Lincolnshire NHS

Prescribing and Clinical Effectiveness Bulletin

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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 Lincolnshire PCT 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: JANUARY UPDATE

Drug	Indication	Traffic Light Status
Mesalazine (Mezavant XL)	**Licensed for the induction and maintenance of remission in patients with mild to moderate active ulcerative colitis.**	**GREEN**
Pimecrolimus 1% cream (Elidel)	**Licensed for the second line short term treatment of mild or moderate atopic dermatitis where the use of topical steroids is inadvisable or not possible. For use in adults and children aged 2 and over.**	**AMBER**
Rufinamide (Inovelon)	**Licensed as an adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 4 years and older.**	**AMBER subject to specialist initiation, titration and the development of shared care guidelines from tertiary care**
Tacrolimus 0.03% ointment and 0.1% ointment (Protopic)	**Licensed for the second line short term treatment of moderate or severe atopic dermatitis unresponsive or intolerant to topical steroids. For use in adults**	**AMBER**

	(0.1% ointment) and children aged 2 and over (0.03% ointment).	
Zoledronic acid infusion (Aclasta)	**Licensed for the treatment of osteoporosis in postmenopausal women at increased risk of fracture**	**RED-RED**

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 LPT **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.

NEW DRUG ASSESSMENTS

RUFINAMIDE (INOVELON)

Rufinamide is a novel antiepileptic drug (AED) structurally unrelated to other currently available therapies. It is an oral tablet licensed as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 4 years and older. The relative rarity of the condition restricts the scale of the trial evidence available. Nonetheless, one small-scale, short-term, placebo controlled double-blind trial of123 patients has been conducted to evaluate rufinamide as adjunctive therapy in patients with LGS. This trial showed a significant reduction in the frequency of tonic-atonic seizures and total seizures, together with a reduction in seizure severity compared to placebo. The most frequent adverse events observed were vomiting (30.6%), pyrexia (25.8%), upper respiratory tract infection (21.8%) and somnolence (21%); possible serious side effects include the development of antiepileptic hypersensitivity syndrome and status epilepticus. Because of the complexity and severity of the condition the prospect of comparative studies versus currently available gold standard therapies are limited and ethically questionable.

The most recent NICE guidance on the treatment of LGS (April and October 2004) advocates lamotrigine and topiramate as the most appropriate first line therapies. A Cochrane Collaboration review of the treatment of LGS published in March 2003 concluded that the optimum treatment for LGS remains uncertain; to date no study has shown any one drug to be highly efficacious although lamotrigine, topiramate and felamate may be helpful as add-on therapy.

PACEF Recommendation:
PACEF recognized the rarity and complexity of this condition and the need for alternative adjunct therapies where standard first line treatments fail. Rufinamide was classified as AMBER subject to specialist initiation and titration and the development of appropriate shared care guidelines. The specialist nature of this condition means that the bulk of new initiations will come from tertiary care.

ZOLEDRONIC ACID INFUSION (ACLASTA)

Zoledronic acid (Aclasta) is a bisphosphonate licensed both as a treatment for Paget's disease of bone and as a once yearly intravenous infusion for the treatment of osteoporosis in post menopausal women. Clinical data to support the role in secondary prevention of osteoporosis comes from the HORIZON trial which demonstrated that once yearly zoledronic acid IV infusion was superior to placebo in reducing rates of both vertebral and hip fractures in post menopausal women. However, comparative data against alternative bisphosphonates is lacking. A recent systematic review published early on line suggests that there is good evidence to support the use of zoledronic acid in the prevention of vertebral fractures, but evidence supporting alendronate and risedronate in the prevention of hip fractures is stronger. In addition, further research is required to demonstrate the impact of zoledronic acid on physical function and quality of life, to confirm long term efficacy and to quantify cost effectiveness.

Recent comparative safety assessments of bisphosphonates have indicated that the incidence of osteonecrosis of the jaw is higher with zoledronic acid than with other bisphosphonates, although most reports have been in patients with cancer. There was also a statistically significant incidence of serious atrial fibrillation associated with zoledronic acid in the HORIZON study.

