NHS Lincolnshire

Prescribing and Clinical Effectiveness Bulletin

Volume 2; Number 18 **November 2008**

What's new this month:

- **The Medicines and Healthcare products Regulatory Agency (MHRA) has imposed restrictions on the import of unlicensed melatonin. Advice is given on the role of melatonin in sleep disturbances in children and adolescents with neurological or neuro-developmental disorders. Preferred products are suggested. The use of melatonin in primary insomnia, jet lag and sleep disturbances linked to shift working is not recommended (see page 3).**
- **Both bimatoprost/timolol eye drops (Ganfort) and glycopyrrolate 0.5% lotion are reviewed (see page 5 and 6).**
- **NICE have issued guidance on the use of ranibizumab (Lucentis) in age-related macular degeneration (see page 7).**
- **NICE have issued guidance on the use of dabigatran (Pradaxa) for the prevention of venous thromboembolism after hip or knee replacement surgery (see page 8).**
- **NICE have updated guidance on the prophylaxis of influenza with oseltamivir and zanamivir (see page 8).**
- **Prednisolone suppositories are currently in short supply; advice on potential alternatives is given (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. 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 LPCT website.

SUMMARY OF PACEF DECISIONS: NOVEMBER UPDATE

Drug	Indication(s)	Traffic Light Status
Amantadine capsules (Lysovir)	Prophylaxis and treatment of influenza A	RED-RED
Bevacizumab (Avastin) infusion	Unlicensed use for the treatment of wet age-related macular degeneration (AMD) within the constraints of NICE criteria.	RED
Bimatoprost 0.03% and timolol 0.5% eye drops (Ganfort)	Ocular hypertension or open angle glaucoma insufficiently responsive to beta blockers or prostaglandin analogues	GREEN
Dabigatran etexilate (Pradaxa) capsules	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.	RED
Entecavir (Baraclude) tablets	Chronic hepatitis B infection in adults with compensated liver disease, evidence of viral replication and histologically documented active liver inflammation or fibrosis.	RED
Glycopyrrolate 0.5% lotion	Unlicensed topical antimuscarinic agent used in the treatment of facial hyperhidrosis and diabetic gustatory sweating.	AMBER Specialist initiation only; no shared care guideline required
Melatonin prolonged release tablets 2mg (Circadin)	Licensed as monotherapy for the short-term treatment of primary insomnia in patients aged 55 or over	RED-RED
Melatonin prolonged release tablets 2mg (Circadin) Melatonin 3mg tablets (Bio-Melatonin) Melatonin preparations (manufactured by Penn Pharmaceuticals)	Unlicensed use in children and adolescents with severe sleep problems linked to neurological or neuro-developmental disorders	AMBER subject to shared care guideline
All alternative imported melatonin preparations	Any indication	RED-RED except where all other options are unsuitable.
All melatonin preparations	Jet lag or sleep disturbance linked to shift working	RED-RED
Oseltamivir (Tamiflu) capsules	Treatment and post-exposure prophylaxis of influenza	GREEN subject to NICE restrictions; all prescriptions should be endorsed 'SLS'.
Pegaptanib (Macugen) intravitreal injection	Treatment of wet age-related macular degeneration (AMD)	RED-RED
Ranibizumab (Lucentis) intravitreal injection	Treatment of wet age-related macular degeneration (AMD) within the constraints of NICE criteria.	RED
Rimonabant (Acomplia) tablets	Previously licensed as an adjunct to diet and exercise for the treatment of obese adults. Marketing authorisation withdrawn due to safety concerns (see *PACE Bulletin*, Vol 2, No 17)	RED-RED
Telbivudine (Sebivo) tablets	Licensed as monotherapy for	RED-RED

	CHB in adults with compensated liver disease and evidence of viral replication, persistently elevated ALT levels and histological evidence of active inflammation and/or fibrosis.	
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.**

MHRA IMPOSES RESTRICTIONS ON THE IMPORT OF UNLICENSED MELATONIN PRODUCTS FOLLOWING THE GRANT OF A MARKETING AUTHORISATION FOR CIRCADIN 2MG TABLETS

In June 2008, a modified release formulation of melatonin (Circadin) was launched in the UK licensed as monotherapy for the short-term treatment of primary insomnia in patients aged 55 or over. Following assessment of the trial data, PACEF designated the product as RED-RED due to lack of compelling evidence of effectiveness (see *PACE Bulletin* Vol 2, No 13 (August 2008)).

