TAYSIDE PRESCRIBER

Tayside D&TC Supplement No. 48

Jan 2005

Produced by Tayside New Medicines Implementation Panel (NMIP)

In this issue:

SMC Detailed Advice Document

From February 2005, the SMC Detailed Advice Document (DAD) following full submissions (including those listed below) will be available via the SMC website.

SMC Advice Issued in January 2005

Caspofungin (Cancidas®) – empirical antifungal therapy in febrile, neutropenic patients

SMC recommendation

Advice: following a full submission

Caspofungin (Cancidas®) is accepted for restricted use within NHS Scotland for the empirical therapy for presumed fungal infections (such as *Candida* or *Aspergillus*) in febrile, neutropenic adult patients.

It should be restricted to patients following the advice of microbiologists or specialists in infectious diseases.

A comparative study found that caspofungin was as effective as a lipid formulation of amphotericin in terms of overall response. In addition it was better tolerated with fewer drug-related adverse events including less nephrotoxicity and infusion-related events. It is less expensive than another formulation of liposomal amphotericin which has a licence for empirical use.

Tayside recommendation

Not currently recommended – pending antifungal policy decision

Points for consideration:

- Caspofungin is also licensed for the treatment of confirmed invasive aspergillosis and candidiasis (refer to DTC Supplement No.25, April 2003 and No.35, Jan 2004 for advice on use in these indications). The above SMC advice relates only to empirical therapy in febrile, neutropenic patients.

Continued over

Caspofungin continued

- In the key caspofungin study, overall response was based on a five-component composite endpoint that included survival and resolution of fever. Due to confounding factors such as concomitant antibacterial therapy and successful treatment of underlying disease, outcomes may not necessarily reflect true efficacy of empirical antifungal therapy.
- Caspofungin is considerably less expensive than AmBisome®, the only other antifungal agent with a specific licence for empirical therapy. (Caspofungin 50mg daily costs £328 per day versus £554 for AmBisome® 180mg daily). Lipid formulations of amphotericin, such as AmBisome®, are considerable more expensive than the conventional formulation (standard amphotericin 70mg daily costs £7 per day).
- A haematology/oncology antifungal policy is currently under development by the ASD Anti-Infectives Sub-Committee in liaison with haematology/oncology specialists.
- **The place of caspofungin in the empirical treatment of febrile, neutropenic patients will be addressed by the ASD Anti-Infectives Sub-Committee. Prescribers are advised to await the antifungal policy decision.**

Efalizumab (Raptiva®) – moderate to severe plaque psoriasis

SMC recommendation

Advice: following a full submission

Efalizumab (Raptiva) is not recommended for use within NHS Scotland for the treatment of adult patients with moderate to severe chronic plaque psoriasis who have failed to respond to, or have a contra-indication to, or are intolerant to other systemic therapies, including ciclosporin, methotrexate and PUVA (photochemotherapy).

For patients with moderate to severe psoriasis, efalizumab was superior to placebo in producing a 75% improvement in the Psoriasis Area Severity Index (PASI). The patient population studied in the Phase III trials was not the same as that identified within this indication, though there is some evidence that they may respond similarly to the overall study group. However cost effectiveness was not demonstrated.

Tayside recommendation

Not recommended

Points for consideration:

- Efalizumab is a humanised anti-CD11a monoclonal antibody that prevents T-cell activation. Etanercept is the only other "biologic" agent currently licensed for the treatment of psoriasis. The SMC is awaiting a submission from the manufacturer for use in this indication.
- Whilst the licence for efalizumab restricts its use to patients who have failed to respond or have a contra-indication or intolerance to other systemic therapies, the key studies included a wider population of patients with moderate to severe psoriasis. Efficacy in the licensed population is therefore unclear.
- Adverse events associated with efalizumab mainly consist of flu-like reactions to the first or second injections, which diminish on continued therapy. In the largest clinical study, efalizumab was associated with an increased incidence of infection rates (24% versus 18% in the placebo group) and slightly higher rates of skin reactions and musculoskeletal disorders. The SPC advises routine platelet monitoring as thrombocytopenia may occur.
- Whilst efalizumab treatment may be continuous, only limited long-term efficacy data are currently available.
- There are no comparative efficacy or safety data for efalizumab versus other systemic treatments for psoriasis (eg methotrexate, ciclosporin and retinoids).
- NICE plans to review new treatments for moderate to severe psoriasis, including efalizumab, and issue guidance in October 2005.
- Efalizumab is not stocked by the hospital pharmacy.

