TAYSIDE PRESCRIBER

Tayside DTC Supplement No 61

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

In this issue:

SMC Advice Issued in September 2006

Bortezomib (Velcade®) - multiple myeloma

SMC recommendation

Advice: following a full submission

Bortezomib (Velcade®) is not recommended for use within NHS Scotland as mono-therapy for the treatment of progressive multiple myeloma in patients who have received at least one prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

Bortezomib, compared to high dose dexamethasone, prolonged time to disease progression by 2.7 months and improved survival in patients who had progressive multiple myeloma despite previous treatment with one to three lines of therapy. However, the economic case has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Bortezomib is also licensed for third-line use in multiple myeloma. Refer to Tayside Prescriber; DTC Supplement No.45, October 2004 for SMC and local advice in this indication.

Budesonide inhaler (Novolizer® Budesonide) – asthma

SMC recommendation

Advice: following an abbreviated submission

Budesonide (Novolizer®) inhaler is accepted for use within NHS Scotland for the treatment of persistent asthma in adults and children over 6 years of age.

Budesonide (Novolizer®) inhaler offers an alternative to existing dry powder inhaled formulations of budesonide at a similar cost.

Tayside recommendation

Non-formulary

Points for consideration:

- Novolizer® is a dry powder inhaler device requiring a peak inspiratory flow rate of at least 35-50L/min. It is licensed for use in adults and children over 6 years as either once or twice daily dosing.
- Whilst Novolizer® Budesonide costs less than Pulmicort® Turbohaler®, it is more expensive than Easyhaler® Budesonide. (£15 for 100 doses of budesonide 200mcg via Novolizer® versus £18 for Pulmicort® Turbohaler® and £9 for the Easyhaler®). A 100 dose Novolizer® refill is also available at £10.
- Within the UK, the Novolizer® range is limited to the budesonide inhaler, which is only available in a single strength of 200mcg per metered dose.

Duloxetine (Cymbalta®) – diabetic peripheral neuropathic pain (DPNP)

SMC recommendation

Advice: following a full submission

Duloxetine (Cymbalta®) is accepted for restricted use for the treatment of diabetic peripheral neuropathic pain in adults.

Duloxetine relieved peripheral neuropathic pain compared with placebo in patients with diabetes. It is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as 2nd or 3rd line therapy.

Click here for SMC link

Tayside recommendation

Non-formulary

Points for consideration:

- Efficacy data from placebo-controlled studies of duloxetine in diabetic peripheral neuropathic pain (DPNP) are limited to 12 weeks duration. These studies did not exclude patients refractory to other DPNP treatments. (48-66% of recruited patients had previously taken at least one medication for DPNP).
- The starting and recommended maintenance dose of duloxetine is 60mg daily. Whilst a maximum of 120mg daily may be given, controlled studies failed to demonstrate any benefit in using the higher dose.
- There are no direct comparative data versus other agents used in the treatment of DPNP eg off-label tricyclic antidepressants or gabapentin. Indirect comparison indicates that treatment with gabapentin may be associated with greater improvement in pain scores.
- Due to risk of serotonin syndrome, caution should be exercised when using duloxetine in combination with antidepressants. In particular, the combination with MAOIs is not recommended. Note that when discontinuing duloxetine, the dose should be tapered for two weeks before discontinuation to decrease the risk of possible discontinuation reactions.
- Duloxetine, at a dose of 60mg daily, is less expensive than generic gabapentin 1800mg daily (£28 versus £83 for 28 days treatment).
- SIGN guidance "Management of diabetes" and local guidance on the treatment of neuropathic pain within the Tayside Area Prescribing Guide (TAPG) recommend an adequate trial of tricyclic antidepressants as first-line therapy in the treatment of DPNP followed by gabapentin. Treatment should be titrated against response and side-effects to maximum recommended doses eg 50-75mg amitriptyline daily, 1800mg gabapentin daily.
- Duloxetine is also marketed under a different brand name (Yentreve®) for the treatment of stress urinary incontinence. Care should be taken to ensure that the appropriate product is prescribed and supplied.

Continued over

Duloxetine continued

- **Locally, duloxetine may be considered as an alternative to gabapentin in patients with diabetic peripheral neuropathic pain (DPNP). Treatment should be used second or third-line following tricyclic antidepressants and should be initiated by the diabetes or pain clinic or by GPs experienced in the management of DPNP.**

Etanercept 50mg injection (Enbrel®) – rheumatoid arthritis

SMC recommendation

Advice: following an abbreviated submission

Etanercept 50mg subcutaneous injection (Enbrel®) is accepted for use within NHS Scotland for the treatment of patients with rheumatoid arthritis for whom treatment with etanercept is considered appropriate.

