NHS Lincolnshire

# Prescribing and Clinical Effectiveness Bulletin

**Volume 6; Number 8** **May 2012**

**What's new this month?**

- **The atorvastatin patent has expired and generic atorvastatin is now available. Reimbursement prices are expected to begin to fall as early as July 2012. Simvastatin 40mg remains the first line statin of choice with pravastatin 40mg for those who are intolerant to simvastatin. Where a higher-potency second line statin is indicated, atorvastatin is preferred. Practices are urged to switch all appropriate patients currently taking rosuvastatin (*Crestor*) to an equivalent dose lower cost alternative (see page 3).**
- **Supply problems with generic orlistat and *Xenical* present an opportunity to review therapy and consider alternatives (see page 5).**
- ***Actikerall* (5-fluorouracil 0.5% and salicylic acid 10%) cutaneous solution has been approved for use for hyperkeratotic actinic keratoses. Designation: GREEN subject to the individual prescriber feeling competent to initiate (see page 6).**
- **Asenapine sublingual tablets 5mg and 10mg (*Sycrest*) have been approved for use within LPFT for moderate to severe manic episodes associated with bipolar disorder in adults. Designation: RED (see page 6).**
- ***Optive* eye drops have not been approved for dry eye syndrome. Designation:RED-RED (see page 7).**
- **Tolvaptan 15mg and 30mg tablets *(Samsca)* have not been approved for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Designation: RED-RED (see page 7).**
- **The RESPeRATE device helps to regulate breathing and reduce blood pressure. It is not recommended for prescribing, although patients may choose to purchase their own RESPeRATE device if they wish. Designation: RED-RED (see page 8).**
- **The *InsuJet* needle free insulin delivery system is approved for use in patients with true and severe needle phobia. It should only be initiated following an assessment by a diabetes specialist nurse. Designation: AMBER (see page 9).**
- **Following a positive NICE technology appraisal, exenatide prolonged release injection (Bydureon) is confirmed as GREEN. Exenatide twice daily injection (Byetta) remains the glucagon-like peptide-1 (GLP-1) mimetic of first choice within NICE initiation criteria. Exenatide prolonged release injection (Bydureon) and liraglutide injection (Vicotoza) are both second line options (see page 11).**

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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.lincolnshire.nhs.uk). Click on 'Commissioning' and follow the links to PACEF.

## SUMMARY OF PACEF DECISIONS: *APRIL 2012 UPDATE*

| Drug | Indication(s) | Traffic Light Status |
|---|---|---|
| Actikerall (5-fluorouracil 0.5% and salicylic acid 10%) cutaneous solution | Licensed for the treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratoses (grade I/II) in immunocompetent patients. | GREEN<br>Subject to the individual prescriber feeling competent to initiate. Where GP initiation is a problem, Actikerall can be initiated and continued by a GP following referral to a dermatologist. |
| Asenapine sublingual tablets 5mg and 10mg (Sycrest) | Licensed for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. | RED<br>For specialist prescribing within LPFT only.<br>GP prescribing is not approved; any requests from consultant psychiatrists to initiate or continue asenapine therapy should be referred back to the specialist mental health service. |
| Exenatide prolonged release injection (Bydureon) | Licensed in combination with metformin or a sulfonylurea or both or with pioglitazone or with both metformin and pioglitazone in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. | GREEN<br>Treatment should be initiated by a diabetologist or a GP with a Special Interest in diabetes (GPSI), although the GREEN status allows for broader GP initiation.<br>Prolonged release once weekly exenatide should be reserved for those patients intolerant of twice daily exenatide. |
| InsuJet needle free insulin delivery system | Needle free insulin delivery system designed for those diabetics with a true needle phobia who are unable to use conventional injectable insulin therapy. | AMBER<br>Reserved for those with true and severe needle phobia only.<br>Refer to diabetes specialist nurse for assessment prior to initiation. |
| Optive eye drops (carmellose sodium 0.5%/glycerine 0.9%) | Licensed to the treatment of dry eye conditions | RED-RED |
| Pharmalgen bee venom extract<br>Pharmalgen wasp venom extract | Used to reduce the risk of severe anaphylaxis and systemic reaction in individuals with hypersensitivity to wasp and bee stings. | RED<br>Can only be used within a specialist centre only |
| RESPeRATE | An electronic device that aims to reduce BP through a series of breathing exercises aimed at reducing respiration rate to less than 10 breaths per minute. | RED-RED |
| Tocilizumab intravenous infusion (RoActemra) | Licensed for use in patients with moderate to severe active rheumatoid arthritis when response to at least one DMARD or TNF inhibitor has been inadequate or in those who are intolerant of these drugs. | RED |
| Tolvaptan tablets 15mg and 30mg (Samsca) | An oral selective vasopressin $V_2$ receptor antagonist licensed for the treatment of hyponatraemia | RED-RED |

