TAYSIDE PRESCRIBER

Tayside D&TC Supplement No. 47

Dec 2004

Produced by Tayside New Medicines Implementation Panel (NMIP)

In this issue:

SMC Advice Issued in December 2004

Creon micro (Creon®) – pancreatic exocrine insufficiency

SMC recommendation

Advice: following an abbreviated submission

New formulation for infants

Creon micro® granule formulation is accepted for restricted use in NHS Scotland for the treatment of pancreatic exocrine insufficiency. It provides a formulation suitable for use in young infants and is expected to be used for young cystic fibrosis sufferers who are unable to swallow capsules. The associated resource implications are expected to be small.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Creon micro® contains lipase 5000 PhEur units, amylase 3600 PhEur units and protease 200 PhEur units.

Eplerenone (Inspra®) – heart failure post-MI

SMC recommendation

Advice: following a full submission

Eplerenone (Inspra®) is accepted for restricted use within NHS Scotland in addition to standard therapy including beta-blockers, to reduce the risk of cardiovascular mortality and mortality and morbidity after recent myocardial infarction (MI) in stable patients with left ventricular dysfunction (left ventricular ejection fraction ≤40%) and clinical evidence of heart failure.

Its use should be restricted to patients who cannot tolerate spironolactone due to sex hormone mediated adverse effects. Eplerenone is the second aldosterone antagonist marketed in the UK. It reduces all-cause mortality and cardiovascular-related mortality and hospitalisation in patients with heart failure post-MI.

Continued over

Eplerenone continued
However, there are no data on its clinical and cost effectiveness in this population compared to the other aldosterone antagonist marketed in the UK, which also reduces mortality and morbidity in patients with heart failure and is considerably cheaper.
The licence holder has indicated their decision to resubmit.

Tayside recommendation

Accepted for restricted use

Points for consideration:

- Eplerenone is the first selective aldosterone receptor antagonist (SARA). Therapy should usually be started within 3-14 days after an acute MI. Spironolactone (the other aldosterone antagonist marketed in the UK) is licensed for the treatment of congestive cardiac failure.
- The EPHESUS (Eplerenone Post-acute myocardial infarction Heart failure Efficacy and SUrvival Study) compared eplerenone 25mg-50mg daily to placebo in patients already receiving standard therapy who had suffered an acute MI (within the last 3-14 days) complicated by left ventricular dysfunction (LVD). Eplerenone was associated with relative risk reductions of 15% for all-cause mortality and 13% for death from cardiovascular mortality or hospitalisation for a cardiac event, and absolute risk reductions of 2.3% and 3.3% respectively over a 16 month period.
- The benefit of spironolactone in patients with NYHA class III or IV heart failure was demonstrated in the RALES (Randomised ALdactone Evaluation Study) which showed relative risk reductions of 30% for all-cause mortality and 32% for death or hospitalisation for cardiovascular causes over a two year period. These risk reductions are larger than observed in EPHESUS and may reflect the variations in severity of heart failure at enrolment, the level of systolic dysfunction (which was worse in RALES), or the number of additional effective therapies administered in EPHESUS.
- There are no studies directly comparing eplerenone and spironolactone in patients with heart failure post-MI, therefore relative efficacy in this population is uncertain.
- Eplerenone appears to have a similar adverse effect profile to spironolactone including incidence of hyperkalaemia. Serum potassium should be measured before initiating eplerenone, within the first week, at one month after the start of treatment or dose adjustment, and as needed periodically thereafter.
- Eplerenone may be less likely than spironolactone to cause sex-hormone mediated adverse events. In RALES, breast pain or gynaecomastia occurred in 10% of men treated with 25mg spironolactone causing 2% to discontinue treatment. Whilst incidence was similar to placebo in EPHESUS, these adverse effects have been observed with eplerenone at doses of 25mg-400mg used in hypertension studies.
- Eplerenone is considerably more expensive than generic spironolactone. (28 days treatment with eplerenone 50mg daily costs £43 versus £2 for spironolactone 25mg daily).
- The 2001 NICE guideline on prophylaxis for patients who have experienced a MI recommends that patients who have had a MI and have moderate to severe heart failure, NYHA classes III or IV, should receive spironolactone.
- **In practice, patients with heart failure post-MI can be treated with spironolactone in accordance with its licence and the above guidance. Eplerenone is reserved for patients who are unable to tolerate spironolactone due to sex-hormone mediated adverse effects eg gynaecomastia or breast pain in men.**
- Eplerenone will be considered for inclusion in the Tayside Area Prescribing Guide (TAPG) by the Formulary Committee.