Levetiracetam 750mg film coated tablets (Keppra®) - epilepsy

SMC recommendation
Advice: following an abbreviated submission
Levetiracetam 750mg film coated tablets are accepted for restricted use in NHS Scotland as an additional dosage form for adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients for whom therapy is appropriate. Its use should be initiated by physicians who have appropriate experience in the treatment of epilepsy. The budget impact for NHS Scotland is likely to be small.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- To date, levetiracetam has been available as 250mg, 500mg and 1000mg film-coated tablets.
- The new 750mg dosage form reduces the number of tablets for patients requiring 750mg or 1500mg levetiracetam twice daily.
- The levetiracetam licence does not cover use in children and adolescents under 16 years of age.
- Levetiracetam is one of the newer anti-epileptic drugs (AEDs) recently recommended by NICE for the management of epilepsy in people who have not benefited from treatment with the older AEDs such as carbamazepine or sodium valproate, or for whom the older AEDs are unsuitable because of contra-indications, interaction or poor tolerance.
- **Levetiracetam is recommended locally, under the direction of a neurologist, for use in accordance with NICE guidance on newer drugs for epilepsy in adults.**

Levetiracetam 100mg/ml oral solution (Keppra®) - epilepsy

SMC recommendation
Advice: following an abbreviated submission
Levetiracetam 100mg/ml oral solution is accepted for restricted use in NHS Scotland as an additional dosage form for adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in patients for whom therapy is appropriate. Its use should be initiated by physicians who have appropriate experience in the treatment of epilepsy. The budget impact for NHS Scotland is likely to be small.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- The oral solution is a useful option in certain patients eg those with learning disability who will not take tablets or those for whom swallowing is difficult.
- See points above

Mycophenolic acid gastro-resistant tablets (Myfortic®) – prophylaxis of transplant rejection

SMC recommendation
Advice: following a full submission
Mycophenolate sodium (Myfortic®) is accepted for use within NHS Scotland for the prophylaxis of acute transplant rejection in adult patients receiving allogeneic renal transplants in combination with ciclosporin and corticosteroids. It is restricted to use by transplant specialists as part of a immunosuppressive regimen.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Myfortic® is an enteric-coated formulation of mycophenolate sodium designed to improve gastrointestinal (GI) tolerability of mycophenolate. Pharmacokinetic studies show that 720mg mycophenolate sodium is equivalent to 1g of the alternative mycophenolate formulation (mycophenolate mofetil, CellCept®).

Continued over

Mycophenolic acid gastro-resistant tablets continued

- Clinical studies, in both de novo renal transplant patients and in patients previously stabilised on mycophenolate mofetil, show no difference in efficacy between mycophenolate sodium and mycophenolate mofetil over a 12-month period.
- The incidence and profile of GI adverse events appear similar for the two formulations. (Therefore the anticipated improvement in GI tolerability due to enteric-coating is unproven). Studies reported lower incidence of serious infection and serious pneumonia in the mycophenolate sodium arm.
- Long-term efficacy data for mycophenolate sodium are currently unavailable.
- Mycophenolate sodium is priced below mycophenolate mofetil (£8.17 per day for mycophenolate sodium 720mg twice daily versus £9.07 for mycophenolate mofetil 1g twice daily).
- 2004 NICE guidance recommends that mycophenolate mofetil should be an option as part of an immunosuppressive regimen only when there is proven intolerance to calcineurin inhibitors, particularly nephrotoxicity leading to risk of chronic allograft dysfunction, or in situations where there is a very high risk of nephrotoxicity necessitating minimisation or avoidance of a calcineurin inhibitor. (Mycophenolate sodium was not licensed at the time of the NICE assessment).
- **Locally, mycophenolate sodium may continue to be prescribed following recommendation from a tertiary Transplantation Unit. It may also be considered in patients with GI intolerance of mycophenolate mofetil 1g twice daily within the first post transplant year, under the direction of a local specialist in renal disease.**

Nicotinic acid modified release tablets (Niaspan®) - dyslipidaemia

SMC recommendation

Advice: following a full resubmission

Nicotinic acid modified release tablets (Niaspan®) is not recommended for use in NHS Scotland for the treatment of dyslipidaemia and primary hypercholesterolaemia as monotherapy in patients who do not tolerate HMG-CoA reductase inhibitors and is not recommended for use when prescribed in combination with HMG-CoA reductase inhibitors (statins).