| | | |
|---|---|---|
| | secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). | |

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 and 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.**

**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.**

## IN THE NEWS

### *ATORVASTATIN PATENT EXPIRY AND THE FUTURE ROLE OF ROSUVASTATIN*

The atorvastatin (Lipitor) patent expires in May 2012 with a number of generic versions already available from wholesalers. Strong competition between different generic atorvastatin manufacturers is likely to drive prices down relatively quickly. As a result, it is expected that generic atorvastatin will move into Category M of the *Drug Tariff* as early as July 2012. In preparation for this, PACEF have already endorsed atorvastatin as our preferred high-cost high-potency statin where lower cost generic statins are either insufficiently effective or poorly tolerated. In a best case scenario where atorvastatin prices fall to a level comparable with the current simvastatin 40mg generic price, the likely annual savings across Lincolnshire are £4M pa broken down across the four Lincolnshire Clinical Commissioning Groups as follows:

| **Clinical Commissioning Group** | **Potential Annual Saving** |
|---|---|
| Lincolnshire East CCG | £1,408,972 |
| Lincolnshire South CCG | £895,574 |
| Lincolnshire SW CCG | £570,574 |
| Lincolnshire West CCG | £1,128,572 |
| | |
| Lincolnshire | £4,003,693 |

The speed and extent to which generic atorvastatin prices will fall remains to be seen; while the financial impact of the atorvastatin patent expiry will be significant, it is likely to be 2013/14 before the full impact is felt. Prescribers, practices, localities and CCGs are urged to review the potential savings data provided down to individual practice level in the recently circulated *Prescribing and Medicines Optimisation Information Pack 2012/13.* This will enable individual practices to determine whether any work remains to be done in terms of optimising statin use, either through increasing use of first line simvastatin or through maximising savings from generic atorvastatin by switching away from rosuvastatin (Crestor) (see below).

**PACEF Recommendations:**
**Practices should continue to follow existing PACEF lipid modification guidance (see *PACE Bulletin* Vol 4 No 13 (August 2010)). Simvastatin 40mg remains the first line drug of choice in both primary and secondary prevention of CVD. In secondary prevention of CVD where treatment to target is advocated (5mmol/l Total Cholesterol; 3mmlol/l LDL-C), atorvastatin is the second line statin of choice (where simvastatin and pravastatin are either insufficiently effective or poorly tolerated). In primary prevention of CVD a standard 'fire-and-forget' dose of simvastatin 40mg (or pravastatin 40mg if not tolerated) should be sufficient for most patients.**

Rosuvastatin (Crestor) has a narrower range of licensed indications than most of the other statins. It is licensed for the treatment of hypercholesterolaemia (including familial hypercholesterolemia) and for the prevention of cardiovascular events in patients at high risk of first cardiovascular event (primary prevention).It is not licensed for the secondary prevention of cardiovascular disease, despite its widespread use for this indication. Until the publication of the JUPITER trial there was no published outcomes data available. The recently published SATURN study compared treatment with atorvastatin 80mg or rosuvastatin 40mg in people with coronary heart disease. Both groups saw a regression in atherosclerosis from baseline in about two-thirds of patients but there was no statistically significant difference between the two groups.