Recent draft NICE guidance on the secondary and primary prevention of osteoporosis advocated low cost generic oral alendronate 70mg weekly as the first line treatment of choice. Zoledronic acid is not covered by current NICE guidance and also not expected to be featured in updated guidance which is expected to be published shortly.

PACEF Recommendation:
There is currently insufficient evidence to support the use of zoledronic acid IV infusion; concerns remain around clinical effectiveness, cost-effectiveness and safety in comparison to other bisphosphonates. As a result of this, zoledronic acid is designated RED-RED.

MESALAZINE (MEZAVANT XL)

Mezavant XL is a new sustained-release (SR) formulation of mesalazine; each gastro-resistant SR tablet contains 1200mg of the active drug. The product is licensed for the induction and maintenance of remission in patients with mild to moderate active ulcerative colitis. It is comparably priced to alternatives and has the advantage of once daily dosing. General *BNF* advice on modified-release mesalazine preparations is that they should not be considered interchangeable.

PACEF Recommendation:
Mezavant XL tablets are designated GREEN on the basis that they are the only once daily mesalazine formulation currently available and may be useful in patients experiencing compliance problems with more frequent dosage regimes. The range of mesalazine preparations advocated by ULHT specialists is currently under review; further advice will be issued shortly.

NICE UPDATE

NICE CLINICAL GUIDELINE 57: ATOPIC ECZEMA IN CHILDREN (DECEMBER 2007)

The key recommendations are as follows:

- Wherever possible potential **trigger factors** should be identified (e.g. soaps, detergents, shampoos, bubble baths, shower gels, washing up liquids, other irritants, skin infections, contact allergens, food allergens, and inhalant allergens).
- A diagnosis of **food allergy** should be considered in children with atopic eczema (AE) who have reacted previously to food with immediate symptoms or in infants and young children with moderate to severe AE that has not been controlled by optimum management (particularly if associated with gut dysmotility or failure to thrive).
- A diagnosis of **inhalant allergy** should be considered in children with seasonal flares of AE or where AE is associated with asthma or rhinitis or in children over 3 years with AE on the face.
- A stepped approach to treatment is recommended. **Emollients** should form the basis of management and should always be used, even when the AE is clear. Management can be stepped up or down according to the severity of symptoms.
- Parents or carers should be taught to recognize **flares** of AE (e.g. increased dryness, itching, redness, swelling and general irritability) and how to manage them.
- **Emollients** should be used every day for moisturising, washing and bathing. They should be used on the whole body even when the AE is clear and used concurrently with other treatments. They should be used instead of shampoos for children under 12 months. Patients may be prescribed a combination of products or one product for all purposes depending on their needs and preferences. Leave-on emollients should be prescribed in large quantities (250-500g weekly).

PACEF Recommendation:
A recent study showed that half of children with eczema treated with a topical steroid were not prescribed a concurrent emollient. In general, emollients tend to be under-prescribed by doctors and under-used by patients. Emollient selection is often driven by patient preference, cosmetic acceptability, severity of the condition, tolerability and packaging. Pump dispensers are popular and convenient, but may be wasteful in terms of residual volume left in the container. A recent study compared currently available pump dispensers and found the Cetraben Cetrapump to be the least wasteful in terms of residual volume left after the pump stops working (2%). Figures recorded for competing products were Diprobase (10.5%), Hydromol (17.6%), Oilatum (20.9%), E45 (21.9%) and Doublebase (30.7%).

- The potency of **topical corticosteroids** should be tailored to the severity of the child's AE, which may vary according to body site. Mild potency steroids should be used for mild AE, moderate potency for moderate AE and potent for severe AE. For the face and neck, use mild potency corticosteroids except for the short-term use (3 to 5 days) of moderate potency for severe flares. Use moderate or potent preparations for short periods (7 to 10 days) for flares

in vulnerable sites such as axillae and groin. Do not use very potent preparations in children without specialist dermatological advice.

- **Topical corticosteroids** should only be applied to areas of active AE or eczema that has been active in the past 48 hours. Do not use potent topical corticosteroids on the face or neck or in children under 12 months (without specialist supervision). Prescribe topical corticosteroids for application only once or twice a day. Within the appropriate potency class, prescribe the drug with the lowest acquisition cost, taking into account pack size and frequency of application.