Etanercept is indicated for the treatment of moderate to severe active rheumatoid arthritis in adults, either alone or in combination with methotrexate when the response to disease-modifying antirheumatic drugs, including methotrexate (unless contraindicated), has been inadequate or for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate.

The 50mg formulation facilitates once weekly administration of etanercept at no additional cost over the existing 25mg formulation that is administered twice weekly.

Tayside recommendation

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

Ibandronic acid injection (Bonviva®) – postmenopausal osteoporosis

SMC recommendation

Advice: following a full submission

Intravenous ibandronic acid (Bonviva®) is accepted for restricted use within NHS Scotland for the treatment of osteoporosis in postmenopausal women in order to reduce the risk of vertebral fractures. Efficacy on femoral neck fractures has not been established.

Intravenous ibandronic acid is restricted to use in patients who are unsuitable for or unable to tolerate oral treatment options for osteoporosis. Treatment initiation should be under specialist supervision.

Click here for SMC link

Tayside recommendation

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

Points for consideration:

- Ibandronate is the only IV bisphosphonate licensed for the treatment of osteoporosis.
- A two-year comparator study in postmenopausal women with osteoporosis show that 3-monthly IV ibandronate 3mg provides greater increase in lumbar spine bone mineral density than daily oral ibandronate 2.5mg.
- No data on reduction in fracture rate are available for IV ibandronate. Daily and intermittent oral formulations of ibandronate have previously shown to reduce the risk of vertebral fractures. However, unlike some other bisphosphonates, efficacy in reducing femoral neck (and other non-vertebral fractures) has not been established.
- IV ibandronate is more expensive than oral ibandronate and a similar cost to off-label IV pamidronate.
- Whilst IV pamidronate is administered by infusion over a period of around 90 minutes, IV ibandronate can be given as a 15-30 second bolus injection.
- **Locally, IV ibandronate is recommended as an alternative to off-label IV pamidronate in women with postmenopausal osteoporosis who are at high fracture risk and unable to tolerate oral treatment options (eg bisphosphonates and strontium ranelate) or in whom oral administration is unsuitable (eg due to malabsorption syndromes). Treatment is restricted to the osteoporosis clinic.**

Inhaled insulin (Exubera®) – diabetes mellitus

SMC recommendation
Advice: following a full submission
Inhaled insulin (Exubera®) is not recommended for use within NHS Scotland for the treatment of adult patients with type 2 diabetes mellitus not adequately controlled with oral antidiabetic agents and requiring insulin therapy or for the treatment of adult patients with type 1 diabetes mellitus, in addition to long or intermediate acting subcutaneous insulin, for whom the potential benefits of adding inhaled insulin outweigh the potential safety concerns. The economic case has not been demonstrated.
Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Inhaled insulin is a rapid-acting, pre-prandial insulin, formulated as a dry powder and administered via a hand-held inhaler device. Inhaled insulin has a bioavailability of 8-13% of subcutaneous (sc) insulin.
- Open-label short-term studies show that inhaled insulin provides similar glycaemic control as sc soluble insulins in type 1 and type 2 diabetic patients.
- Whilst the adverse event profile of inhaled insulin is similar to sc soluble insulin, there is some concern over the long-term effect of pulmonary delivery of insulin to the lungs. Contraindications to treatment include smoking, or smoking within six months of treatment and lung disease eg asthma and chronic obstructive pulmonary disease.
- There are no comparative data versus newer short-acting sc insulin analogues.
- At an average cost of £1,250 per patient per year, inhaled insulin is considerably more expensive than short-acting sc insulins.
- NICE guidance on inhaled insulin is expected in November 2006.
- Inhaled insulin is not stocked by the hospital pharmacy.

Insulin glulisine (Apidra®) – diabetes mellitus

SMC recommendation
Advice: following a full submission
Insulin glulisine (Apidra®) is accepted for restricted use within NHS Scotland for the treatment of adult patients with diabetes mellitus in whom treatment with a short-acting insulin analogue is appropriate. Insulin glulisine has similar efficacy to other short-acting insulins in reducing glycated haemoglobin and a similar pharmacokinetic profile to at least one other insulin analogue. It is restricted to use in patients where regular human insulin in inappropriate.
Click here for SMC link

Tayside recommendation

Recommended within specialist treatment pathway (GPs may prescribe under the direction of the diabetes clinic)

Points for consideration:

- Insulin glulisine is an alternative to insulin lispro (Humalog®) or insulin aspart (NovoRapid®).
- Insulin glulisine cartridges are compatible with OptiPen® Pro and Autopen® 24 pen devices.
- Unlike lispro and aspart, insulin glulisine is not licensed for use in children.
- Local guidance on diabetes care is available in the Tayside Diabetes Handbook.