**PACEF Recommendations:**
**Rosuvastatin (Crestor) is not licensed for the secondary prevention of CVD despite the fact that the majority of prescriptions written for rosuvastatin each year are for this indication. Safety concerns remain around the risk of muscle disorders and rhabdomyolysis at the higher doses and have been recently reiterated by the MHRA (see *PACE Bulletin*, Vol 6 No 3 (January 2012)). As a result of this, the prescribing of rosuvastatin is only justified if a patient does not respond adequately to maximal doses of other statins or if a patient cannot tolerate alternatives. Advice from local cardiologists is that a low dose of rosuvastatin (5mg) may be tolerated where intolerance to other statins has been proven to be a problem. Rosuvastatin should always be considered prior to introducing ezetimibe as it is comparable in cost, substantially more effective at lowering TC and LDL-C and has published outcomes data. Rosuvastatin (Crestor) remains under patent until 2018 and is now the only remaining high-cost, high-potency branded statin. Prescribers are urged to review all patients currently taking rosuvastatin to ensure that: (1) rosuvastatin is not being inadvertently prescribed for primary prevention of CVD where simvastatin 40mg or pravastatin 40mg should be the dominant products; (2) the majority of patients prescribed rosuvastatin for secondary prevention of CVD are switched to simvastatin 40mg where this has never been tried or an equivalent dose of atorvastatin where a high-potency agent is clinically necessary. Patients who are intolerant to alternatives or who have failed to respond sufficiently to alternative statins can remain on rosuvastatin therapy, although this is envisaged to be far fewer patients than are currently treated with the drug.**

We currently spend almost £2Mpa on rosuvastatin in Lincolnshire; almost half of the rosuvastatin prescribed in the whole of the East Midlands is in our county. Now that the atorvastatin patent has expired, rosuvastatin to atorvastatin switches are likely to release an additional annual saving in Lincolnshire of £1.7Mpa (assuming that the price of generic atorvastatin will fall to a level comparable with generic simvastatin and that 80% of rosuvastatin scripts are appropriate to switch to generic

atorvastatin). The potential annual savings at CCG level from pursuing such a strategy are detailed below:

| Clinical Commissioning Group | Potential Annual Saving |
|---|---|
| Lincolnshire East CCG | £657,314 |
| Lincolnshire South CCG | £341,767 |
| Lincolnshire SW CCG | £232,366 |
| Lincolnshire West CCG | £465,034 |
| | |
| Lincolnshire | £1,696,482 |

**PACEF Conclusions;**
**The atorvastatin (Lipitor) patent expiry alone will potentially save £4Mpa across Lincolnshire. However, the full impact of this patent expiry is unlikely to be felt until 2013/14. Lincolnshire has high residual use of rosuvastatin and must tackle this problem to avoid continued investment in a high-cost long patent life statin until 2018. Rosuvastatin to atorvastatin switches are encouraged in 2012/13 in order to maximise the financial impact of the atorvastatin patent expiry as far as possible. Additional savings of £1.7Mpa across Lincolnshire could be achieved if rosuvastatin to atorvastatin switch programmes are implemented. The *Prescribing and Medicines Optimisation Information Pack 2012/13* provides a useful resource to enable practices and CCGs to identify problem areas and realise available efficiency savings.**

(This is a shortened and updated version of an article that originally appeared in *PACE Bulletin* Vol 6 No 4 (February 2012)).

## SUPPLY PROBLEMS WITH ORLISTAT (XENICAL)

Due to manufacturing problems, Roche are currently reporting that orlistat (Xenical) is out of stock and is likely to remain so for at least the next few weeks. There are also supply problems with the Teva orlistat generic. This presents an ideal opportunity to review orlistat use in accordance with the criteria defined in NICE Clinical Guideline 43.

NICE CG43 recommends that orlistat should only be started in people with a body mass index (BMI) of at least 30 kg/m$^2$ or at least 28kg/m$^2$ if other risk factors are present. It should be used as part of an overall plan for managing obesity after diet, exercise and behavioural approaches have been tried. Treatment should continue beyond 3 months only if the person loses at least 5% of their initial body weight. Less strict goals may be agreed with people with type 2 diabetes. The decision to use orlistat for longer than 12 months (usually for weight maintenance) should be made after discussing potential benefits and limitations with the patient. Regular review of orlistat, particularly after the first three months of treatment, can help to ensure that only those patients experiencing genuine benefit continue with treatment. A recent small study in one GP practice found that two-thirds of adults taking orlistat continued to be prescribed the drug beyond 3 months despite failure to achieve sufficient weight loss.