Prior to June 2008, melatonin was only available in the UK in a range of unlicensed formulations, many of which were non-pharmaceutical grade products imported from the USA. Because of fears over the standard of manufacture of these products, the Medicines and Healthcare products Regulatory Agency (MHRA) has recommended that **whenever melatonin is prescribed in the UK, the licensed formulation should be used wherever possible.** This includes off-label use of the licensed product, if deemed suitable by the clinician. Although the MHRA would not normally recommend the "off-label" use of products, the UK licensed product has been assessed for quality, safety and efficacy and its use carries less risk than that of an unlicensed product of unknown quality imported from abroad. Where use of a formulation other than Circadin is deemed to be necessary to meet the needs of a particular patient, prescribers will need to provide written details of the special clinical need to the importer for submission to the MHRA. Details need to be provided with every order.

The bulk of the prescribing of melatonin in Lincolnshire is for immediate release formulations for children with neurological or neuro-developmental disorder suffering from severe sleep disturbances. This is invariably initiated by a specialist and prescribed either on an ongoing basis by that specialist or under shared care arrangements by the patient's GP. There is also some prescribing of melatonin initiated by GPs for the treatment of irregular sleep patterns due to shift working or jet lag. As part of our review of melatonin we undertook to review the evidence base for each of these indications; a further review of shared care arrangements for children with severe sleep disorders linked to neurological or neuro-developmental disorder is in progress.

There are data from systematic reviews, meta-analyses and randomised controlled trials which assess the safety and efficacy of melatonin in children and adolescents with neurological or neuro-developmental disorder. Results show that melatonin improves onset and quality of sleep in these children; however trials are generally of short duration and have very low patient numbers. A large multi-centred UK based trial is underway but is not due to report until 2010. A review published by the London New Drugs Group on the use of melatonin in paediatric sleep disorders concluded that, despite a limited evidence base, the evidence in support of melatonin is actually more substantial that that available to support the use of alternative hypnotics in this patient group. The majority of the existing evidence supports the use of immediate release preparations which are used primarily to induce sleep rather than maintain it. Melatonin is generally well tolerated with few adverse effects; most commonly reported are headaches, dizziness, nausea and drowsiness.

There is no strong evidence to support the role of melatonin in the treatment of jet lag or sleep restriction linked to shift work and there are no licensed preparations for either of these conditions.

PACEF Recommendations:
Melatonin MR tablets (Circadin) remain RED-RED for primary insomnia.
All melatonin formulations are designated RED-RED for jet lag and sleep restriction (e.g. due to shift work). PACEF acknowledge that there is a role for melatonin in the treatment of children and adolescents with severe sleep disturbances linked to neurological or neuro-developmental disorder. The MHRA have advised that, where possible, Circadin, the licensed formulation of melatonin should be used preferentially. A review of local prescribing patterns has revealed that the majority of prescribing of melatonin is for unlicensed immediate release products. Where the patient can swallow tablets and a sustained release formulation is suitable, Circadin 2mg MR tablets should be prescribed. If the patient requires an immediate release formulation and can swallow tablets, Pharma-Nord Bio-Melatonin 3mg tablets should be prescribed (by brand name). This is a product which is a licensed medical product in its country of origin (Hungary) and is available with English language packaging. The MHRA have advised that this may be an appropriate second line choice if Circadin does not meet the clinical needs of the patient. If an immediate release formulation is required and the patient cannot swallow tablets, a UK manufactured unlicensed special formulation such as those obtained from either PENN pharmaceuticals or Special Products Ltd is recommended. If none of these options are viable, an unlicensed, imported product sourced from outside the UK can be used. These recommendations are summarized below. All of these formulations of melatonin are designated AMBER within the criteria specified. An updated shared care guideline for the use of melatonin in children and adolescents with severe sleep disturbances linked to neurological or neuro-developmental disorder is in preparation.