Ertapenem (Invanz®) – intra-abdominal infection

SMC recommendation

Advice: following a full submission

Ertapenem (Invanz®) is accepted for restricted use within NHS Scotland for the treatment of intra-abdominal infections in adults.

Ertapenem should only be used second or third-line treatment of community acquired intra-abdominal infections resistant to the current conventional treatments and under the advice of local microbiologists or specialists in infectious diseases.

Continued over

Ertapenem continued

Tayside recommendation

Recommended within specialist treatment pathway - HOSPITAL ONLY

Points for consideration:

- Ertapenem is a group 1 carbapenem with a long plasma half-life which allows it to be given once daily. It has a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria including extended-spectrum β-lactamase (ESBL) and AmpC β-lactamase producing strains. At present, ESBL-producing organisms are unusual as community acquired infections in Tayside.
- Ertapenem is also licensed for treatment of community acquired pneumonia and acute gynaecological infections. The SMC is awaiting submissions from the manufacturer for use in these indications.
- Clinical studies in patients with complicated intra-abdominal infection show that ertapenem has similar cure rates to ceftriazone plus metronidazole and piperacillin/tazobactam (Tazocin®). Efficacy in patients with more severe disease (with a high APACHE II score) has not been confirmed due to small population numbers.
- Other carbapenems (imipenem and meropenem) are also active against *Pseudomonas spp* and therefore have a broader range of antibacterial activity than ertapenem and are reserved for treatment of severe infection or infection caused by drug resistant bacteria. Prudent use of this class of antibiotics is important to limit the development of resistance.
- The ASD Antibiotic Policy recommends cefuroxime plus metronidazole for first-line treatment of intra-abdominal infections, with the addition of gentamicin for patients with severe sepsis or septic shock.
- **Locally, ertapenem is restricted to the Outpatient and Home Parenteral Antibiotic Therapy (OHPAT) service, on the recommendation of an ID Specialist or Microbiologist, for the treatment of ambulant patients who have proven infection with an ESBL producing organism.**

Etomidate-Lipuro® – induction of general anaesthesia

SMC recommendation

Advice: following an abbreviated submission

New formulation of existing product

Etomidate-Lipuro® 2mg/ml is accepted for use in NHS Scotland for the induction of general anaesthesia in patients aged six months and above where etomidate is an appropriate agent. Compared with high-osmolality etomidate formulations based on propylene glycol, this formulation may be associated with a reduction in adverse events, including pain on administration and the requirement for a local anaesthetic, at no additional cost.

Tayside recommendation

Not currently recommended – pending price review

Points for consideration:

- Etomidate-lipuro® has the same pharmacokinetic profile and pharmacodynamic effects as etomidate (Hypnomidate®).
- Formulation as a lipid emulsion allows physiological osmolality and pH thus reducing pain on injection.
- Local contract prices of etomidate and etomidate-lipuro® are currently under review.
- Etomidate-lipuro® is not stocked by the hospital pharmacy.

Laronidase (Aldurazyme®) – mucopolysaccharidosis I (MPS I)

SMC recommendation

Advice: following a re-submission

Laronidase is not recommended for use within NHS Scotland for the treatment of mucopolysaccharidosis I. Laronidase was approved by the EMEA under exceptional circumstances and has been granted orphan drug status. No information is presented in the submission to support the therapy being cost-effective.

Tayside recommendation

Not recommended

Points for consideration:

- Refer to DTC Supplement 41, July 2004 regarding original submission.

Miglustat (Zavesca®) – mild to moderate type 1 Gaucher disease

SMC recommendation
Advice: following a full submission
Miglustat is accepted for use within NHS Scotland for the treatment of mild to moderate type 1 Gaucher disease in patients for whom enzyme replacement therapy is unsuitable.
Miglustat should only be initiated by physicians experienced in the management of Gaucher's disease.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Type 1 Gaucher disease is a rare inherited disease caused by a lack of β-glucocerebroside enzyme which is needed for the intralysosomal catabolism of glucocerebroside. Accumulation of glucocerebroside leads to multi-organ problems and patients with type 1 disease have liver, spleen and bone problems. Miglustat reduces the synthesis of glucocerebroside.
- Enzyme replacement therapy (ERT) with imiglucerase intravenous infusion is used for first-line treatment of Gaucher disease. Miglustat is available as an oral preparation.
- Open-label non-comparative studies of miglustat show significant reductions in liver and spleen volumes measured at six, 12 and 36 months. Comparative data indicate that miglustat may not increase platelets as successfully as imiglucerase.
- In clinical trials, high percentages of patients reported diarrhoea.
- There are no data on the long-term safety or efficacy of miglustat. The major problems associated with type 1 Gaucher disease are due to severe bone disease and trials are of insufficient duration to assess the effects on bone.
- Miglustat is less expensive than imiglucerase. (The annual cost of treatment with miglustat 100mg three times daily is £58,000 versus £78,000 or £330,000 for imiglucerase 15 units/kg or 60 units/kg every two weeks respectively).
- **Miglustat is recommended locally for the treatment of type 1 Gaucher disease, under the direction of a specialist from a recognised lysosomal storage disorder centre, in patients unwilling or unable to have ERT.**