PACEF Recommendation:
For mild topical corticosteroid preparations, the lowest acquisition cost products are: hydrocortisone (Efcortelan) cream and ointment 0.5% (30g, 61p), 1% (30g, 75p) and 2.5% ointment (30g, £1.70). Prescribing hydrocortisone cream or ointment generically as 15g packs can be expensive due to the high price of these packs; ideally 30g packs should be prescribed (either generically or as Efcortelan).
For moderate topical steroid preparations, Betnovate RD emerges as the lowest cost option in terms of cost per gram; the product is not recommended for use in children under 1 year and should not be used for longer than 5 days in children over 1 year. Occlusives should not be used. Alternative products with smaller pack sizes are likely to be more cost-effective where patient use is low or irregular.
For potent topical corticosteroids, generic betamethasone or Betnovate preparations emerge as the lowest cost options; the products are not recommended for use in children under 1 year and should not be used for longer than 5 days in children over 1 year. Occlusives should not be used.

- **Topical calcineurin inhibitors** (such as tacrolimus and pimecrolimus) should not be used for mild AE, as first line for AE of any severity or under bandages or dressings without specialist dermatological advice.
- **Topical calcineurin inhibitors** are options for treatment in those patients not controlled by topical corticosteroids or where there is a risk of important adverse effects from topical corticosteroids. Tacrolimus may be used for moderate to severe AE in children aged 2 and over; pimecrolimus may be used for moderate AE on the face and neck in children aged 2 to 16 years. Topical calcineurin inhibitors should only be initiated by physicians with a special interest and experience in dermatology.

PACEF Recommendation:
Both tacrolimus (Protopic) 0.03% ointment (the recommended strength in children) and pimecrolimus (Elidel) 1% cream are designated AMBER on the Traffic Lights List.

- Antihistamines should not be used routinely. A one month trial of a non-sedating antihistamine may be indicated in a child with severe AE or mild to moderate AE with severe itching or urticaria. Continue if successful while symptoms persist. Sedating antihistamines may be offered as a 7 to 14 day trial for children over 6 months during acute flares if sleep disturbance has a significant impact.
- Children, parents or carers should be offered information on how to recognize the symptoms and signs of **bacterial infection** with staphylococcus and/or streptococcus (e.g. weeping, pustules, crusts, AE unresponsive to therapy, rapidly worsening AE, fever and malaise). Information should also be

provided on how to recognize **eczema herpeticum** (e.g. rapidly worsening, painful eczema, clustered blisters, punched-out erosions, possible fever, lethargy or distress).

- A 6-8 week trial of an extensively hydrolysed protein formula or amino acid formula in place of cow's milk formula for bottle-fed infants under 6 months is recommended with uncontrolled moderate or severe AE. Do not use diets based on unmodified proteins of other species' milk (e.g. goat's or sheep's milk) or partially hydrolysed formulas for the treatment of suspected cow's milk allergy.
- Referral for **specialist dermatological advice** is recommended if: the diagnosis is uncertain; management has not controlled the AE; AE on the face has not responded to appropriate treatment; specialist advice on treatment application is required (e.g. bandaging techniques); contact allergic dermatitis is suspected; the AE is creating significant social or psychological problems; or the AE is associated with severe or recurrent infections.

CLOSTRIDIUM DIFFICILE REMINDER

Readers will remember from the November 2007 issue of the *PACE Bulletin* (Vol 1 No 7) that emerging patterns of bacterial resistance to antibiotics and the increasing incidence nationally of *Clostridium difficile* remain significant problems within the NHS across both primary and secondary care. Prescribers are reminded that particular concerns have been raised by local Microbiologists around the inappropriate use of broad spectrum antibiotics and the increased risk of *Clostridium difficile*. Specifically, the over-frequent use of broad-spectrum penicillins (amoxicillin, ampicillin, co-amoxiclav and co-fluampicil), cephalosporins (cefalexin, cefaclor, cefradine, cefuroxime, cefpodoxime, cefixime, but particularly second and third generation agents), clarithromycin, quinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin) and clindamycin have contributed to the rising incidence of antibiotic associated diarrhoea nationally.

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