TAYSIDE PRESCRIBER

Tayside DTC Supplement No 56

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Produced by NHS Tayside Drug and Therapeutics Committee Medicines Advisory Group (MAG)

In this issue:

SMC Advice Issued March 2006

Aprepitant (Emend®) – prevention of CINV with moderately emetogenic cancer chemotherapy

SMC recommendation

Advice: following a full submission

Aprepitant (Emend®) as part of combination therapy is not recommended for use within NHS Scotland for the prevention of nausea and vomiting associated with moderately emetogenic cancer chemotherapy.

The aprepitant regimen showed a significant difference compared to the standard regimen in terms of the primary end-point of complete response for the acute phase only. No superiority for the aprepitant regimen could be demonstrated for the prevention of nausea.

The economic case for aprepitant in the prevention of nausea and vomiting associated with moderately emetogenic chemotherapy has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Aprepitant is also licensed for the prevention of chemotherapy induced nausea and vomiting (CINV) associated with highly emetogenic cisplatin chemotherapy. Refer to Tayside Prescriber; DTC Supplement No.46, November 2004 for SMC advice in this indication.
- Aprepitant is given together with dexamethasone and a $5HT_3$ antagonist as part of an antiemetic regimen. The comparator regimen used in the pivotal clinical study did not include corticosteroid after day 1. This difference from standard practice raises concerns over the relevance of the study results.
- The aprepitant antiemetic regimen used in the key study costs £62 per chemotherapy cycle, compared to £44 for a standard local antiemetic regimen (see below).
- **Locally, an antiemetic regimen of ondansetron 8mg twice daily plus dexamethasone 2mg three times daily on days 1 to 3 is used for the prevention of CINV associated with moderately emetogenic chemotherapy eg regimens containing cyclophosphamide.** Aprepitant is reserved for the

Continued over

Aprepitant continued

prevention of cisplatin-induced nausea in patients who have previously failed to respond to other available antiemetics, or are receiving particular highly emetogenic cisplatin regimens where standard antiemetic therapy is known to be ineffective (ref Tayside Prescriber; DTC Supplement No.46, November 2004).

Budesonide inhaler (Easyhaler® Budesonide) – asthma

SMC recommendation

Advice: following an abbreviated submission

Budesonide inhaler (Easyhaler® Budesonide) is accepted for use within NHS Scotland for the treatment of mild, moderate or severe persistent asthma in adults and children over 6 years of age.

Easyhaler® Budesonide offers an alternative to existing dry powder inhaled formulations of budesonide at a reduced cost.

Tayside recommendation

Recommended within formulary

Points for consideration:

- Easyhaler® is a dry powder inhaler device. In general, press-and-breath pressurised metered dose inhalers (pMDIs) are considered first-choice inhaler devices, provided that the correct inhaler technique can be taught. The Easyhaler® device requires a peak inspiratory flow rate of at least 30L/min.
- Easyhaler® Budesonide is available as 100mcg, 200mcg and 400mcg budesonide per metered dose. It is licensed for use in adults and children over 6 years as once daily dosing in mild to moderate asthma, and twice daily dosing in mild, moderate or severe asthma.
- Easyhaler® Budesonide is half the price of Pulmicort® Turbohaler® (28 days treatment with budesonide 200mcg twice daily costs £5 via the Easyhaler® versus £10 via Pulmicort® Turbohaler®).
- The Easyhaler® range also includes salbutamol and beclometasone. Easyhaler® Salbutamol is priced below that of terbutaline (Bricanyl®) Turbohaler®.
- Further advice on the management of patients with asthma is available within the Respiratory Guidance Notes in the Tayside Area Prescribing Guide (TAPG).

Lumiracoxib (Prexige®) – osteoarthritis (OA)

SMC recommendation

Advice: following a full submission

Lumiracoxib (Prexige®) is accepted for use within NHS Scotland for symptomatic relief in the treatment of osteoarthritis only for patients in whom a COX-2 inhibitor is deemed appropriate.

It appears similar in efficacy to other COX-2 inhibitors and costs slightly less. As with other COX-2 inhibitors, lumiracoxib is contra-indicated in patients with established ischaemic heart disease, cerebrovascular disease, peripheral arterial disease and moderate or severe congestive heart failure. It should be used with caution in patients who have significant risk factors for cardiovascular events.

