NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 3; Number 1 **January 2009**

What's new this month:

- **The 'flu trigger has now been activated and the use of antiviral drugs for post-exposure prophylaxis and treatment of influenza is advocated (see page 3).**
- **Two prolonged release granule formulations of sodium valproate are assessed (Episenta and Epilim Chronosphere) (see pages 3 and 4).**
- **Quetiapine prolonged release tablets (Seroquel XL) are assessed and approved for use subject to specialist initiation (see page 5).**
- **Rasagiline tablets (Azilect) are not approved for use in Parkinson's Disease (see page 5).**
- **ULHT Drug and Therapeutics Committee have opted to use rivaroxaban (Xarelto) as an alternative to dabigatran (Pradaxa) in the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery (see page 6).**
- **The implications of the Prevention of Progression of Arterial Disease and Diabetes Trial (POPADAD) are assessed (see page 8).**
- **The Melatonin Shared Care Guideline is now available (see page 10).**
- **The new NICE Clinical Guideline on Attention Deficit Hyperactivity Disorder is reviewed (see page 10).**

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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. Steps will be taken to ensure the widest possible distribution across NHS Lincolnshire and within United Lincolnshire Hospitals Trust and Lincolnshire Partnership Trust. Both paper and electronic copies will be circulated initially with a view to evolving into complete electronic distribution as soon as we are confident that all key stakeholders can access E-mail. There are also plans to make all bulletins, guidelines, formularies, new product assessments, care pathways and other PACEF publications available through the NHS Lincolnshire website.

SUMMARY OF PACEF DECISIONS: JANUARY UPDATE

Drug	Indication(s)	Traffic Light Status
Atomoxetine (Strattera) capsules	Licensed for the treatment of attention deficit hyperactivity disorder (initiated by a specialist physician experienced in managing the condition).	AMBER N.B. For specialist initiation only; a shared care guideline **is** required.
Dexamfetamine (Dexedrine) tablets	Licensed for the treatment of refractory attention deficit hyperactivity disorder (under specialist supervision).	AMBER N.B. For specialist initiation only; a shared care guideline **is** required.
Erlotinib (Tarceva) tablets	Licensed for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.	RED
Methylphenidate tablets (Ritalin)	Licensed for the treatment of attention deficit hyperactivity disorder (under specialist supervision).	AMBER N.B. For specialist initiation only; a shared care guideline **is** required.
Methylphenidate MR (Concerta XL) tablets Methylphenidate MR (Equasym XL) capsules Methylphenidate MR (Medikinet XL) capsules	Licensed for the treatment of attention deficit hyperactivity disorder (under specialist supervision).	AMBER N.B. For specialist initiation only; a shared care guideline **is** required.
Oseltamivir (Tamiflu) capsules	Treatment and post-exposure prophylaxis of influenza	GREEN subject to NICE restrictions; all prescriptions should be endorsed 'SLS'.
Quetiapine prolonged release tablets (Seroquel XL)	Licensed for schizophrenia and manic episodes associated with bipolar disorder	AMBER N.B. For specialist initiation only; **no** shared care guideline is required.
Rasagiline tablets (Azilect)	Licensed for the treatment of Parkinson's disease, used alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor	RED-RED
Rivaroxaban (Xarelto) tablets	Licensed for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery**.**	RED N.B. Patients discharged from ULHT on rivaroxaban will have the complete course dispensed by the initiating hospital; GP prescribing is not recommended under any circumstances.
Sodium valproate modified release granules (Epilim Chronosphere)	Licensed for the treatment of general, partial or other epilepsy	RED-RED
Sodium valproate prolonged release granules (Episenta)	Licensed for all forms of epilepsy	GREEN
Thalidomide Pharmion capsules	Licensed for use in combination with melphalan and prednisone as first line treatment of untreated multiple myeloma in patients aged 65 and over or ineligible for high-dose chemotherapy.	RED
Zanamivir (Relenza) dry powder for inhalation	Treatment and post-exposure prophylaxis of influenza	GREEN subject to NICE restrictions; all prescriptions should be endorsed 'SLS'.