Summary

Step 1

If the patient can swallow tablets and a sustained release preparation is suitable use CIRCADIN 2mg M.R tablets

Step 2

If an immediate release preparation is suitable and the patient can swallow tablets use Pharma-Nord Bio-Melatonin 3mg tablets

Step 3

If an immediate release preparation is required and the patient is unable to swallow tablets, use a suitable preparation manufactured in the UK such as a PENN pharmaceuticals product or a UK manufactured 'special'

Step 4

If none of the products listed above are suitable, consider importing an unlicensed product from outside the UK. Unlicensed formulations of melatonin including immediate release 2.5mg, 3.0mg, 5.0mg and 10mg and slow release 3.0mg; can be obtained from IDIS.

N.B Clinician letters detailing why an imported product is required will be needed every time products listed in steps 2 or 4 are prescribed. Even though the Pharma-Nord product is the second line product of choice, it is an imported product and a clinician's letter is necessary to comply with the MHRA guidance on the use of imported medication without a UK product license. It is entirely possible that some specials manufacturers supplying products listed in step 3 may also require clinician letters as, although there is no official notification requirement for UK manufactured specials, the MHRA has advised that manufacturers must be able to provide evidence of special clinical need for the products they supply.

RAPID ASSESSMENT: BIMATOPROST/TIMOLOL EYE DROPS (GANFORT)

Ganfort is a combination eye drop licensed for use in glaucoma which contains bimatoprost 0.03% and timolol 0.5%. It is comparable in efficacy and tolerability to the existing prostaglandin analogue/beta blocker combination eye drop Xalacom and is less costly (see cost comparison).

Bimatoprost/timolol eye drops (Ganfort) 3ml £14.58
Latanoprost/timolol eye drops (Xalacom) 2.5ml £15.07

PACEF Recommendation:
Bimatoprost 0.03%/ timolol 0.5% eye drops (Ganfort) are designated GREEN.

RAPID ASSESSMENT: GLYCOPYRROLATE 0.5% LOTION

Glycopyrrolate 0.5% lotion is a topical antimuscarinic agent used in the treatment of facial hyperhidrosis and diabetic gustatory sweating. The evidence for its effectiveness is from case reports and small studies. There is a potential for clinically significant systemic antimuscarinic side-effects such as dry mouth and throat, blurred vision, urinary retention, mydriasis and accommodation failure. Alternative treatments for hyperhidrosis include topical aluminium chloride and oral antimuscarinic agents. Aluminium chloride causes skin irritation so may not be suitable for use on the face while oral antimuscarinics frequently cause systemic anticholinergic effects.

PACEF Recommendation:
Glycopyrrolate 0.5% lotion is designated AMBER. Subject to specialist initiation, this preparation can be prescribed in primary care without a formal shared care guideline.

NICE UPDATE

NICE TECHNOLOGY APPRAISAL 153: *ENTECAVIR FOR THE TREATMENT OF CHRONIC HEPATITIS B* (AUGUST 2008)

The key recommendations are as follows:

- Entecavir (Baraclude), within its marketing authorisation, is recommended as an option for the treatment of people with chronic HBeAg-positive or HBeAg-negative hepatitis B in whom antiviral treatment is indicated.
- Entecavir is an oral nucleoside analogue licensed for the treatment of chronic hepatitis B virus (HBV) infection in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.

PACEF Recommendation:
Entecavir (Baraclude) is designated RED for this indication. Shared care arrangements are not approved at this time.

NICE TECHNOLOGY APPRAISAL 154: *TELBIVUDINE FOR THE TREATMENT OF CHRONIC HEPATITIS B* (AUGUST 2008)

The key recommendation is as follows:

- Telbivudine (Sebivo) is **not recommended** for the treatment of chronic hepatitis B.

PACEF Recommendation:
Telbivudine (Sebivo) is designated RED-RED for this indication.

NICE TECHNOLOGY APPRAISAL 155: *RANIBIZUMAB AND PEGAPTANIB FOR THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION* (AUGUST 2008)

The key recommendations are as follows:

- **Ranibizumab (Lucentis)**, within its marketing authorisation, is **recommended** as an option for the treatment of **wet age-related macular degeneration** if all of the following circumstances apply in the eye to be treated: (1) the best-corrected visual acuity is between 6/12 and 6/96; (2) there is no permanent structural damage to the central fovea; (3) the lesion size is less than or equal to 12 disc areas in greatest linear dimension; and (4) there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes).
- **The cost of ranibizumab beyond 14 injections in the treated eye must be met by the manufacturer.**
- Ranibizumab should only be continued in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed.
- **Pegaptanib** is **not recommended** for the treatment of **wet age-related macular degeneration.**

Ranibizumab (Lucentis) is a humanised therapeutic antibody fragment licensed for the treatment of neovascular (wet) AMD that binds to VEGF-A isoforms of vascular endothelial growth factor (VEGF). VEGF is a protein that induces new blood vessel formation, vascular permeability and inflammation and has been implicated in the development of wet AMD. Ranibizumab is administered by intravitreal injection.