Potential alternatives to orlistat include:

- For BMI greater than 40 kg/m$^2$ (or greater than 38 kg/m$^2$ with co-morbidities) consider referral to the Phoenix Weight Management Service (Tel: (01522) 550683).

- For BMI greater than 30 kg/m$^2$ (or greater than 28 kg/m$^2$ with co-morbidities) consider GP medical referral for 12 weeks attendance at Weight Watchers.
- Referral into either the Phoenix Weight Management Service or Weight Watchers is possible if BMI is greater than 30 kg/m$^2$ (or greater than 28 kg/m$^2$ with co-morbidities).
- The Practice Nurses Phoenix Weight Management Step 2 service remains available.

**PACEF Recommendation:**
**Practices currently prescribing either generic orlistat or Xenical will need to review patients in response to the current supply difficulties. In the short to medium term, therapy will need to be discontinued until the supply situation improves. This provides an ideal opportunity to review the patient's progress and to consider signposting the patient to alternative weight management support services.**

## NEW PRODUCTS UPDATE

### NEW DRUG ASSESSMENT: *ACTIKERALL (5-FLUOROURACIL 0.5%/SALICYLIC ACID 10%) CUTANEOUS SOLUTION*

Actikerall is a new cutaneous solution containing 5-fluorouracil 0.5% and salicylic acid 10% licensed for the treatment of slightly palpable and/or moderately thick hyperkeratotic actinic keratoses (grade I/II) in immunocompetent patients. The product is administered using an applicator brush and is generally applied once daily.

Evidence to support the use of Actikerall comes from a single RCT in which Actikerall was compared with both diclofenac 3%/hyaluronic acid (HA) gel and with the Actikerall vehicle. Actikerall was superior to its vehicle and diclofenac 3%/ HA gel in terms of histological clearance of one representative lesion eight weeks post treatment. Significantly more lesions were cleared with Actikerall than with diclofenac 3%/HA gel or with the vehicle alone. Application site disorders were more common in the Actikerall arm, but were of mild to moderate intensity only.

The cost of Actikerall is £42.22 per bottle; this is broadly comparable to alternatives including 5-fluorouracil 5% cream (Efudix), diclofenac 3%/HA gel (Solaraze) and imiquimod 5% cream (Aldara). The Scottish Medicines Consortium approved Actikerall for use in NHS Scotland in September 2011 and published a cost-effectiveness assessment that concluded that Actikerall is more cost effective than both diclofenac 3%/HA gel and fluorouracil 5% cream.

**PACEF Recommendation:**
**Actikerall (5-fluorouracil 0.5%/salicylic acid 10%) cutaneous solution is approved for use. Designation: GREEN subject to the individual prescriber feeling competent to initiate. Where GP initiation is a problem, Actikerall can be initiated and continued by a GP following referral to a dermatologist.**

### NEW DRUG ASSESSMENT: ASENAPINE 5MG AND 10MG SUBLINGUAL TABLETS (SYCREST)

Asenapine (Sycrest) is licensed for the treatment of moderate to severe manic episodes associated with bipolar I disorder in adults. In trials, asenapine monotherapy demonstrated superior efficacy to placebo in reducing manic symptoms as measured using the Young Mania Rating Score at 3 weeks with maintenance of

effect at 12 weeks. In addition, asenapine in combination with lithium or valproate demonstrated superior efficacy to lithium or valproate monotherapy. There are no direct comparative data when asenapine is used as add-on treatment; indirect comparisons with other second generation antipsychotic agents used as monotherapy and as adjunctive therapy suggest equivalent efficacy. Asenapine has not been approved for use within NHS Scotland due to failure of the submitting company to present a sufficiently robust economic analysis to gain acceptance by the Scottish Medicines Consortium (SMC).

