

Tayside D&TC Supplement No. 45

Oct 2004

Produced by Tayside New Medicines Implementation Panel (NMIP)

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SMC Advice Issued in October 2004

Bortezomib (Velcade®) – multiple myeloma

SMC recommendation

Advice: following a full submission.

Bortezomib (Velcade®) is accepted for use within NHS Scotland for the treatment of patients with multiple myeloma who have received at least two prior therapies, have demonstrated disease progression on the last therapy and who are refractory to alternative licensed treatments for this stage of the disease.

Bortezomib produced a disease response in approximately one third of these patients in an open-label uncontrolled study. Any other use of bortezomib should only take place within the context of a controlled study.

The manufacturers are encouraged to mount an observational study in collaboration with haemato-oncologists to gain more information on the benefits and risks of this therapy.

Tayside recommendation

Not currently recommended – pending specialist treatment pathway

Points for consideration:

- Bortezomib is the first of a new class of anti-neoplastic agents called proteasome inhibitors. It induces myeloma-cell apoptosis by inhibiting the 26S proteasome enzyme, which catalyses degradation of ubiquitinated proteins (eg tumour suppressors).
- It is administered by bolus intravenous injection twice weekly in the first two weeks of a three-week treatment cycle.
- To date, no controlled trials have assessed survival as a primary outcome. The median survival of all patients in the key open-label uncontrolled study was 17.5 months versus seven months for non-responders.
- Fatigue and gastrointestinal effects are the most common undesirable events. The most troublesome adverse event for patients is a cumulative dose related peripheral neuropathy.
- There are no efficacy or safety data for bortezomib compared with possible alternative third-line treatment options (eg thalidomide, high dose dexamethasone etc), all of which are unlicensed for this indication.
- Bortezomib costs £762 per injection and £3,050 per 21-day treatment cycle. Duration of treatment is variable.

Continued over

Bortezomib continued

- A local protocol for the use of bortezomib in the treatment of multiple myeloma is currently under development by haematologists.
- Further information on the [diagnosis and management of multiple myeloma](#) is available in guidelines produced by the British Committee for Standards in Haematology (BCSH) in 2001.

Duloxetine (Yentreve®) – moderate to severe stress urinary incontinence (SUI) in women

SMC recommendation

Advice: following a full submission.

Duloxetine is accepted for restricted use within NHS Scotland for the treatment of moderate to severe stress urinary incontinence (SUI). It should be used only as part of an overall management strategy for SUI in addition to pelvic floor muscle training. Patients should be reviewed after 12 weeks of therapy to assess progress and determine whether it is appropriate to continue treatment.

Because of the short duration of treatment in the studies supplied, it is recommended that the manufacturers collect further data on the long-term effects of this pharmacological approach to the management of SUI.

Tayside recommendation

Recommended within specialist treatment pathway.

Points for consideration:

- Duloxetine is a dual serotonin and noradrenaline re-uptake inhibitor (SNRI) thought to act by increasing urethral tone only during the storage phase of the micturition cycle.
- It is the first pharmacological therapy for SUI and is only licensed for use in women. Non-pharmacological strategies for SUI include pelvic floor muscle training (PFMT), lifestyle interventions and surgery (eg tension-free vaginal tape). Surgery is usually considered only when conservative management has failed or is unsuitable.
- A meta-analysis of 12-week duloxetine studies in women with moderate to severe SUI shows a significantly decreased frequency of incontinence episodes versus placebo (52% reduction with duloxetine versus 33% reduction with placebo). This represents a modest clinical benefit to patients, with duloxetine preventing about one incontinent episode every other day more than placebo in patients with around 18-19 episodes per week at baseline.
- Around 20% of women who received duloxetine in clinical studies discontinued treatment due to adverse effects eg nausea, dry mouth, fatigue, insomnia and constipation.
- When discontinuing duloxetine, the dose should be tapered for two weeks before discontinuation to decrease the risk of possible discontinuation symptoms.
- Data on the long-term efficacy and safety of duloxetine are unavailable and duloxetine has not been studied in combination with other medicines in the treatment of mixed incontinence.
- Duloxetine costs £31 for 28 days treatment at a dose of 20mg or 40mg twice daily.
- [National guidance](#) recommends that the initial treatment of UI should be carried out in the most appropriate setting, which is usually primary care. Within Tayside, Community Continence Services are available in each LHCC and should be the first point of general practice referral (contact details below).
- **Locally, women presenting with SUI symptoms in general practice should be referred¹ to a Continence Adviser for assessment. A three month trial of duloxetine, given in combination with PFMT, is recommended only if moderate to severe symptoms fail to improve following a three to six month period of PMFT² and lifestyle changes.**