There is evidence that nicotinic acid modified release tablets lowers LDL cholesterol levels to a small extent and raises HDL-cholesterol levels to a greater extent. However, the evidence for use in combination with HMG-CoA reductase inhibitors is less convincing. The economic case for use as monotherapy or co-therapy in the licensed indication was not demonstrated.

Tayside recommendation

Not recommended

Points for consideration:

- Refer to DTC Supplement No. 38, April 2004.
- Nicotinic acid modified release tablets are not stocked by the hospital pharmacy.

Pregabalin (Lyrica®) – adjunctive epilepsy therapy

SMC recommendation

Advice: following a full submission

Pregabalin (Lyrica®) is accepted for restricted use within NHS Scotland as adjunctive therapy in adults with partial seizures with or without secondary generalisation.

It should be initiated only by physicians who have appropriate experience in the treatment of epilepsy and should be used principally in patients who have not benefited from treatment with an older anti-convulsant drug such as carbamazepine or sodium valproate, or for whom these drugs are unsuitable because of contra-indications, interaction or poor tolerance.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Pregabalin is an alpha$_2$-delta ligand that has analgesic, anxiolytic and anticonvulsant activity. It has a similar pharmacological profile to gabapentin, with three to ten-fold increased potency.
- Pregabalin is licensed as an adjunctive therapy in the treatment of epilepsy and also for the treatment of

Continued over

Pregabalin continued

neuropathic pain. The above SMC advice relates only to the epilepsy indication. Advice on use in the treatment of neuropathic pain is due in quarter one 2005.

- Clinical studies show reduced seizure frequency in patients receiving pregabalin versus placebo as adjunctive therapy over a 12-week period.
- Like other anti-epileptic drugs (AEDs), pregabalin is associated with central nervous system and gastro-intestinal adverse effects. In common with levetiracetam and gabapentin, it does not interact with other anti-epileptics or oral contraceptives.
- No long-term efficacy data comparing pregabalin to other anti-epileptics are available. There are also no data to assess whether patients who have limited response to, or who do not respond to, gabapentin will respond to pregabalin.
- Pregabalin has a flat pricing structure for any strength of capsule. Across the dose range (150mg-600mg per day), it is more cost-effective to prescribe in two rather than three divided doses (£64 versus £97 for 28 days treatment). The cost of pregabalin therapy falls within the range of other newer AEDs (gabapentin, vigabatrin, oxcarbazepine, lamotrigine, tiagabine, topiramate, and levetiracetam).
- 2004 NICE guidance recommends the use of newer AEDs for the management of epilepsy in people who have not benefited from treatment with the older AEDs such as carbamazepine or sodium valproate, or for whom the older AEDs are unsuitable because of contra-indications, interaction or poor tolerance. Combination (adjunctive) therapy should only be considered when attempts at monotherapy with AEDs have not resulted in seizure freedom. 2003 SIGN guidance notes that combination therapy should be considered when treatment with two first-line AEDs has failed or when the first well-tolerated drug substantially improves seizure control but fails to produce seizure-freedom at maximal dosage. The choice of drugs in combination should be matched to the patient's seizure type(s) and should be limited to two or at most three AEDs.
- **Pregabalin is recommended locally, under the direction of a neurologist, as an alternative newer adjunctive anti-epileptic therapy for use in accordance with NICE guidance on newer drugs for epilepsy in adults.**

Fondaparinux Update

Fondaparinux was recommended for restricted use (hospital only) by Tayside DTC in December 2002. Dalteparin (Fragmin®) is the antithrombotic used locally for venous thromboembolic prophylaxis during orthopaedic surgery, and for this reason the Tayside fondaparinux advice has been revised to **not recommended**. (Requests to use fondaparinux in exceptional circumstances should be considered by the Clinical Group.)

Promogran® dressing

Promogran® dressing is recommended by the Wound Management Sub-Group of the DTC for the treatment of diabetic foot ulcers, leg ulcers and pressure sores that do not respond to conventional wound management. Within hospital, Promogran® dressing may be used in specialist areas or on the recommendation of specialist staff involved in wound management after completion of a mandatory order form. Guidelines for the use of Promogran® and mandatory order forms are available from the pharmacy dispensary at Ninewells, Perth Royal Infirmary and Stracathro.