Paracetamol infusion (Perfalgan®) – short-term treatment of moderate pain

SMC recommendation
Advice: following a full submission
Paracetamol 1g/100ml infusion (Perfalgan®) is accepted for use within NHS Scotland for the short-term treatment of moderate pain following surgery and fever, when administration by intravenous route is clinically justified.

Tayside recommendation

Recommended within specialist protocol – HOSPITAL ONLY

Points for consideration:

- Clinical trials concentrate on the morphine-sparing effects of propacetamol (a pro-drug of paracetamol) for post-operative pain.
- In placebo-controlled studies, both paracetamol IV and propacetamol IV have been shown to reduce post-operative morphine consumption via a patient controlled analgesia (PCA) pump by approximately one third over 24 hours. The clinical significance of this degree of morphine–sparing in terms of reduction in morphine related adverse events is unclear.
- There are no direct comparative data for paracetamol IV versus alternative parenteral analgesics. Studies of propacetamol IV show similar post-operative pain relief to morphine IM, diclofenac IM and ketorolac IV.
- In respect of systemic adverse effects, paracetamol IV appears to have a similar safety profile to oral paracetamol.
- Paracetamol IV infusion is approximately twice the cost of IM or SC morphine. (1g paracetamol IV costs £1.50 versus 72p for 10mg morphine IM). Whilst morphine consumption may reduce when paracetamol IV is used in conjunction with morphine, this may not produce cost savings in practice (eg

Continued over

Paracetamol infusion continued

if the proportion of a PCA solution used is reduced but not the number of syringes prepared).

- Oral paracetamol should replace the IV infusion once the patient is able to eat solids and swallow oral drugs.
- **Paracetamol IV infusion is recommended locally for the relief of post-operative pain in patients who require paracetamol but are unable to take oral or rectal medication eg patients who are nil-by-mouth and have had surgery to the lower GI tract.**

Rituximab (MabThera®) –first-line treatment of stage III-IV follicular lymphoma

SMC recommendation

Advice: following a full submission

Rituximab is accepted for use within NHS Scotland for the treatment of previously untreated patients with stage III-IV follicular lymphoma in combination with cyclophosphamide, vincristine and prednisolone (CVP) chemotherapy.

Rituximab is for use only by oncologists or haematologists who have expertise in treating lymphoma. It should be administered in a hospital environment where full resuscitation facilities are available. Limited results show that rituximab plus CVP significantly increased the time to treatment failure compared with CVP alone.

Tayside recommendation

Not currently recommended – pending specialist treatment pathway

Points for consideration:

- Follicular lymphoma is the most common form of low-grade lymphoma. Lymphoma is staged (stages I to IV) by how widely dispersed affected lymph nodes and extra-lymphatic disease are around the body. Low-grade lymphomas are currently incurable at advanced stages with a median survival of eight to ten years.
- Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody. It is also licensed for third-line use in resistant or relapsed stage III-IV follicular lymphoma, and for CD20 positive diffuse large B-cell aggressive non-Hodgkin's lymphoma in combination with standard chemotherapy.
- In a single 18-month open-label study untreated patients with stage III or IV follicular lymphoma receiving rituximab plus CVP (R-CVP) had a significantly prolonged time to treatment failure, median 26 months versus seven months for CVP alone. Due to the relatively short follow-up, this study provided no evidence of survival benefit from the addition of rituximab. (However, this is not surprising since the median survival in these patients is nine years).
- In the above study, signs and symptoms of severe or life-threatening infusion-related reactions occurred in 9% of patients receiving R-CVP. Neutropenia was the only haematological event to differ between the two groups, with 24% in the R-CVP group experiencing grade 3 or 4 neutropenia versus 14% in the CVP group. The higher incidence of neutropenia in the R-CVP group was not associated with a higher infection rate.
- Eight cycles of rituximab (as used in clinical studies) cost approximately £9,800 per patient in addition to eight cycles of CVP at £260.
- A local protocol for the use of rituximab in the treatment of follicular lymphoma is currently under development by haematologists.