Click here for SMC link

Tayside recommendation

Non-formulary

Points for consideration:

- Lumiracoxib is a further COX-2 inhibitor. It is licensed for symptomatic relief in the treatment of osteoarthritis (OA) and for short-term relief of moderate to severe acute pain associated with primary dysmenorrhoea, dental surgery and orthopaedic surgery. The above SMC advice applies only to the OA indication.
- Lumiracoxib is the most selective COX-2 inhibitor currently available *in vitro* (note this may not necessarily translate to *in vivo* activity).
- A recent EMEA review (Jun 2005) found an increased risk of thrombotic adverse cardiovascular reactions (heart attacks and strokes) for COX-2 inhibitors – hence the contra-indication and cautions listed above. This risk increases further with high doses and prolonged treatment. Evidence suggests

Continued over

Lumiracoxib continued

that any gastrointestinal safety advantage for COX-2 inhibitors is substantially reduced when given with aspirin.

- COX-2 inhibitors have a similar rate of renal adverse events to standard NSAIDs.
- There is no evidence that lumiracoxib has advantages or disadvantages compared with other COX-2 inhibitors. There are no comparative safety data for lumiracoxib versus a standard NSAID plus gastroprotectant.
- Lumiracoxib is slightly less expensive than other COX-2 inhibitors (28 days of treatment with lumiracoxib 100mg daily costs £16 versus £20 for celecoxib 200mg daily and £23 for etoricoxib 60mg daily).
- **Locally, lumiracoxib may be considered as an alternative to celecoxib or etoricoxib for the treatment of osteoarthritis in patients who require a non-steroidal anti-inflammatory drug (NSAID) and are at high risk of GI complications and unable to tolerate co-prescription of acid suppression therapy.**
- Further advice on the management of patients with OA, including the place of COX-2 inhibitors, is available within the TAPG.

Modafinil (Provigil®) – obstructive sleep apnoea/hypopnoea syndrome

SMC recommendation

Advice: following a re-submission

Modafinil (Provigil®) is not recommended for use within NHS Scotland for the treatment of excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome.

Modafinil demonstrated modest improvement in sleepiness and quality of life, the clinical significance of which is difficult to estimate. The economic case has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Refer to Tayside Prescriber; DTC Supplement No.32, October 2003 and No.52, July 2005 for previous SMC advice.

Rasagiline (Azilect®) – Parkinson's Disease (PD) - monotherapy

SMC recommendation

Advice: following a full submission

Rasagiline (Azilect®) is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson's disease as monotherapy (without levodopa).

Rasagiline provides symptomatic improvement for patients with early Parkinson's disease. However, there are no comparative data with the other monoamine-oxidase-B inhibitor, which is less expensive. The economic case has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Rasagiline is a monoamine-oxidase-B (MAO-B) inhibitor believed to increase dopamine levels in the brain by inhibition of dopamine metabolism. It is licensed for use both as monotherapy in early Parkinson's Disease (PD) and as an adjunct to levodopa in advanced disease (see below).
- The key study to support the use of rasagiline in early PD involved a 6-month comparison with placebo, after which the rasagiline group continued on treatment for a further 6 months and patients in the placebo group were switched to rasagiline (delayed-treatment group). Whilst a significant improvement in the unified PD rating scale was shown in the early treatment group compared to delayed group after the second 6-month phase, follow up data shows that this did not translate into longer time to initiation of levodopa or dopamine agonist therapy. Hence there is no convincing evidence that rasagiline shows disease-modifying or neuroprotective effects.

Continued over

Rasagiline – monotherapy - continued

- Adverse events seen with rasagiline did not differ greatly from those seen with placebo during trials.
- There are no comparative data versus the other available MAO-B inhibitor, selegiline, or with dopamine agonists. Therefore relative efficacy and safety is uncertain.
- Whilst rasagiline is not as expensive as higher doses of some dopamine agonists, it is considerably more expensive than selegiline (28 days treatment with rasagiline costs £71 versus £8 for selegiline).
- Further advice on drug therapy in the management of Parkinson's Disease is available within Tayside Prescriber No.73, 74 and 75. A national patient pathway to assist Primary Care professionals in the wider management of Parkinson's disease is also available. NICE is currently developing a PD clinical guideline for issue in July 2006.
- Rasagiline is not stocked by the hospital pharmacy.