**PACEF Recommendation:**
**Concerns regarding the cost effectiveness of asenapine (Sycrest) for the treatment of moderate to severe manic episodes associated with bipolar disorder in adults remain unresolved. Nonetheless, asenapine is approved for limited use within Lincolnshire Partnership Foundation Trust as a second-line option after the use of a generic atypical antipsychotic (e.g. risperidone, olanzapine, quetiapine). Designation: RED. At this stage, GP prescribing is not approved; any requests from consultant psychiatrists to initiate or continue asenapine therapy should be referred back to the specialist mental health service.**

## RAPID DRUG ASSESSMENT:*OPTIVE EYE DROPS (CARMELLOSE SODIUM 0.5%/GLYCERINE 0.9%) FOR DRY EYE SYNDROME*

Optive eye drops (carmellose sodium 0.5%/glycerine 0.9%) are licensed for the treatment of dry eye conditions. The manufacturer claims a dual mechanism of action providing both lubrication and osmoprotection. In addition, a new preservative called purite is bactericidal in the bottle yet breaks down to harmless components when in contact with the eye. The addition of purite enables Optive eye drops to be used up to 180 days after opening. There are no published studies comparing Optive eye drops with hypromellose or any other product currently licensed for dry eye syndrome. At £7.49 for a 10ml bottle, Optive eye drops are significantly more expensive than established alternatives with no published comparative evidence to justify a role in treatment.

**PACEF Recommendation:**
**In view of the lack of comparative data and the significant additional cost, Optive eye drops are designated RED-RED.**

## NEW DRUG ASSESSMENT: *TOLVAPTAN 15MG AND 30MG TABLETS (SAMSCA)*

Tolvaptan (Samsca) is an oral selective vasopressin $V_2$ receptor antagonist licensed for the treatment of hyponatraemia secondary to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). It specifically targets the $V_2$ receptor, blocks the binding of arginine vasopressin in the kidneys and induces free water clearance without depleting electrolyes. Evidence from two randomised controlled trials known as Study of Ascending Levels of Tolvaptan in hyponatraemia 1 (SALT1) and SALT2 has shown superiority against placebo in the correction of hyponatraemia in patients with non-acute euvolaemic or hypervolaemic hyponatraemia. There are a number of limitations to the SALT studies: no indication is given of how hyponatraemia was treated in the placebo group and almost a quarter of patients taking tolvaptan and a third of patients taking placebo withdrew from the studies for undisclosed reasons.

An open-label study in a small number of patients has also shown a significantly larger increase in serum sodium and a quicker response to tolvaptan than fluid restriction.

Tolvaptan is significantly more expensive than established alternative therapy costing up to £5,000 per patient per month. Demeclocycline is a commonly used and much lower cost alternative; comparative data against demeclocycline is not currently available.

The most recent edition of the MHRA *Drug Safety Update* (April 2012) draws attention to the risk of over-rapid correction of hyponatraemia with tolvaptan and the risk of serious neurological events such as osmotic demyelination leading to dysarthria, mutism, dysphagia, lethargy, spastic quadriparesis, seizures, coma or death. Close monitoring of serum sodium during tolvaptan treatment is recommended.

**PACEF Recommendation:**
**PACEF remain concerned about the high cost of this therapy, the lack of comparative data against key alternatives such as demeclocycline and recent safety concerns raised by the MHRA. As a result of this, tolvaptan (Samsca) is designated RED-RED.**

## NEW DEVICE ASSESSMENT: *RESPeRATE*

Inappropriately high sympathetic nervous outflow from the central nervous system is believed to be an important component in the pathophysiology of acute and chronic hypertension. Elevated sympathetic activity is often associated with desensitization of arterial and cardiopulmonary baroreceptors, which leads to increased blood pressure (BP) fluctuation and sustained elevations in resting pressures. Slow breathing (less than 10 breaths per minute), especially with prolonged exhalation, appears to reduce sympathetic nerve traffic, resulting in arteriolar dilatation and a lowering of BP.

RESPeRATE is an electronic device that guides an individual through a series of breathing exercises aimed at reducing respiration rate to less than 10 breaths per minute. The device consists of a breathing sensor which is placed on the upper abdomen and generates a series of sounds linked to a person's breathing patterns; there are different tones for both exhaling and inhaling. The device gradually prolongs the exhalation tone and, if the person matches their breathing pattern to this pattern, their respiration rate will slow. It is claimed that using the device regularly will result in a 14/8 mm/hg reduction in blood pressure within eight weeks.

The recently published NICE Clinical Guideline on the management of hypertension was reviewed in detail in *PACE Bulletin* Vol 6 No 1 (January 2012). NICE recognise the potential benefits of relaxation therapies, but the guideline does not recommend the routine use of such therapies in primary care.