PACEF Recommendations:
Ranibizumab (Lucentis) is designated RED for the treatment of wet AMD within the constraints of NICE criteria. Bevacizumab (Avastin) is also designated RED for this indication within the same constraints. Bevacizumab is not licensed for the treatment of wet AMD, but is significantly lower in cost. Both treatment options are likely to be offered to Lincolnshire patients. Pegaptanib (Macugen) is designated RED-RED.

NICE TECHNOLOGY APPRAISAL 156: *ROUTINE ANTENATAL ANTI-D PROPHYLAXIS FOR WOMEN WHO ARE RHESUS D NEGATIVE* (AUGUST 2008)

The key recommendations are as follows:

- Routine antenatal anti-D prophylaxis (RAADP) is recommended as a treatment option for all pregnant women who are rhesus D (RhD) negative and who are not known to be sensitised to the RhD antigen. This is a review of TA41 and makes no change to the recommendations around eligibility and the indications for use.
- When RAADP is to be administered, the preparation with the lowest acquisition cost should be given, taking into account local negotiated prices and the cost of administration.

NICE TECHNOLOGY APPRAISAL 157: *DABIGATRAN ETEXILATE FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM AFTER HIP OR KNEE REPLACEMENT SURGERY IN ADULTS* (SEPTEMBER 2008)

The key recommendation is as follows:

- Dabigatran etexilate, within its marketing authorisation, is recommended 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.

Dabigatran etexilate (Pradaxa) is a direct inhibitor of thrombin and 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. Treatment should be started within 1-4 hours of surgery at a dose of 110mg. Thereafter, treatment is continued on a standard dose of 220mg once daily for 10 days after knee replacement and for 28-35 days after hip replacement.

PACEF Recommendations:
Dabigatran etexilate (Pradaxa) is designated RED. It is currently under consideration by ULHT Drug and Therapeutics Committee (DTC) as a possible alternative to injectable low molecular weight heparins (e.g. enoxaparin, tinzaparin) within licensed indications. A New Drug Assessment of rivaroxaban (Xarelto), a recently launched direct competitor, is currently underway and will be reviewed imminently by ULHT DTC and PACEF. These 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.

NICE TECHNOLOGY APPRAISAL 158: *OSELTAMIVIR, AMANTADINE AND ZANAMIVIR FOR THE PROPHYLAXIS OF INFLUENZA* (SEPTEMBER 2008)

The key recommendations are as follows:

- 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.
- During localised outbreaks of influenza-like illness (outside periods when influenza virus is confirmed by the Health Protection Agency (HPA) as circulating in the community), oseltamivir and zanamivir may be used for post-exposure prophylaxis in at-risk people living in long-term residential or nursing homes, whether or not they are vaccinated. There should be a high level of certainty that influenza is the causative agent (usually based on virological evidence of infection with influenza in the index case or cases).
- Oseltamivir and zanamivir are not recommended for seasonal prophylaxis of influenza.
- Amantadine is not recommended for prophylaxis of influenza.

- The choice of drug should take into account delivery system, potential adverse effects and contra-indications. If all other considerations are equal, the drug with the lower acquisition cost should be used.

Licensed indications

Oseltamivir (Tamiflu) and zanamivir (Relenza) are licensed for the treatment of influenza if started within 48 hours of the first symptoms (within 36 hours for zanamivir in children) when influenza is circulating in the community. Oseltamivir is licensed in adults and children over one year; zanamivir is licensed in adults and children of 5 and over. Oseltamivir and zanamivir are also licensed for post-exposure prophylaxis of influenza in adults and children over one year who have been exposed to a clinically diagnosed case when influenza is circulating in the community.
Both drugs are also licensed for use in exceptional circumstances to prevent influenza in an epidemic (e.g. when vaccination does not cover the infecting strain).