RED-RED: This signifies that a product is **not recommended** for prescribing in **both** primary and 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 ULHT and/or LPFT **only** and has **no role in primary 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; in the coming months PACEF will be 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.**

INFLUENZA SEASON 2008/09 – USE OF ANTIVIRALS

Before Christmas, Professor Salisbury, the Director of Immunisation at the Department of Health, wrote out to all prescribers to activate the so-called 'flu trigger'. Normal seasonal flu activity is defined as 30 consultations per 100,000 people; just before Christmas, particularly among 15 to 44 year olds, activity was identified as higher than this. This means that there is now a substantial likelihood that patients presenting with influenza-like illnesses are infected with influenza virus. The Health Protection Agency (HPA) have identified that the majority of influenza A viruses currently circulating in England are H3N2 viruses which are sensitive to oseltamivir. Following NICE guidance from Technology Appraisal 158, oseltamivir and zanamivir are recommended within their marketing authorisations, for the **post exposure prophylaxis** of influenza if all of the following apply: (1) National surveillance schemes have indicated that influenza virus is circulating; (2) The person is in an at risk group; (3) The person has been exposed to an influenza-like illness and is able to begin prophylaxis within 36 hours for zanamivir or 48 hours for oseltamivir; and (4) The person has not been effectively protected by vaccination. TA 58 provides additional guidance on the **treatment** of influenza with antiviral drugs.

More detailed guidance appeared in *PACE Bulletin*, Vol 2, No 18 (November 2008).

NEW DRUG ASSESSMENTS

RAPID DRUG ASSESSMENT: SODIUM VALPROATE (EPILIM CHRONOSPHERE) MODIFIED RELEASE GRANULES

The Epilim Chrono tablet is a well-established controlled release formulation of sodium valproate accounting for approximately half of the sodium valproate items prescribed in Lincolnshire primary care. The advantage of the Chrono tablet is that it can be taken once or twice daily compared to the more frequent dosage of standard release sodium valproate formulations. The new Epilim Chronosphere modified release granule formulation is available in strengths of 50mg, 100mg, 250mg, 500mg

and 750mg; it is licensed for the treatment of general, partial or other epilepsy. In common with the Epilim Chrono tablet, it can be taken once or twice daily and presents a possible alternative for patients with swallowing difficulties unable to take other modified release formulations.

One open label single and repeat dose cross over study conducted in healthy male volunteers has confirmed bio-equivalence between Epilim Chronosphere modified release granules and Epilim Chrono controlled release tablets. There is no evidence to suggest that any Chrono/Chronosphere formulation offers any benefit in terms of improved epilepsy control over any alternative valproate product.

A cost comparison reveals the following:

	Dose	Cost of 28 days' treatment
Sodium valproate controlled release tablets (Epilim Chrono)	500mg twice daily	£13.58
Sodium valproate modified release granules (Epilim Chronosphere)	500mg twice daily	£28.00
Sodium valproate prolonged release granules (Episenta)	500mg twice daily	£10.08

PACEF Recommendation

PACEF accept that there is a role for a modified release sodium valproate granule formulation for patients with swallowing difficulties who are unable to take alternative modified release formulations such as Epilim Chrono tablets. Unfortunately, the high cost of Epilim Chronosphere granules in comparison to Epilim Chrono tablets and competitor products renders them a poor choice in terms of cost-effectiveness. As a result of this, Epilim Chronosphere granules are designated: RED-RED. Episenta prolonged release sodium valproate granules present an equivalent lower cost option and are designated: GREEN (see below).

RAPID DRUG ASSESSMENT: SODIUM VALPROATE (EPISENTA) PROLONGED RELEASE GRANULES

Episenta prolonged release capsules have been previously evaluated by PACEF and are designated as GREEN. Episenta prolonged release granules are licensed for all forms of epilepsy and are available as 500mg and 1000mg strengths; they are taken once or twice daily and may be of benefit in patients with swallowing difficulties unable to take alternative oral dosage forms.