Rasagiline (Azilect®) – Parkinson's Disease - adjunct therapy

SMC recommendation

Advice: following a resubmission

Rasagiline (Azilect®) is not recommended for use within NHS Scotland for the treatment of idiopathic Parkinson's disease as adjunct therapy (with levodopa) in patients with end of dose fluctuations.

Rasagiline reduces off-time in patients with Parkinson's disease and end of dose fluctuations on levodopa, similar to reductions shown with the less effective of two currently marketed catechol-O-methyl transferase inhibitors. However, there are no comparative data with the other monoamine-oxidase-B inhibitor, which is less expensive. The economic case has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Rasagiline appears to have similar efficacy to entacapone when given as an adjunct to levodopa in late PD. However, indirect comparisons indicate that entacapone produces smaller improvements in on-time than the other COMT-inhibitor, tolcapone, and the dopamine agonist, pramipexole. There are no direct comparative data versus these agents or versus selegiline. Therefore, relative efficacy and safety is uncertain.
- Whilst rasagiline is not as expensive as higher doses of some dopamine agonists, it is considerably more expensive than selegiline (28 days treatment with rasagiline costs £71 versus £8 for selegiline).
- Rasagiline is not stocked by the hospital pharmacy.

Sildenafil (Revatio®) – pulmonary arterial hypertension (PAH)

SMC recommendation

Advice: following an abbreviated submission

Sildenafil citrate (Revatio®) is accepted for restricted use within NHS Scotland for the treatment of patients with pulmonary arterial hypertension classified as WHO functional class III, to improve exercise capacity. This is an orphan indication for sildenafil with limited clinical evidence from short-term clinical trials. It is restricted to initiation by specialists working in the Scottish Pulmonary Vascular Unit and by physicians experienced in the management of pulmonary vascular disease.

Click here for SMC link

Tayside recommendation

Restricted to the Scottish Pulmonary Vascular Unit

Points for consideration:

- Clinical trial data for sildenafil in this orphan indication are limited. Epoprostenol infusion is the only treatment for pulmonary arterial hypertension (PAH) to show survival benefit in clinical studies.
- The oral formulation of sildenafil offers an advantage in administration over IV epoprostenol and nebulised iloprost. Unlike oral bosentan, sildenafil has not been associated with hepatotoxicity or potential teratogenicity.
- The dose of sildenafil for the treatment of PAH is 20mg three times daily.
- Revatio® is not stocked by the hospital pharmacy.

Somatropin (Genotropin®) – short children born small for gestational age (SGA)

SMC recommendation
Advice: following an abbreviated submission
Somatropin (Genotropin®) injection is accepted for restricted use within NHS Scotland for the treatment of growth disturbance (current height Standard Deviation Score (SDS) <-2.5 and parental adjusted height SDS <-1) in short children born small for gestational age (SGA), with a birth weight and/or length below –2 Standard Deviations, who failed to show catch-up growth (height velocity SDS <0 during the last year) by 4 years of age or later.
Treatment should be initiated and monitored by a paediatrician with expertise in managing childhood growth disorders and growth hormone therapy.

Tayside recommendation

Recommended within specialist treatment pathway – **HOSPITAL ONLY**

Points for consideration:

- Treatment of SGA is a recent licence extension for somatropin.
- Guidance on initiation and monitoring of somatropin in children with growth failure are available in NICE Health Technology Appraisal No.42. The SPC provides further advice on discontinuation.

Temozolomide (Temodal®) – high grade glioblastoma multiforme (GBM)