National surveillance scheme

The HPA uses information from a range of clinical, virological and epidemiological influenza surveillance schemes to identify periods when there is a substantial likelihood that people presenting with influenza-like illness are infected with influenza virus.

Cost Comparison

	Dose	**Cost**
Oseltamivir caps 75mg (Tamiflu)	Prevention of influenza (adults and adolescents): 75mg once daily for 10 days	£16.36
Oseltamivir caps 75mg (Tamiflu)	Treatment of influenza (adults and adolescents): 75mg every 12 hours for 5 days	£16.36
Zanamivir dry powder for inhalation 5mg (Relenza)	Prevention of influenza (adults and children over 5): 10mg once daily for 10 days.	£24.55
Zanamivir dry powder for inhalation 5mg (Relenza)	Treatment of influenza (adults and children over 5): 10mg twice daily for 5 days	£24.55

From this we can conclude that **the drug of lowest acquisition cost is oseltamivir (Tamiflu).**

At Risk Patients

The Chief Medical Officer has defined the following patient groups as at risk from influenza. Those with:

- Chronic respiratory disease (including asthma that requires continuous or repeated use of inhaled steroids or with previous exacerbations requiring hospital admission).
- Chronic heart disease
- Chronic renal disease
- Chronic liver disease
- Chronic neurological disease
- Immunosuppression

- Diabetes mellitus

People aged 65 or older are also considered at risk for the purposes of this guidance.

Definition of 'exposure'

Exposure to an influenza-like illness is defined as close contact with a person in the same household or residential setting who has had recent symptoms of influenza.

Definition of 'people not effectively protected by vaccination'

These include:

- Those who have not been vaccinated since the previous influenza season.
- Those for whom vaccination is contra-indicated or has yet to take effect.
- Those who have been vaccinated with a vaccine not well matched to the circulating strain.

PACEF Recommedations:
Both oseltamivir and zanamivir are designated GREEN subject to NICE restrictions. Both drugs are included in the Selected List Scheme (SLS) and are only approved for use within the NHS as designated by NICE. All prescriptions should be endorsed 'SLS'. Oseltamivir (Tamiflu) is currently the agent of lowest acquisition cost.

MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) SAFETY UPDATE; SEPTEMBER 2008

FENTANYL PATCHES

The MHRA have received reports of life-threatening adverse reactions associated with the use of fentanyl patches; potential causes have included dosing errors, accidental exposure and inappropriate prescribing. As a result of these reports, the Agency has issued the following advice:

- GPs and other healthcare professionals must fully inform patients and carers on the safe use of fentanyl patches, in particular drawing attention to correct application of the patch, safe disposal and the importance of not exceeding the prescribed dose.
- Increased body temperature and exposure of the patch to an external heat source may lead to potentially dangerous rises in serum fentanyl levels.
- Concomitant use of CYP3A4 inhibitors (e.g. amiodarone, azole antifungals, such as itraconazole, cimetidine, and macrolide antibiotics) may raise serum fentanyl levels. Concomitant use of other CNS depressants may also potentiate adverse effects.
- Health care professional who prescribe or dispense fentanyl should ensure that all patients and carers are aware of the signs and symptoms of an overdose (i.e. troubled or shallow breathing, tiredness, extreme sleepiness or sedation, inability to think, walk or talk normally; and feeling faint, dizzy or confused). Patients and carers should be advised to seek urgent medical attention if overdose is suspected.
- Patients who experience serious adverse effects should have the patches removed immediately and should be monitored for up to 24 hours after patch removal.

HUMAN PAPILLOMAVIRUS VACCINE

The MHRA have also summarized the main adverse reactions associated with the HPV vaccine to support the start of the UK HPV immunisation programme. The main points are as follows:

- The commonest side-effects are injection-site infections, fever, headache, fatigue, muscle pain, nausea, vomiting and diarrhoea.
- All prescribers are reminded to report all suspected adverse reactions via the Yellow Card Scheme, preferably online at www.yellowcard.gov.uk.
- The Agency particularly highlights the incidence of fainting and panic attacks which may occur prior to, during or following an immunisation session. These are unlikely to be a true side effect of the vaccine itself and are probably a psychogenic response to the injection process. Healthcare professionals are asked not to report these using the yellow card scheme.
- When submitting a yellow card for vaccines, all healthcare professionals are reminded they must include details of the vaccine brand name and batch number.
- If, on considering the above advice, the healthcare professional still wishes to report a suspected psychogenic episode, they should only report the suspected reaction (e.g. vasovagal syncope) and not the signs and symptoms (e.g. hyperventilation and limb jerking).