PACEF Recommendation

Following consultation with colleagues in Lincolnshire Partnership Foundation Trust (LPFT), including representatives from the learning disability service, PACEF have designated Episenta prolonged release granules as GREEN. Where a prolonged release sodium valproate formulation is indicated but swallowing difficulties preclude the use of Episenta prolonged release capsules or Epilim Chrono tablets, Episenta prolonged release granules should be considered. Studies have shown that Episenta formulations are bioequivalent to comparable doses of other sodium valproate preparations.

RAPID DRUG ASSESSMENT: QUETIAPINE PROLONGED RELEASE TABLETS (SEROQUEL XL)

Quetiapine is an atypical antipsychotic drug licensed for the treatment of schizophrenia and for manic episodes associated with bipolar disorder. Current national guidelines support the use of quetiapine in both of these treatment areas. However, immediate release quetiapine requires twice daily dosage and a prolonged titration period. Quetiapine prolonged release tablets (Seroquel XL) offer a convenient once daily formulation and a simplified titration process. A cost comparison has revealed that quetiapine prolonged release tablets are marginally lower in price than quetiapine immediate release tablets in primary care. The patent of the immediate release formulation (Seroquel) is due to expire in 2012.

PACEF Recommendation

PACEF are convinced that quetiapine prolonged release tablets (Seroquel XL) offer potential benefits in terms of once daily dosing, simplified titration and marginally lower treatment costs. The product is designated: AMBER. It can be prescribed in primary care subject to specialist initiation; no shared care guideline is required.

RAPID DRUG ASSESSMENT: THALIDOMIDE PHARMION CAPSULES

In recent years, unlicensed oral thalidomide has become well established in specialist units for the treatment of multiple myeloma. Celgene have recently launched a licensed product known as Thalidomide Pharmion. This new formulation is licensed for use in combination with melphalan and prednisone as first line treatment of untreated multiple myeloma, in patients aged 65 and over or ineligible for high-dose chemotherapy.

PACEF Recommendation

Now that a licensed formulation of thalidomide is available, ULHT Drug and Therapeutics Committee have expressed their intention to advocate the use of this product within ULHT. As a result of this Thalidomide Pharmion capsules are designated: RED.

NEW DRUG ASSESSMENT: RASAGILINE TABLETS (AZILECT)

Rasagiline (Azilect) is indicated for the treatment of idiopathic Parkinson's disease (PD) as monotherapy (without levodopa) or as adjunct therapy (with levodopa) in patients with end of dose fluctuations. It is a selective, irreversible inhibitor of monoamine-oxidase- B (MAO-B). This enzyme is found in the neurons of the hypothalamus and is responsible for the metabolism of dopamine. Inhibition of MAO-B is thought to help conserve dopamine supplies and therefore delay the need for levodopa therapy for the treatment of Parkinson’s disease or allow for the use of lower doses in patients with advanced disease. The clinical effectiveness of rasagiline compared to placebo in the treatment of PD has been demonstrated in three randomised double blind trials. Unfortunately, there has been no head to head comparative study against selegiline, the other MAO-B inhibitor with a UK product license.

Both MAO-B inhibitors are associated with a wide range of adverse effects. Unlike selegiline, rasagiline is not converted into amphetamine metabolites and it has been suggested that, as a result of this, rasagiline may have an improved adverse effect

profile compared with selegiline. However, there is no evidence that this theoretical advantage translates into real clinical benefit. There are also claims that rasagiline has a slightly cleaner profile than selegiline in terms of the number of reported serious drug interactions.