PACEF reviewed the combined results of five randomised controlled studies involving a total of 507 people (mean age 58); 78% of patients in the studies were taking antihypertensive medication with a third of these taking three agents or more; the average baseline BP was 150/90. The patients were randomly allocated to 15 minutes daily on the RESPeRATE device or 15minutes of relaxing music played on a Walkman. After 8 weeks, the RESPeRATE group demonstrated a 14/8 mmHg reduction in BP compared to 9/4 mmHg in the control group. A clinically sustained

reduction in BP typically occurred within three to four weeks of treatment; the most responsive group of patients were those over the age of 65.

There are no comparative studies between the RESPeRATE device and any other relaxation therapies such as meditation. The NHS price of the RESPeRATE device is £132.

**PACEF Recommendation:**
**Evidence from trials suggests that the RESPeRATE device can offer modest additional BP reduction beyond that achieved by antihypertensive medication in motivated individuals, However, additional benefit is small and, in the absence of further comparative trails, it is difficult to determine whether RESPeRATE offers any advantage over alternative relaxation strategies such as meditation. While NICE recognise the potential benefits of relaxation therapies, they do not recommend their routine use in primary care. As a result of this, RESPeRATE is not recommended for prescribing in Lincolnshire primary care; designation RED-RED. Patients interested in using this device should be advised to purchase their own either directly from the manufacturer or from an alternative retailer.**

## NEW DEVICE ASSESSMENT: *INSUJET NEEDLE FREE INSULIN DELIVERY SYSTEM*

InsuJet is one of two needle free insulin delivery systems currently available in the *Drug Tariff*. The device administers insulin at high pressure as a fine stream which penetrates the skin and produces a 'cone-like' spread of insulin through the subcutaneous tissue. It is intended to be used for those diabetics with a true needle phobia who are unable to use conventional injectable insulin therapy. The alternative device in the *Tariff* is the Injex device.

Needle free devices are not necessary pain free; the high speed jet of insulin delivered directly into the subcutaneous tissue can cause a stinging or burning sensation. As a result, this method of insulin delivery is unsuitable for patients with bleeding disorders, those with skin conditions at the intended injection site and those currently taking antithrombotic drugs.

Based on the assumption that only one type of insulin is used, InsuJet costs approximately £215 per year (in addition to the cost of insulin therapy). As one InsuJet device is required for each insulin used, costs can increase significantly with multiple insulin use or where insulin is required more than four times a day. The InsuJet device has to be replaced annually or more frequently if used more than 4 times a day.

PACEF compared InsuJet with the Injex spring loaded device. The Injex device requires the dose of insulin to be transferred from the original cartridge via a 'transporter' device to a disposable ampoule. The ampoule containing the required dose is placed into the Injex device; when the trigger is released a thin stream of insulin under pressure is forced through the skin where it disperses into the subcutaneous adipose tissue. The ampoule can then be removed from the device and disposed of. Because the required dose is transferred to a disposable ampoule, the Injex device allows for insulins to be mixed immediately prior to administration; this means that the same device can be used for more than one type of insulin. The Injex device is broadly comparable in price to the InsuJet.

**PACEF Recommendation:**
**Needle free insulin delivery systems should be reserved for people with true and severe needle phobia; they are not appropriate for those who dislike the idea of regular injections. The number of patients with a true needle phobia is very low. With adequate support during the initial stages of treatment, the majority of patients, who express an initial fear or dislike of needles, cope well. Needle covers and guards are available for some pen devices and should be considered as a preferred option for those who do not like the sight of needles (e.g. Novofine Autocover, NovoNordisk Penmate). Of the two needle free insulin delivery devices, InsuJet appears to be the easiest to use as it is easiest to manipulate and avoids the need to decant the insulin into another container prior to administration. It also avoids the potential risk of inadvertent mixing of incompatible insulins in the same device. All potential patients requiring a needle free device should be referred to a diabetes specialist nurse in either community or secondary care for assessment and appropriate training. Within this context, the Insujet device is approved for use. Designation: AMBER.**

## NICE UPDATE

## NICE TECHNOLOGY APPRAISAL 246: *PHARMALGEN FOR THE TREATMENT OF BEE AND WASP VENOM ALLERGY* (FEBRUARY 2012)

Key Recommendations:

1. Pharmalgen is recommended as an option for the treatment of IgE-medicated bee and wasp venom allergy in people who have had:
    - a severe systemic reaction to bee or wasp venom, or
    - a moderate systemic reaction to bee or wasp venom and who have had one or more of the following: a raised baseline serum tryptase, a high risk of future stings or anxiety about future stings.

