are not overweight or hypertensive, they have no microalbuminuria, are a non-smoker, have no high-risk lipid profile, no history of CV disease and no family history of CVD.
- If the person is considered not to be at high CV risk, estimate risk annually using the UKPDS risk engine: (www.dtu.ox.ac.uk/index.php?maindoc=/riskengine/)
- For patients under 40 with a poor CV risk factor profile, consider a statin. Simvastatin 40mg or a statin of similar efficacy and cost [i.e. pravastatin] is advocated.
- For patients over 40 with a low CV risk for someone with type 2 DM, assess CV risk using the UKPDS risk engine. If CV risk is greater than 20% in 10 years utilize simvastatin 40mg or a statin of similar efficacy and cost {i.e. pravastatin}.
- If the patient is over 40 with a normal to high CV risk for someone with type 2 DM utilize simvastatin 40mg or a statin of similar efficacy and cost [i.e. pravastatin].
- Targets of 4mmol/l (TC) and 2mmol/l (LDL-C are advocated with simvastatin 80mg endorsed second line.

PACEF Recommendations:
Prescribers are reminded of standard advice on Lipid Modification that appeared in *PACE Bulletin* Vol 2, No 11 (July 2008):
Statin treatment should be initiated with simvastatin 40mg. If there are potential drug interactions, or simvastatin 40mg is contraindicated, an alternative low-cost preparation such as pravastatin should be chosen. If simvastatin 40mg is not tolerated, a lower dose or pravastatin should be chosen.
Targets of 4mmol/litre (TC) and 2mmol/litre (LDL-C) have been endorsed by NICE as an aspiration, but achievement is not an absolute necessity.
If the patient does not reach target on simvastatin 40mg, increase the dose to 80mg. If the patient does not reach the 4mmol/l and 2mmol/l targets on simvastatin 80mg (over half of patients will not), reduce aspiration to the minimum audit standard and QOF target of 5mmol/l (TC).
Maintain the patient on the dose of simvastatin that has either reached the 4 and 2mmol/l targets or the minimum audit standard of 5mmol/l (TC). Only consider higher-cost, higher-potency agents in those patients that remain above the minimum audit standard of 5mmol/l (TC) despite taking simvastatin 80mg or who are intolerant to simvastatin and pravastatin or have contra-indications or potential interactions.
Remember that high-cost high-potency statins like atorvastatin and rosuvastatin are effective, but have emerged from NICE cost-effectiveness evaluations as not cost-effective in most patients. As a result of this, their use should be restricted to the exceptional circumstances outlined above.

- More intensive statin therapy or the addition of ezetimibe is advocated if there is existing or newly diagnosed CV disease or increased albumin excretion rate. HDL-C should not exceed 1.4mmol/l; targets of 4mmol/l (TC) and 2mmol/l (LDL-C are advocated.
- Nicotinic acid preparations are not advocated routinely. They may have a role in those intolerant of other therapies with more extreme disorders of blood metabolism.

- Omega 3 fish oils are not recommended for primary prevention of CVD. Highly concentrated, licensed omega-3 fish oils [i.e. Omacor, Maxepa] may be considered for refractory hypertriglyceridaemia if lifestyle measure and fibrate therapy have failed.

PACEF Recommendation:
Prescribers are reminded that Omacor has been reviewed by PACEF and is classified as RED-RED both for hypertriglyceridaemia and for secondary prevention after myocardial infarction.

- If the patient has a high serum triglyceride (TG) assess possible secondary causes (e.g. poor glycaemic control).
- If TG remains above 4.5mmol/l despite optimised glycaemic control, offer a fibrate.

Anti-thrombotic therapy

- If the patient is 50+ and has a BP <145/90mmHg low dose aspirin 75mg is advocated (or clopidogrel if there is clear aspirin intolerance).
- If the patient is < 50 and has significant other CV risk factors (e.g. features of metabolic syndrome, strong early family history of CV disease, smoking, hypertension, extant CV disease, microalbuminuria), low dose aspirin 75mg is advocated (or clopidogrel if there is clear aspirin intolerance).

PACEF Recommendation:
PACEF are continuing to monitor the unfolding evidence base relating to the use of aspirin in the primary prevention of CVD. Most recently we published our review of the POPADAD study in *PACE Bulletin* Vol 3, No1 (January 2009). Our conclusions were as follows: POPADAD contributes to an expanding range of complementary trials that question current thinking around the assumed benefits of aspirin in the primary prevention of CV disease. Diabetics without CV disease who are experiencing harm, or are likely to experience harm from aspirin could reasonably discontinue aspirin since the risks are likely to exceed any possible benefits. Examples include patients experiencing dyspepsia (which may require symptomatic treatment), patients at high gastrointestinal risk and patients taking a large number of medicines who may wish to simplify their medicines regime.

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