A cost comparison between rasagiline and selegiline reveals that rasagiline is 10 to 16 times the cost of the established product:

Drug	Daily dose range	Cost (£) pa
Rasagiline 1mg tablets (Azilect)	1mg od	£919
Selegiline 5mg tablets (generic)	5mg bd	£55
Selegiline 10mg tablets (generic)	10mg od	£97

PACEF Recommendation

Both PACEF and ULHT Drug and Therapeutics Committee are concerned about the lack of comparative data between selegiline and rasagiline and the lack of evidence to support some of the claims made for the newer and more expensive agent. PACEF are concerned that rasagiline is significantly more expensive than selegiline and remain unconvinced about its cost-effectiveness. As a result of this, rasagiline is designated: RED-RED. It is acknowledged that there are existing patients in Lincolnshire currently receiving prescriptions for rasagiline from their GP; these patients should be enabled to continue therapy until they or their clinician consider it is appropriate for them to stop. All further approaches to GPs from specialists requesting the initiation of rasagiline should be refused.

NEW DRUG ASSESSMENT: RIVAROXABAN TABLETS (XARELTO)

Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor licensed for the primary prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip replacement surgery or total knee replacement surgery. The recommended dose is 10mg daily (initial dose given 6 to10 hours after surgery) for a total of 14 days for knee replacement surgery and for a total of 35 days following hip replacement surgery.

PACEF reviewed three randomised controlled double-blind clinical trials comparing rivaroxaban with subcutaneous enoxaparin; collectively these studies involved over 9,500 patients (7,050 undergoing total hip replacement surgery and 2,531 total knee replacement surgery). Results from these trials show that oral rivaroxaban is significantly more effective than enoxaparin at reducing the rate of total VTE (i.e. any venographically detected or symptomatic deep vein thrombosis (DVT), non fatal pulmonary embolism (PE) and death) and major VTE (proximal DVT, non fatal PE and VTE-related death) in patients undergoing both major hip and knee replacement surgery. The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

Rivaroxaban offers the advantage of an oral formulation that, in contrast to subcutaneous enoxaparin, does not require regular monitoring, dosage adjustment or special training for patients on self-administration. It is a competitor to the recently launched alternative: dabigatran etexilate (Pradaxa). Dabigatran is a direct inhibitor of thrombin that helps to inhibit clot formation; it is an oral treatment licensed for the primary prevention of venous thromboembolic events in adult patients who have undergone elective total hip replacement surgery or elective total knee replacement surgery. In September 2008, NICE published Technology Appraisal 157: *Dabigatran*

etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults and recommended:

- Dabigatran etexilate, within its marketing authorisation, as an option for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery.

PACEF Recommendations:
ULHT Drug and Therapeutics Committee have recently completed a comparative assessment of both rivaroxaban and dabigatran etexilate. There are no trials currently available that directly compare one agent with the other, although there is good trial evidence for both agents that compares each drug with subcutaneous enoxaparin. Following a detailed review of this data, ULHT DTC detected superior performance to enoxaparin in the rivaroxaban trials whereas the dabigatran trials showed non-inferiority to the enoxaparin comparator. As a result of this, ULHT DTC have decided to recommended rivaroxaban as the treatment of choice for the primary prevention of venous thromboembolic events in adults who have undergone elective total hip replacement surgery or elective total knee replacement surgery. PACEF have reviewed the same data and have ratified this decision. As a result if this, rivaroxaban (Xarelto) is designated RED. Dabigatran etexilate (Pradaxa) remains RED, but is unlikely to be used within ULHT due to the preference for rivaroxaban. Both drugs are for hospital prescribing only; patients discharged on either drug will have the complete course dispensed by the initiating hospital; GP prescribing is not recommended under any circumstances.