SMC recommendation
Advice: following a full submission
Temozolomide (Temodal®) is not recommended for use within NHS Scotland for the treatment of newly diagnosed glioblastoma multiforme (GBM) concomitantly with radiotherapy and subsequently as monotherapy.
In the pivotal phase III study, an increase in median survival was seen in patients with good performance status and favourable prognostic markers. The benefit seems to increase over time with 16% more patients surviving at 24 months in the temozolomide plus radiotherapy group rather than the radiotherapy alone. However, the economic case has not been demonstrated.
Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Temozolomide is an oral alkylating agent derived from dacarbazine. It is also licensed, and recommended by NICE, for the treatment of malignant glioma showing recurrence or progression after standard therapy. The above SMC advice applies only to the newly diagnosed GBM indication.
- The median overall survival benefit in the pivotal study was 2.5 months; 14.6 months in patients receiving temozolomide plus radiotherapy versus 12.1 months in those receiving radiotherapy alone. Recruited patients were relatively healthy, most were under 70 years of age with good performance status and were eligible for de-bulking surgery and therefore may not reflect the presenting Scottish patient population. Also, study therapy began within six weeks of diagnosis, which may not be feasible in practice, depending on radiotherapy waiting lists.
- The most frequently occurring treatment-related undesirable effects seen in clinical trials were grade 1 or 2 gastrointestinal disturbances, specifically nausea (43%) and vomiting (36%) which were either self-limiting or readily controlled with standard anti-emetic therapy.
- Data comparing temozolomide with alternative treatments eg carmustine implants are unavailable.
- NICE guidance on "Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma" is due for issue in August 2006.

Summary of "GP not recommended" new medicines

A summary of new medicines not recommended for use in NHS Tayside general practices will shortly be available on the New Medicines pages of the DTC website. This summary will be regularly updated, and is designed to be printed and used as a handy quick reference guide.

MAG Frequently Asked Questions (FAQs)

A list of MAG FAQs is now available on the MAG pages of the DTC intranet site.

TAPG Update

Below are the main changes to the TAPG agreed by the Medicines Advisory Group in February 2006. Updated sections in A5 format are available on the TAPG pages of the DTC intranet site. Where possible and appropriate, first-line drug choices are clearly indicated in reviewed sections. An updated GPASS-TADF fly file for use in general practice will also be available shortly.

	TAPG section	Drug(s) / topic	Changes
1.1	Antacids	Gaviscon® Advance	Added as a further alginate-containing antacid.
3.1	Bronchodilators	Terbutaline Long-acting beta-2 agonists	Terbutaline MDI discontinued, dry powder formulation (Turbohaler®) added. Statement to reinforce advice that LABAs should not be used without inhaled steroids in asthma. Other minor revisions
3.7	Mucolytics	Carbocisteine	Promoted to full entry in formulary
3	Respiratory Guidance Notes	Volumatic® Tiotropium and LABAs	Re-insertion of Volumatic® spacer device due to it becoming available once again. Revised statement on use of combined tiotropium and LABAs in patients with severe COPD. Other minor revisions

Forthcoming SMC Advice

Gastro-intestinal system
Esomeprazole (Nexium®)
Beclometasone Dipropionate 5mg (Clipper®)
Mesalazine (Asacol®) - ***Abbreviated***
Glyceryl trinitrate (Rectogesic®) – ***Resubmission***
Cardiovascular system
Perindopril (Coversyl®)
Nebivolol (Nebilet®)
Olmesartan (Olmetec Plus®) - ***Abbreviated***
Losartan/hydrochlorothiazide (Cozaar®–Comp)
Respiratory
Omalizumab (Xolair®)
Beclometasone inhaler (Clenil® Modulite®)
Ciclesonide (Alvesco®) paed
Central nervous system
Escitalopram (Cipralex®)
Ropinirole (Adartrel®)
Rivastigmine (Exelon®)
Pregabalin (Lyrica®) – ***IRP***
Sodium oxybate (Xyrem®)
Pramipexole (Mirexapin®)
Zonisamide (Zonegran®)
Fentanyl patch (Durogesic® D Trans)

Infections
Daptomycin (Cubicin®)
Tigecyclin (Tygacyl®)
Posaconazole (Noxafil®)
Interferon-alpha-2b/ribavirin (Viraferon/Rebetol®)
Endocrine system
Somatropin (Norditropin SimpleXx®)
Pioglitazone/metformin - ***Abbreviated***
Inhaled insulin (Exubera®)
Pegvisomant (Somavert®) - ***Resubmission***
Malignant disease & immunosuppression
Lanreotide (Somatuline® LA)
Mitotane (Lysodren®)
Letrozole (Femara®)
Fludarabine (Fludara® Oral)
Sunitinib (Sutent®)
Bevacuzimab (Avastin®) - ***Resubmission***
Erlotinib (Tarceva®) - ***Resubmission***
Nutrition & Blood
Darbepoetin alfa (Aranesp®)
Lanthanum carbonate (Fosrenol®)
Cinacalcet (Mimpara®) – ***Resubmission***
Eye
Dorzolamide (Trusopt®)

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