2. Treatment with Pharmalgen should be initiated and monitored in a specialist centre experienced in venom immunotherapy.

**PACEF Recommendations:**
**Pharmalgen is a desensitising vaccine available as both extracts of wasp and bee venom in a variety of strengths; it is used to reduce the risk of severe anaphylaxis and systemic reaction in individuals with hypersensitivity to wasp and bee stings. Those requiring immunotherapy must be referred to a specialist centre for accurate diagnosis, assessment and treatment. Pharmalgen can only be used and monitored within a specialist centre. As a result of this, all Pharmalgen products are designated RED.**

**NICE TECHNOLOGY APPRAISAL 247: *TOCILIZUMAB FOR THE TREATMENT OF RHEUMATOID ARTHRITIS* (FEBRUARY 2012)**

Key Recommendations:

Tocilizumab in combination with methotrexate is recommended as an option for the treatment of rheumatoid arthritis in adults if:

- the disease has responded inadequately to disease-modifying anti-rheumatic drugs (DMARDs) **and** it is used as described for tumour necrosis factor (TNF) inhibitor treatments in *Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis* (NICE TA 130), specifically the recommendations on disease activity and choice of treatment **or**
- the disease has responded inadequately to DMARDs and a TNF inhibitor and the person cannot receive rituximab because of a contraindication to rituximab, or because rituximab is withdrawn because of an adverse event, **and** tocilizumab is used as described for TNF inhibitor treatments in *Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor* (NICE TA 195), specifically the recommendations on disease activity **or**
- the disease has responded inadequately to one or more TNF inhibitor treatments and to rituximab
- **and** the manufacturer provides tocilizumab with the discount agreed as part of the patient access scheme.

**PACEF Recommendations:**
**Tocilizumab intravenous infusion (RoActemra) remains RED for the treatment of RA subject to NICE criteria.**

**NICE TECHNOLOGY APPRAISAL 248: *EXENATIDE PROLONGED RELEASE SUSPENSION FOR INJECTION IN COMBINATION WITH ORAL ANTIDIABETIC THERAPY FOR THE TREATMENT OF TYPE 2 DIABETES MELLITUS* (FEBRUARY 2012)**

Key Recommendations:

Prolonged-release exenatide in triple therapy regimens ( in combination with metformin and a sulfonylurea, or metformin and a thiazolidinedione) is recommended as a treatment option for people with type 2 diabetes as described in *Type 2 diabetes: the management of type 2 diabetes* (NICE clinical guideline 87); that is, when control of blood glucose remains or becomes inadequate ($HbA_{1c} \geq 7.5\%$ [59 mmol/mol] 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 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).

Prolonged-release exenatide in dual therapy regimens (that is, in combination with metformin or a sulfonylurea) is recommended as a treatment option for people with type 2 diabetes, as described in *Liraglutide for the treatment of type 2 diabetes mellitus* (NICE TA 203); that is, only if:

- The person is intolerant of either metformin or a sulfonylurea, or treatment with metformin or a sulfonylurea is contraindicated **and**
- The person is intolerant of thiazolidinediones and dipeptidyl peptidase - 4 (DPP-4) inhibitors or treatment with thiazolidinediones **and** DPP-4 inhibitors is contraindicated.

Treatment with prolonged-release exenatide in a dual therapy regimen should only be continued as described in *Liraglutide for the treatment of type 2 diabetes mellitus* (NICE TA 203); that is, if a beneficial metabolic response has been shown (defined as a reduction of at least 1 percentage point in $HbA_{1c}$ [11 mmol/mol] at 6 months).