PATENT EXPIRIES

Prescribers are reminded of the recent patent expiries of risperidone (December 2007) and bicalutamide (July 2008). Generic risperidone is currently half the price of branded and orodispersible risperidone (Risperdal/Risperdal Quicklet) and significantly lower in cost than alternative atypical antipsychotics. Similarly, bicalutamide is now lower in price than branded Casodex with further price reductions expected in the coming months. December 2008 *Drug Tariff* prices are tabulated below:

Risperidone Prices

Drug	Dose	Cost of 28 days supply
Risperidone 500mcg tablets (generic)	**500mcg twice daily**	**£11.68**
Risperidone 500mcg tablets (Risperdal))	500mcg twice daily	£19.77
Risperidone 500mcg tablets orodispersible (generic)	500mcg twice daily	£18.10
Risperidone 500mcg tablets orodispersible (Quicklet)	500mcg twice daily	£22.86
Risperidone 1mg tablets (generic)	**1mg twice daily**	**£19.28**
Risperidone 1mg tablets (Risperdal)	1mg twice daily	£32.52
Risperidone 1mg tablets orodispersible (Quicklet)	1mg twice daily	£36.78
Risperidone 2mg tablets (generic)	**2mg twice daily**	**£37.37**

Risperidone 2mg tablets (Risperdal)	2mg twice daily	£64.11
Risperidone 2mg tablets orodispersible (Quicklet)	2mg twice daily	£66.60
Risperidone 4mg tablets (generic)	**4mg twice daily**	**£72.59**
Risperidone 4mg tablets (Risperdal)	4mg twice daily	£124.45
Risperidone 4mg tablets orodispersible (Quicklet)	4mg twice daily	£129.68

Bicalutamide prices

Drug	Dose	Cost of 28 days supply
Bicalutamide 50mg tablets (generic)	**50mg once daily**	**£113.29**
Bicalutamide 150mg tablets (generic)	**150mg once daily**	**£214.14**
Bicalutamide 50mg tablets (Casodex)	50mg once daily	£128.00
Bicalutamide 150mg tablets (Casodex)	150mg once daily	£240.00

NEW TRIAL ASSESSMENT: PREVENTION OF PROGRESSION OF ARTERIAL DISEASE AND DIABETES TRIAL (POPADAD)

There is an established evidence base that confirms the effectiveness of aspirin for the secondary prevention of cardiovascular (CV) events. However, it is less clear whether aspirin prevents primary CV events in people who are at risk of CV disease, such as those with type 2 diabetes mellitus. Current NICE guidance recommends aspirin 75mg daily for the primary prevention of CV events in diabetics ≥ 50years with a BP below 145/90 mmHg and those aged under 50 years with significant CV risk factors. POPADAD is a double blind randomised controlled trial (RCT) set up to determine whether aspirin (100mg) and antioxidant therapy, either alone or in combination, are more effective than placebo in reducing the development of CV events in patients with type 1 or 2 diabetes and asymptomatic peripheral arterial disease.

The study recruited 1276 patients with a median length of follow up of 6.7 years. Diabetic patients (type 1 or 2), aged ≥ 40 years who had asymptomatic peripheral arterial disease (ankle brachial pressure ≤ 0.99) were recruited from diabetic clinics in Scotland. The antioxidant capsule contained alfa-tocopherol 200mg, ascorbic acid 100mg, pyridoxine 25mg, zinc sulphate 10mg, nicotinamide 10mg, lecithin 9.4mg and sodium selenite 0.8mg.

Results showed no significant difference between patients randomised to the aspirin group as compared to the no aspirin group. Similarly, no significant benefits were demonstrated in the antioxidant group. A composite end point was used which included death from CHD or stroke, non-fatal MI or stroke or above ankle amputation for critical limb ischaemia; death from CHD or stroke was also used as a composite end point.

In terms of tolerability, the incidence of gastrointestinal symptoms and gastrointestinal bleeding were not increased in those patients taking aspirin compared to those not taking aspirin, although pre-study exclusion of patients with

peptic ulcer, severe dyspepsia, bleeding disorders or intolerance to aspirin is likely to have influenced these findings significantly.

A detailed review of the study raised a number of concerns. For example, POPADAD was underpowered to answer the question posed. The study was originally designed to recruit 1600 participants and follow up each for 4 years. An estimated 392 events occurring during the trial would have provided 90% power to detect a 25% relative reduction in primary outcomes at the 5% level of significance. Unfortunately, recruitment was slower than anticipated (n=1276) and the event rate was lower than predicted (233 events after a median follow up of 6.7 years). A retrospective power calculation by the authors suggests that 256 events occurring during the trial would provide 73% power to detect a 25% relative reduction in event rate. This is a lower level of power than would normally be acceptable and makes it problematic to draw any conclusions from POPADAD in isolation. Further studies with sufficient power are required to confirm these findings, because a small absolute benefit from aspirin still remains a possibility.