Tayside Palliative Care Guidelines

Practical advice on the care of patients with advanced, non-curative illness is available in pocket-sized Tayside Palliative Care Guidelines developed by Roxburghe House, the Ninewells Hospital Palliative Care Team and the Tayside Macmillan Pharmacist. These guidelines are available from the DTC website located under Approved Documents and Policies (click here).

Recommended Procedures Governing the Activities of Medical Representatives within NHS Tayside Hospitals

The following policy document was agreed at the Tayside DTC meeting in November 2004. Hospital staff are asked to support the points stated.

Recommended Procedures Governing the Activities of Medical Representatives within NHS Tayside Hospitals

In order to reinforce the appropriate use and management of medicines, promote formulary compliance and reinforce security measures within NHS Tayside hospitals, it has been agreed that the activities of Medical Representatives should be regulated as follows:

1. As a general principle, contact between representatives and hospital staff should be limited to those circumstances where hospital staff have a genuine wish to obtain information from representatives.

2. Representatives should see Consultants by appointment only.

3. Representatives should only see medical staff below Consultant grade with the full knowledge and agreement of their Consultant, and by appointment only.

4. Representatives should be seen at Pharmacy by appointment only.

5. **NO** medicinal or wound management product samples are to be left in clinical areas or Pharmacy departments. It is NHS Tayside policy not to accept such product samples. A mechanism exists for Consultants wishing to use newly launched, licensed products prior to SMC evaluation on a one-off named-patient basis.

6. Medical representatives **MUST NOT** visit wards, departments or theatres without a specific invitation from, or appointment with, the relevant Consultant.

7. Medical representatives wishing to introduce products, or deliver training to nursing staff will do so through the appropriate Operational Nurse Manager. The regulation concerning samples (see 5 above) applies.

8. Representatives should be aware that medicinal products are used in NHS Tayside within the context of the relevant local and national guidance, therefore promotion outwith such guidance is not supported.

Healthcare workers are also reminded of the NHS Tayside policy on receiving hospitality/gifts etc from medical representatives.

NHS Tayside Area Drug & Therapeutics Committee
November 2004

Review by November 2006

Forthcoming SMC Advice

Gastro-intestinal system
Beclometasone Dipropionate 5mg
Esomeprazole (Nexium®)
Cardiovascular system
Candesartan (Amias®)
Perindopril (Coversyl®)
Bivalirudin (Angiox®)
Valsartan (Diovan®)
Anagrelide hydrochloride (Xagrid®)
TachoSil®
Respiratory
Ciclesonide (Alvesco®)
Montelukast (Singulair®)
Central nervous system
Methylphenidate (Equasym XL®)
Atomoxetine (Strattera®)
Buprenorphine (Transtec®) patch
Tramadol (Tramacet®)
Pregabalin (Lyrica®) – *neuropathic pain*
Galantamine (Reminyl XL®)
Ropinirole (Adartrel®)
Infections
Lamivudine OD (Epivir®) & Abacavir OD (Kivexa®)
Fosamprenavir (Telzir®)
Abacavir (Ziagen®)
Abacavir-lamivudine (Kivexa®)
Adefovir dipivoxil (Hepsera) - ***Re-submission***

Endocrine system
Strontium ranelate (Protelos®)
Somatropin (Norditropin SimpleXx®)
Pegvisomant (Somavert®)
Metformin hydrochloride (Glucophage SR®)
Insulin detemir (Levemir®)
Triptorelin (Gonapeptyl® Depot)
Obstetrics, gynae and urinary-tract disorders
Tamsulosin hydrochloride (Flomaxtra®)
Malignant disease & immunosuppression
Letrozole (Femara®)
Ibritumomab (Zevalin®)
Cytarabine liposomal (DepoCyte®)
Gliadel® wafer
Docetaxel (Taxotere®)
Cetuximab (Erbitux®)
Darbepoetin alfa (Aranesp®)
Oxaliplatin (Eloxatine®)
Gemcitabine (Gemzar®)
Imiquimod 5% Cream (Aldara®)
Nutrition & Blood
Lanthanum carbonate (Fosrenol®)
Musculoskeletal & joint diseases
Lumiracoxib (Prexige®)
Skin
Eflornithine 11.5% Cream (Vaniqa®)

Contact details: Local implementation of SMC recommendations is being taken forward by the Tayside Medicines Unit – contact Jan Jones, Pharmaceutical Prescribing Adviser (jan.jones@tpct.scot.nhs.uk) if you have any queries in relation to the introduction of new drugs within NHS Tayside