Rosiglitazone/metformin (Avandamet®) – type 2 diabetes mellitus

SMC recommendation

Advice: following an abbreviated submission

New formulation of existing combination

Rosiglitazone maleate/metformin hydrochloride (Avandamet®) in the undernoted formulations is accepted for use in NHS Scotland for the treatment of Type 2 diabetes mellitus in patients for whom a combination of rosiglitazone and metformin is appropriate. The new formulations facilitate dosage adjustment and, at a given dose combination, are not associated with increased cost compared with existing formulations. As previously stated by SMC (March 2004), Avandamet® may be used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone, and cannot be treated with a sulphonylurea in combination with metformin. *Continued over*

Rosiglitazone/metformin continued
Rosiglitazone maleate 2mg and metformin hydrochloride 1000mg
Rosiglitazone maleate 4mg and metformin hydrochloride 1000mg

Tayside recommendation

Not currently recommended – pending formulary decision

Points for consideration:

- Existing low dose Avandamet® preparations containing rosiglitazone 1mg/metformin 500mg and rosiglitazone 2mg/metformin 500mg are not currently included in the formulary.
- **The place of Avandamet® in relation to separate rosiglitazone and metformin preparations will be revisited by the Formulary Committee. Prescribers are advised to await the outcome of the formulary decision.**

Voriconazole (VFEND®) – serious fungal infections

SMC recommendation
Advice: following an abbreviated submission
Voriconazole (VFEND®) as a powder for oral suspension (40mg/ml) is accepted for restricted use in NHS Scotland. As previously stated by SMC (January 2003), voriconazole should be used only in suspected or confirmed cases of invasive aspergillosis; for infections caused by *Fusarium spp* and *Scedosporium spp*; or serious invasive candidiasis refractory to fluconazole. It should be administered primarily to immuno-compromised patients with progressive, possibly life-threatening infections.
The oral bio-availability of voriconazole is almost complete, allowing patients to be switched between intravenous and oral therapy, and the oral liquid formulation of voriconazole provides an alternative for patients who cannot take tablets. The cost per day is similar to that with tablets, and markedly less than with infusion.

Tayside recommendation

Recommended within specialist treatment pathway – HOSPITAL ONLY

Points for consideration:

- **Voriconazole is recommended locally, under the direction of an ID Specialist or Microbiologist, for the treatment of fluconazole resistant serious invasive candida infections, and as first-line treatment for haematology patients with confirmed or highly suspected invasive aspergillus infection.**
- A haematology/oncology antifungal policy is currently under development by the ASD Anti-infectives Sub-Committee in liaison with haematology/oncology specialists.

Formulary Decisions – December 2004

The following SMC recommendations were deferred to the Formulary Committee for consideration of local place in therapy. The Tayside Area Formulary includes first and second-line treatment options for the majority of conditions seen in both primary and secondary care. Decisions made at the December 2004 meeting of the Formulary Committee are summarised below:

Deferred Medicine	Indication	Decision
Losartan	Type 2 diabetic nephropathy	Non-formulary
Valsartan/hydrochlorothiazide (Co-Diovan®)	Hypertension not controlled by valsartan alone	Non-formulary
Rabeprazole	On demand therapy for GORD without oesophagitis	Non-formulary
Sumatriptan fast disintegrating tablets	Migraine treatment	Non-formulary

As part of a rolling program of review the Formulary Committee has updated sections 8, 9 & 10 (Malignant disease, Nutrition & Blood and Musculoskeletal) of the Tayside Area Prescribing Guide (TAPG). In section 8 there is an expanded note on breast cancer treatment with hormone antagonists with the inclusion of anastrozole. Section 9 has an expanded note on hydroxocobalamin. No drugs have been added or deleted

from this section. In section 10, the possible ibuprofen/aspirin interaction is noted and a statement about the ongoing review of the cardiovascular safety of the COX-2 inhibitors following the withdrawal of rofecoxib has been added. When the CSM/EMEA have concluded their reviews, this section will be revisited. Where possible and appropriate, first and second-line drug choices are now clearly indicated. The updated sections replace the old sections and will soon be posted on the TAPG pages of the DTC website. These can be printed off to replace the sections in your ring binder if you prefer to use hard copy.