A large, long-term, RCT (ASCEND) is currently in progress to determine whether there is a role for aspirin in the primary prevention of CV events in diabetics. This trial aims to recruit at least 10,000 people with type 1 or type 2 diabetes and without clinical evidence of occlusive arterial disease. These patients will be randomised to aspirin 100mg and/or 1g omega-3 fatty acids. By the summer of 2008, only 4000 patients had been recruited to this study, so it is likely to be several years before the trial is completed and results are published.

Publication of POPADAD has stimulated debate on the wider issue of aspirin for primary prevention of CV disease. A *British Medical Journal* editorial commented on the trial, reviewed the evidence and placed it within the context of a further six well conducted RCTs that had similarly found no benefit of aspirin in primary prevention (*BMJ* 2008;337:1005 – 6, 1st Nov).The authors comment that it is striking that in POPADAD the negative result for aspirin was found despite an event rate of 3% a year. They also emphasize that other primary prevention studies have usually recruited patients at lower risk. They conclude that these results suggest that the only predictor of clinical response to aspirin is a history of a major coronary or cerebral ischaemic event.

PACEF Recommendation

In isolation, POPADAD does not present a sufficiently robust case to warrant change in practice. However, it contributes to an expanding range of complementary trials that suggest that existing assumptions around the potential benefits of aspirin in the primary prevention of CV disease may be seriously flawed. PACEF conclude that diabetics without CV disease who are experiencing harm, or are likely to experience harm from aspirin could reasonably discontinue aspirin since the risks will 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.

Reference: Belch J, MacCuish A, Campbell I et al., 'The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease', *British Medical Journal* 2008; 337:a1840.

SHARED CARE GUIDELINES

PACEF have approved one shared care guidelines this month. This is:

- Unlicensed use of melatonin in the treatment of severe sleep disorders in children with neurological or neuro-developmental disorders

Copies are available from Cathy Johnson, Interface Lead Pharmacist at cathy.johnson@lpct.nhs.uk

NICE TECHNOLOGY APPRAISAL 162: *ERLOTINIB FOR THE TREATMENT OF NON-SMALL-CELL LUNG CANCER* (NOVEMBER 2008)

The key recommendations are as follows:

- **Erlotinib is recommended, within its licensed indication, as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC)** only on the basis that it is provided by the manufacturer at an overall treatment cost (including administration, adverse events and monitoring costs) equal to that of docetaxol.
- The decision to use erlotinib or docetaxel should be made after a discussion between the responsible clinician and the individual about potential benefits and adverse effects of each treatment.
- Erlotinib is not recommended for the second line treatment of locally advanced or metastatic NSCLC in patients for whom docetaxel is unsuitable (where there is intolerance of or contraindication to docetaxel) or for third line treatment after docetaxel therapy.
- People currently receiving treatment with erlotinib, but for whom treatment would not be recommended, should have the option to continue treatment until they or their clinicians consider it appropriate to stop.
- Erlotinib is an orally active inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase. It is licensed for the treatment of locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.

PACEF Recommendations:
Erlotinib (Tarceva) is designated RED within licensed indications as an alternative to docetaxel as a second-line treatment option for patients with non-small-cell lung cancer (NSCLC).