Nebivolol (Nebilet®) – chronic heart failure

SMC recommendation

Advice: following a full submission

Nebivolol (Nebilet®) is not recommended for use within NHS Scotland for the treatment of stable mild and moderate chronic heart failure (CHF) in addition to standard therapies in elderly patients ≥70 years.

Nebivolol, added to standard therapy, was associated with improved left ventricular function and a reduction in a composite endpoint combining all cause mortality and cardiovascular hospitalisation rates in elderly patients with chronic heart failure. There is no comparison with other beta-adrenoceptor blockers.

Cost effectiveness relative to other beta-adrenoceptor blockers in common use in chronic heart failure has not been demonstrated.

Click here for SMC link

Tayside recommendation

Not recommended

Points for consideration:

- Nebivolol is the third β-blocker licensed for the treatment of heart failure in the UK. It is indicated for use in stable mild and moderate CHF. Alternative β-blockers include bisoprolol (licensed for moderate to severe CHF) and carvedilol (licensed for mild, moderate and severe CHF).
- There are no direct comparative data for nebivolol versus bisoprolol or carvedilol.
- Post-hoc subgroup analysis of one of the key studies (SENIORS) indicates that the benefit of nebivolol is similar to other β-blockers in patients less than 75 years with impaired left ventricular (LV) function. However, the magnitude of benefit in older patients and those with normal LV function are uncertain.
- Nebivolol is considerably more expensive than generic bisoprolol. (28 days treatment with nebivolol 10mg daily costs £18 versus £3 for bisoprolol 10mg daily).
- Local guidance on the treatment of confirmed heart failure is available within the TAPG.
- Nebivolol is not stocked by the hospital pharmacy.

Pioglitazone/metformin (Competact®) – type 2 diabetes mellitus

SMC recommendation

Advice: following an abbreviated submission

Pioglitazone 15mg/metformin 850mg hydrochloride (Competact®) is accepted for restricted use in NHS Scotland for the treatment of type 2 diabetes mellitus. It should be used for overweight patients who are unable to achieve sufficient glycaemic control at their maximally tolerated doses of oral metformin alone. It is restricted to patients who cannot be treated with a sulphonylurea in combination with metformin. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient, though less flexible, dosing regimen.

Tayside recommendation

Non-formulary

Points for consideration:

- Unlike the rosiglitazone/metformin combination, Avandamet®, Competact® is currently only available in a single dose combination.

Tipranavir (Aptivus®) – HIV-1 infection

SMC recommendation
Advice: following a re-submission
Tipranavir (Aptivus®) in combination with low dose ritonavir is accepted for restricted use within NHS Scotland for the treatment of HIV-1 infection in highly pre-treated adult patients with virus resistant to multiple protease inhibitors.
At 48 weeks, tipranavir, in combination with low dose ritonavir, showed a significant improvement in the reduction of viral load compared with other protease inhibitor plus ritonavir regimens. Although the overall rate and type of adverse events were similar, tipranavir had a higher incidence of hepatotoxicity, hyperlipidaemia, bleeding events and rash.
Tipranavir is more expensive than other protease inhibitors and it is restricted to patients with a tipranavir mutation score of less than 4.
Click here for SMC link

Tayside recommendation

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

Points for consideration:

- Refer to Tayside Prescriber; DTC Supplement No.55, February 2006 for original SMC advice.
- A flow diagram to assist the local use of tipranavir is under development by the HIV Team.
- **Locally, tipranavir is reserved for use as part of a salvage regimen in patients with multi-resistant HIV infection. Use is restricted to the HIV Clinic.**

Topiramate (Topamax®) – migraine prophylaxis

SMC recommendation
Advice: following a full submission
Topiramate (Topamax®) is accepted for restricted use within NHS Scotland for the prophylaxis of migraine headache in adults. It should be restricted to initiation by specialists and treatment should be managed under specialist supervision or shared care arrangements in patients who have not responded to prophylactic treatment with at least one other agent.
Click here for SMC link

Tayside recommendation

Recommended within specialist treatment pathway (GPs may prescribe under the direction of the neurology clinic)

Points for consideration:

- Topiramate is an antiepileptic drug with multiple modes of action that may contribute to migraine prevention. It is unclear which mechanism is most important in the prevention of migraine.
- 26-week studies show that topiramate is associated with reduced migraine frequency and use of migraine rescue medication versus placebo. Comparative data show similar efficacy to propranolol. Sub-group analysis indicates that efficacy is unaffected when patients have previously taken a prophylactic treatment.
- Topiramate has a high frequency of unwanted effects, and patients need to be monitored regularly for signs of depression and weight loss. Rarely, topiramate has been associated with acute myopia with secondary angle-closure glaucoma. Symptoms typically occur within one month of starting treatment and include decreased visual acuity and/or ocular pain.
- Abrupt withdrawal of topiramate should be avoided to minimise the possibility of rebound migraine headaches.
- Topiramate is considerably more expensive than other migraine prophylactic treatments. (28 days treatment with topiramate 100mg daily costs £30 versus £5-7 for propranolol LA and £4-£13 for pizotifen).
- Local headache guidance within the TAPG recommends the use of β-blockers eg propranolol as first-line prophylactic migraine treatment followed by tricyclic antidepressants (off-label), pizotifen and sodium valproate (off-label). Use of topiramate should be considered as a further option after these agents. Both topiramate and sodium valproate should be avoided during pregnancy. A local protocol to

Continued over

Topiramate continued

support the prescribing of topiramate for migraine prophylaxis has been developed by the Neurology Team.

- **Locally, use of topiramate is reserved for patients who have not responded to, cannot tolerate, or have contraindications to established prophylactic treatments (ie beta-blockers, tricyclic antidepressants, pizotifen and sodium valproate). Treatment should be initiated by the neurology clinic and patients should be monitored according to the local protocol.**

TAPG Update

Below are the main changes to the TAPG agreed by the Medicines Advisory Group in August 2006.

	TAPG section	Drug(s)/topic	Changes
4	**Neuropathic Pain Guidelines**	Duloxetine*	Duloxetine added as an alternative option to gabapentin in the treatment of diabetic peripheral neuropathic pain.
	Headache Guidelines	Topiramate*	Topiramate added as a final option in migraine prophylaxis.
6.1	**Diabetes**	Rosiglitazone/metformin (Avandamet)*	Minor entry for Avandamet* replaced with a generic statement on use of combination glitazone/metformin products.

* SMC accepted medicine

HTML version of the TAPG

A new browsable html version of the TAPG is now available and can be accessed directly from the Prescribing Guide link located on the NHS Tayside intranet top menu bar. The new electronic version has replaced previous pdf files and is extensively hyperlinked both internally within the TAPG and externally to the BNF and national guidance.

Paracetamol IV infusion Update

Further to feed back from local clinicians, December 2004 local advice for the use of paracetamol infusion 1g/100mls has been revised as follows:

Tayside recommendation

Recommended within specialist protocol – **HOSPITAL ONLY**

- Paracetamol IV infusion is recommended locally for the relief of short-term post-operative pain or fever in patients who are nil-by-mouth and are unable or unwilling to tolerate suppositories (eg diarrhoea, agitated).

Forthcoming SMC Advice

Gastro-intestinal system
Beclometasone dipropionate 5mg (Clipper®)
Mesalazine (Asacol®)
Cardiovascular system
Ivabradine (Procoralan®)
Lercanidipine (Zanidip®)
Perindopril (Coversyl®)
Central nervous system
Lidocaine (Versatis®)
Rasagline (Asilect®)
Co-careldopa (Duodopa®)
Donepezil orodispersible tablets (Aricept Evess®)
Levetiracetam IV formulation (Keppra®)
Infections
Lopinavir (Kaletra®)
Entecavir (Baraclude®)
Tobramycin (Bramitob®)
Endocrine system
Choriogonadotropin alfa (Ovitrelle®)
Triptorelin (Decapeptyl®)
Zoledronic acid (Aclasta®)
Malignant disease & immunosuppression
Anastrozole (Armidex®)
Gemcitabine (Gemzar®)
Natalizumab (Tysabri®)

Malignant disease & immunosuppression cont.
Vinorelbine (Navelbine® Oral)
Clofarabine (Evoltra®)
Fludarabine (Fludara® Oral)
Lanreotide (Somatuline® LA)
Mitotane (Lysodren®)
Rituximab (Mabthera®)
Sorafenib (Nexavar®)
Sunitinib (Sutent®)
Temozolomide (Temodal®)
Nutrition & Blood
Pegfilgrastim (Neulasta®)
Carglumic acid (Carbaglu®)
Lanthanum carbonate (Fosrenol®)
Musculoskeletal and joint diseases
Methotrexate (Metoject®)
Adalimumab (Humira®)
Etoricoxib (Arcoxia®) - ***Abbreviated***
Eye
Bimatoprost 0.03%/timolol (Ganfort®)
Skin
Etanercept (Enbrel®) - ***Abbreviated***
Infliximab (Remicade®)

Contact details: Local implementation of SMC recommendations is being taken forward by the Tayside Medicines Unit - contact Jan Jones, Principal Pharmacist - Pharmacoeconomics (janjones@nhs.net) if you have any queries in relation to the introduction of new drugs within NHS Tayside.