ANTIEPILEPTIC DRUGS

There has been a European wide review of data from clinical trials and adverse drug reaction reports following concerns over the risk of suicidal thoughts and behaviour associated with the use of antiepileptic drugs. The review concluded that there is a small increased risk and the MHRA has issued the following advice for healthcare professionals:

- Antiepileptic treatment is associated with a small risk of suicidal thoughts and behaviour; this applies to all drugs and is seen as early as one week after starting treatment.
- Patients should be advised to be alert to mood changes, distressing thoughts or feelings about suicide or self harm at any time during their treatment, and to seek medical advice if this occurs.
- Patients should be advised not to stop or alter their treatment without speaking to a healthcare professional.

SHORTAGE OF PREDNISOLONE SUPPOSITORIES: ADVICE TO PRESCRIBERS

Manufacturing problems have resulted in a shortage of prednisolone suppositories and it is unlikely that there will be any further supplies until June 2009. ULHT gastroenterologists have recommended the following alternatives:

- The recommended first choice alternative to prednisolone suppositories is mesalazine suppositories. The *BNF* recommended dose is 0.75-1.5g daily. 1g suppositories are often required as patients may not respond to lower strengths.
- For patients who fail to respond to mesalazine or who have failed to respond in the past, steroidal foam enemas (e.g. prednisolone or hydrocortisone) may be suitable alternatives.

- For some patients with severe symptoms, it may be necessary to use a combination of both high dose suppository in the morning and a steroid enema at night. The use of mesalazine enemas could also be considered.
- Unlicensed prednisolone suppositories should only be used as a last resort for patients who are unable to tolerate or do not respond to any of the alternative treatments. Predsol manufactured by Sigma in Australia is available as an unlicensed import from IDIS.
- Foam enemas do not deliver an effective dose of steroid to the rectum and may not be effective against proctitis; suppository based treatment is often preferable.

A cost comparison of the currently available preparations is given below:

Mesalazine suppositories	**Pack size**	**Cost**
Asacol 250mg suppositories	20	£5.12
Asacol 500mg suppositories	10	£5.12
Pentasa 1 gram suppositories	28	£41.55
Salofalk 500mg suppositories	30	£15.90
Steroidal rectal preparations	**Pack size**	**Cost**
Prednisolone 20mg enema (Predenema) Standard	10	£7.10
Prednisolone 20mg enema (Predenema) Long tube	7	£8.47
Prednisolone foam (Predfoam)	14 doses	£6.32
Predsol retention enema	7 dose	£7.50
Hydrocortisone 10% foam (Colifoam)	14 doses	£9.85
Budesonide 2mg/100mg enema (Entocort)	7 doses	£33.00
Unlicensed prednisolone preparations		
Prednisolone (Specials laboratory)	6	£123
Prednisolone 5mg (IDIS)	10	£11.40

If prednisolone suppositories remain the only treatment option then there are two unlicensed preparations currently available:

- Predsol 5mg suppositories manufactured by Sigma. This product is manufactured and licensed in Australia, but does not have a UK product licence. It can be obtained as an unlicensed import from IDIS.
- Prednisolone 5mg suppositories. This is an unlicensed product manufactured in the UK by Specials Laboratories at a cost £123 for 6 suppositories.

In their statement on unlicensed melatonin preparations issued in September 2008, the MHRA established the principle that an imported product which has a full product licence in its country of origin is a preferable option to a UK manufactured unlicensed product. Applying this principle to prednisolone suppositores would suggest that the imported Sigma product should be used first line if an unlicensed prednisolone suppository is required. Prescribers are advised that they may be required to provide a written letter to the wholesaler detailing the clinical need for an unlicensed medicine which may be submitted to the MHRA on request.

Acknowlegements

Many thanks to Cathy Johnson, Interface Lead Pharmacist, for her contributions to this edition of the *PACE Bulletin*.

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