NICE CLINICAL GUIDELINE 72: *ATTENTION DEFICIT HYPERACTIVITY DISORDER* (SEPTEMBER 2008)

The key recommendations are as follows:

Diagnosis of ADHD

- For a diagnosis of ADHD, symptoms of hyperactivity/impulsivity and/or inattention should: (1) meet the diagnostic criteria in DSM-IV or ICD-10 and (2) be associated with at least moderate psychological, social and/or educational or occupational impairment based on interview and/or direct observation in multiple settings and (3) be pervasive, occurring in two or more important settings including social, familial, educational and/or occupational settings.
- **Diagnosis of ADHD should only be made by a paediatrician, specialist psychiatrist or other healthcare professional with training and expertise in the diagnosis of ADHD.**

Pre-School Children with ADHD

- Parents or carers of pre-school children with ADHD should be referred first line to a parent training/education programme. **Drug treatment is not recommended in pre-school children.**

School Age Children and Young People with ADHD

- **In school age children/ young people with moderate ADHD and moderate impairment, drug treatment is not indicated first line**; parents should be offered a group-based parent-training/education programme either on its own or with a group treatment programme (cognitive behavioural therapy (CBT) and/or social skills training) for the child or young person. If non-drug interventions are refused or significant impairment persists following a parent-training/education programme or group psychological treatment, drug treatment may be indicated.
- **In school age children and young people with severe ADHD (hyperkinetic disorder) and severe impairment, drug treatment should be offered first-line.** Parents should also be offered a group-based parent-training/education programme.

Adults with ADHD

- Young people treated in CAMHS or paediatric services would usually transfer to adult services by the age of 18.
- **Drug treatment is usually first line in adults unless the person prefers psychological treatment.**

Drug Treatment

- Drug treatment should always form part of a comprehensive treatment plan that includes psychological, behavioural and educational advice and interventions.
- **ADHD should not be diagnosed in primary care.**
- **Drug treatment for children and young people with ADHD should only be initiated by a healthcare professional with expertise in ADHD.**
- If a child or young person is currently receiving drug treatment for ADHD and has not yet been assessed in secondary care, refer to a paediatrician, child psychiatrist or to a specialist ADHD CAMHS as a clinical priority.
- **GPs may continue prescribing and monitoring drug treatment under shared care arrangements.**
- **Methylphenidate, atomoxetine and dexamfetamine are recommended, within their licensed indications, as options for the management of ADHD**
- If there is a choice of more than one drug, use the drug of lowest overall cost.
- Do not use antipsychotics for ADHD in children and young people.

Treatment Choice: Children or Young people with ADHD:

- Methylphenidate should be considered for ADHD without significant comorbidity and ADHD with co-morbid conduct disorder.
- Methylphenidate or atomoxetine should be considered when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present.
- Atomoxetine should be considered if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or if the child or young person is intolerant to low or moderate doses of methylphenidate.

Treatment Choice: Adults:

- Methylphenidate should normally be tried first. Consider atomoxetine or dexamfetamine if symptoms do not respond to methylphenidate (after a 6 week trial) or the person is intolerant to it. Consider atomoxetine first line if there are concerns about drug misuse and diversion (e.g. in prison)
- Treatment should always form part of a comprehensive treatment programme that addresses psychological, behavioural and educational or occupational needs

Pre-drug Assessment

Pre-drug treatment assessment is recommended including:

- A full history and physical examination including history of exercise syncope, undue breathlessness, and other CV symptoms, heart rate and BP, height and weight and family history of cardiac disease.
- If there is a past medical history or family history of serious cardiac disease, a history of sudden death in young family members or abnormal findings on cardiac examination, an ECG is indicated.
- Risk assessment for substance misuse or drug diversion.

Compliance

- Potential problems with compliance need to be considered as part of treatment selection (i.e. if a mid-day dose is needed, how practical is this at school)

Methylphenidate

If using methylphenidate, consider:

- modified release preparations for convenience, their pharmacokinetic profile, improving adherance, reducing stigma (because the drug does not need to be taken in school) and reducing problems of storing and administering controlled drugs at school.
- immediate release preparations if more flexible dosing is required or during initial titration to determine correct dosing levels.

Atomoxetine

- Closely observe children or young people taking atomoxetine for agitation, irritability, suicidal thinking and self-harming behaviour, and unusual changes in behaviour, particularly during the initial months of treatment or after a dose change.
- Warn parents and carers about the potential for suicidal thinking and self harm and rare cases of liver damage.