**PACEF Recommendation:**
**Following this positive NICE technology appraisal, exenatide prolonged release injection (Bydureon) is confirmed 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 twice daily injection (Byetta) remains the glucagon-like peptide-1 (GLP-1) mimetic of first choice within NICE initiation criteria. Exenatide prolonged release injection (Bydureon) and liraglutide injection (Vicotoza) are both second line options to be considered for patients intolerant of the exenatide twice daily formulation.**

## MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY: *DRUG SAFETY UPDATE* (MARCH 2012)

### Aliskiren (Rasilez) risk of cardiovascular and renal adverse reactions – new contraindications and warnings

The combination of aliskiren (Rasilez) with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs) has been associated with serious adverse cardiovascular and renal outcomes in a recent large clinical trial known as ALTITUDE.

Advice for healthcare professionals:

- Prescribers should review the treatment of all patients taking aliskiren in combination with an ACEI or an ARB at a routine appointment.
- In patients who are taking an ACE inhibitor or an ARB, aliskiren should be stopped and new treatment should not be initiated in those who are diabetic or non diabetic patients with an eGFR<60ml/min per 1.73$m^2$.
- The combination of aliskiren with either an ACEI or an ARBs is not recommended. The benefits versus risks of continuing aliskiren treatment should be considered carefully.
- If aliskiren is discontinued, then alternative antihypertensives should be used as necessary.
- Use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in patients with severe renal impairment (i.e. GFR <30ml/min per 1.73$m^2$).
- In all patients where aliskiren treatment is continued or initiated, eGFR and glucose tolerance should be monitored at appropriate intervals.
- All healthcare professionals are reminded to report suspected adverse reactions to aliskiren on a yellow card.

The results of this trial were first highlighted to all prescribers through a MHRA safety notice. PACEF was briefed on the emerging safety concerns around aliskiren at its February 2012 meeting and advised that all patients currently receiving aliskiren (approximately 158 across NHS Lincolnshire) should be reviewed at their next routine appointment. This was communicated to all clinicians in *PACE Bulletin* Vol 6 No 5 (March 2012).

**The MHRA have now revised their original advice and extended the contraindications to aliskiren therapy to include all patients with severe renal impairment (GFR <30ml/min per 1.73m$^2$) and those taking aliskiren in combination with either an ACEI or an ARB with a GFR <60ml/min per 1.73m$^2$.**

**Teva levothyroxine 100 microgram tablets: potential reduced efficacy – suspension of marketing authorisation**

Following a review by the Commission on Human Medicines (CHM) the marketing authorisation (license) for levothyroxine 100microgram tablets manufactured by Teva has been suspended. This is due to sporadic reports of potential reduced efficacy when switching to Teva branded tablets from other brands. This temporary suspension only affects the Teva and Numark brands of levothyroxine 100mcg tablets.

The MHRA have issued the following advice to health care professionals

- Prescribers should be alert to the possibility that a change in patient's symptoms and TSH status may be attributed to switching to a Teva product from another levothyroxine product.
- Certain patient groups such as pregnant women, patients with heart disease and patients receiving treatment with levothyroxine following treatment for thyroid cancer should be closely monitored. If these patients are taking Teva tablets they should have an early appointment with their doctor for a clinical review and blood test.
- The majority of patients will be able to continue their medication and change to a different levothyroxine product at their next prescription.
- Patients who experience a significant change in their symptoms especially after switching should have their TSH status reviewed and their dose of levothyroxine adjusted accordingly.

**Unlicensed imported vitamin D (colecalciferol) capsules: potential peanut oil and soya oil allergens.**

The MHRA have alerted health care professionals to the potential risk of allergy associated with the use of two imported colecalciferol products imported from Germany. Dekristol capsules contain arachis (peanut) oil and Vigantoletten contain soya oil. Although the livery of the products contain warnings this is unlikely to be evident to non-German speakers.

The MHRA have also highlighted that two additional products, vitamin D Osto D2 capsules from Canada and Drisdol capsules from the USA may pose a similar risk. Although they are labelled in English the products may not explicitly state they contain soya oil.

Advice to healthcare professionals

- Allergy to soya oil or arachis oil may lead to sever allergic reactions, including anaphylaxis.
- These products are contraindicated in patients with relevant allergies. Doctors and pharmacists should enquire whether patients have any relevant allergies before supplying these medicines.
- Importers are also advised that prescribers must be made aware of this contraindication.

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