Pimecrolimus update

Further to the development of a local protocol for the prescribing of topical pimecrolimus, the Tayside recommendation for the use of pimecrolimus cream has been updated as follows:

Tayside recommendation
Recommended within specialist treatment pathway

- **Pimecrolimus is recommended locally, under the direction of a dermatologist, as an alternative to systemic therapy in children above 2 years who have facial/neck moderate atopic eczema that has not been controlled by topical corticosteroids and where there is a serious risk of skin atrophy from further topical corticosteroid use.**

The local protocol is available from the 2004 NMIP Recommendations table on the DTC website.

Post Study Management of Patients in Drug Trials

Within NHS Tayside, decisions about continued treatment of patients following the completion of a clinical trial should take account of national and local advice on the use of new medicines. To assist this process, Tayside R&D now provides the following statement to researchers and research sponsors at the time drug trials are given approval to proceed.

The NHS Tayside Drug & Therapeutics Committee does not recommend the prescribing of new medicines until they have been evaluated and approved by the Scottish Medicines Consortium (SMC). Therefore, where patients are treated with new medicines in clinical trials, the following post-study options should apply.

Post-study management options

Treatment with an *unlicensed medicine* should only be continued for an individual patient where it is provided free of charge by the manufacturer/supplier.

- A licensed medicine that *has been approved* for use by the SMC can continue to be prescribed where indicated*.
- A licensed medicine *not yet submitted* for evaluation by the SMC should not be prescribed at the end of a study. See appeal mechanism below**.
- A licensed medicine that has been submitted but *not yet evaluated* by the SMC may continue to be prescribed subject to review once SMC advice is available*.
- A licensed medicine *not approved* for use by the SMC should not be prescribed at the end of a study. See appeal mechanism below**.
- *Cancer chemotherapy agents* may continue to be prescribed where supplied free of charge for use within a named-patient programme by arrangement with the manufacturer or supplier.

* The GP will make decisions about the continued use of a trial drug where it is to be prescribed in Primary Care. The researcher should provide sufficient information on the outcome of the study to inform such a decision. The GP should be advised of the continued use of specialist drugs prescribed in secondary care and be party to any decision to continue trial drugs as part of a shared care agreement.

** An appeal mechanism exists to allow the consideration of exceptional treatment of individual patients funded from existing budgets within Clinical Groups and with the knowledge and approval of the Clinical Group Director (further advice from DTC). There is also an appeal mechanism in the Mental Health Directorate and each of the LHCCs (Community Health Partnerships from April 2005).

Tayside Drug & Therapeutics Committee, November 2004

For further details see *"Post-Study Management of Patients in Drug Trials"*, available on request from the Medical Advisor, R&D/Ethics Office, Level 9, Ninewells Hospital & Medical School, Dundee, DD1 9SY (Telephone 01382 632589 or Ninewells extension 32589).

Forthcoming SMC Advice

Gastro-intestinal system
Beclometasone Dipropionate 5mg (clipper)
Esomeprazole (Nexium®)
Cardiovascular system
Candesartan (Amias®)
Nicotinic acid (Niaspan®) ***Resubmission***
Perindopril (Coversyl®)
Bivalirudin (Angiox®)
Valsartan (Diovan®)
Anagrelide hydrochloride (Xagrid®)
Eplerenone (Inspra®) ***Resubmission***
Respiratory
Ciclesonide (Alvesco®)
Central nervous system
Methylphenidate (Equasym XL®)
Atomoxetine (Strattera®)
Buprenorphine (Transtec®) patch
Tramadol (Tramacet®)
Pregabalin (Lyrica®): epilepsy
Pregabalin (Lyrica®): neuropathic pain
Reminyl XL®
Ropinirole (Adartrel®)
Levetiracetam (Keppra®) 750mg tabs
Levetiracetam (Keppra®) 100mg oral solution
Infections
Mycophenolate (Myfortic®)
Lamivudine OD (Epivir®) & Abacavir OD (Kivexa®)
Fosamprenavir (Telzir®)
Caspofungin acetate (Cancidas®)
Abacavir (Ziagen®)
Adefovir dipivoxil (Hepsera®) ***Resubmission***

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®)
Ibritumomab (Zevalin ®)
Imiquimod 5% Cream (Aldara®)
Nutrition & Blood
Lanthanum carbonate (Fosrenol®)
Musculoskeletal & joint diseases
Lumiracoxib (Prexige®)
Skin
Eflornithine 11.5% Cream (Vaniqa®)
Efalizumab (Raptiva®)

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