Poor response to treatment

- After review and consultation with a tertiary or regional centre consider increasing the dose of methylphenidate to 0.7mg/kg up to three times a day or a total daily dose of 2.1mg/kg/day (up to a total maximum of 90mg/day for immediate release or the equivalent MR dose).
- After review and consultation with a tertiary or regional centre consider increasing the dose of atomoxetine to 1.8mg/kg/day (up to a maximum dose of 120mg/day).
- These doses are higher than the BNF recommended dose ranges.
- Consider dexamfetamine when symptoms are unresponsive to a maximum tolerated dose of methylphenidate or atomoxetine.
- If there is no response to methylphenidate, atomoxetine or dexamfetamine, refer to tertiary services. Further treatment may include drugs unlicensed for

ADHD (e.g. bupropion, clonidine, modafinil, imipramine) or psychological treatments.

Licensing

- **Neither methylphenidate nor atomoxetine are licensed for children under 6 years.**

Nutrition and Exercise

- The value of a balanced diet, good nutrition and regular exercise should be stressed for children and young people with ADHD. Eliminating artificial colours and additives from the diet is not generally applicable. Dietary fatty acid supplements are not recommended for ADHD.
- Food/drink diaries can be useful in determining possible foods and drinks that appear to affect behaviour. If the diary supports such a link, referral to a dietitian may be helpful.

PACEF Recommendations

Methylphenidate, atomoxetine and dexamfetamine are all designated AMBER for these indications. NICE recommend that both diagnosis of ADHD and initiation of treatment should only be a paediatrician, specialist psychiatrist or other healthcare professional with training and expertise in the diagnosis and treatment of ADHD. A shared care guideline for all three drugs is required; local arrangements are currently under review. Treatment choice should be determined through individual patient assessment and follow NICE first line/second line recommendations (see above). The cost comparison below illustrates that methylphenidate has a lower acquisition cost than atomoxetine; immediate release methylphenidate is lower in cost than modified release formulations; of the methylphenidate modified release formulations, Concerta XL has a higher acquisition cost than Equasym XL and Medikinet XL.

Cost comparison

Products and doses in bold enable cost comparison of an equivalent dose across all four methylphenidate formulations

Drug	Dose	28 days supply
Atomoxetine (Strattera) capsules	40mg daily	£60.06
Atomoxetine (Strattera) capsules	60mg daily	£60.06
Atomoxetine (Strattera) capsules	80mg daily	£120.12
Dexamfetamine (Dexedrine) tablets	2.5mg daily	£1.50
Dexamfetamine (Dexedrine) tablets	2.5mg twice daily	£3.00
Dexamfetamine (Dexedrine) tablets	5mg twice daily	£6.00
Dexamfetamine (Dexedrine) tablets	10mg twice daily	£12.00
Methylphenidate tablets (Ritalin)	5mg three times daily	£7.78
Methylphenidate tablets (Ritalin)	**10mg three times daily**	**£16.24**
Methylphenidate tablets (Ritalin)	20mg three times daily	£27.94
Methylphenidate MR (Concerta XL) tablets	18mg once daily	£27.72
Methylphenidate MR (Concerta XL) tablets	27mg once daily	£32.72
Methylphenidate MR	**36mg once daily**	**£37.73**

(Concerta XL) tablets		
Methylphenidate MR (Equasym XL) capsules	10mg once daily	£23.33
Methylphenidate MR (Equasym XL) capsules	20mg once daily	£28.00
Methylphenidate MR (Equasym XL) capsules	**30mg once daily**	**£32.67**
Methylphenidate MR (Medikinet XL) capsules	10mg once daily	£21.00
Methylphenidate MR (Medikinet XL) capsules	20mg once daily	£28.00
Methylphenidate MR (Medikinet XL) capsules	**30mg once daily**	**£33.72**
Methylphenidate MR (Medikinet XL) capsules	40mg once daily	£44.95

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