¹ includes referrals from health visitors, district nurses, general practitioners and self-referrals.

² under the direction of the continence service

- The above duloxetine guidance will form part of a wider incontinence guideline currently under development by the Tayside Continence Group.
- A SIGN guideline “Urinary Continence Within Primary Care” is due this winter.

Community Continence Service contacts: *Dundee LHCC: Wallacetown Health Centre 01382 443527*
P&K LHCC: Drumhar Health Centre 01738 564258
Angus LHCC: Forfar Infirmary 01307 468383

Esomeprazole intravenous formulation (Nexium IV®) – gastroesophageal reflux disease

SMC recommendation

Advice: following a full submission.

Intravenous esomeprazole (Nexium IV®) is accepted for use within NHS Scotland for the treatment of gastroesophageal reflux disease in patients with esophagitis and/or severe symptoms of reflux as an alternative to oral therapy when oral intake is not appropriate.

Intravenous esomeprazole seems to be as effective as oral esomeprazole in terms of gastric acid suppression and healing of erosive oesophagitis. However comparisons with other IV proton pump inhibitors are restricted to pre-clinical studies. Esomeprazole has similar acquisition costs to other IV proton pump inhibitors.

Tayside recommendation

Not recommended.

Points for consideration:

- The above SMC advice relates only to the IV formulation of esomeprazole.
- No clinical outcome data are available for esomeprazole IV versus other proton-pump-inhibitors (PPIs) available in an IV formulation (omeprazole and pantoprazole).
- The level of acid suppression following IV administration of 40mg esomeprazole and 40mg omeprazole can be expected to be similar. (Differences following oral administration are due to differences in bioavailability).
- Both omeprazole IV and pantoprazole IV are available under hospital contract and at a lower price than esomeprazole IV.
- **Locally, intravenous PPIs for the treatment of severe oesophagitis are reserved for particular cases of immune suppression or bowel obstruction. Omeprazole is the intravenous PPI of choice.**
- Esomeprazole IV is not stocked by the hospital pharmacy

Ibandronic acid (Bondronat®) – hypercalcaemia of malignancy (HCM)

SMC recommendation

Advice: following a full submission.

Ibandronic acid is accepted for use within NHS Scotland for the treatment of tumour-induced hypercalcaemia with or without metastases.

It has been shown to be a cost-effective option in reducing serum calcium in patients with hypercalcaemia of malignancy.

Tayside recommendation

Not currently recommended – pending specialist treatment pathway

Points for consideration:

- Ibandronic acid is the fourth bisphosphonate indicated for the treatment of HCM. It is also licensed for the prevention of skeletal events in patients with breast cancer and metastatic bone disease (see below).
- Ibandronic acid infusion produces similar response rates (normalisation of albumin-corrected serum calcium levels) as pamidronate in patients with hypercalcaemia associated with proven malignancy.
- The safety profile of ibandronate appears similar to pamidronate.
- No comparative efficacy or safety data versus zoledronic acid are available.
- Ibandronic acid infusion is priced slightly below zoledronic acid and above generic pamidronate (£190 per infusion for ibandronic acid 4mg versus £195 for zoledronic acid 4mg, £110 for pamidronate 60mg and £165 for pamidronate 90mg).
- Generic pamidronate is the bisphosphonate used locally for the treatment of HCM.
- **The place of ibandronate in the local treatment of HCM, and in relation to pamidronate, is being addressed as part of a wider bisphosphonate guideline currently under development by oncologists.**
- Ibandronic acid is not currently stocked by the hospital pharmacy.

Ibandronic acid (Bondronat®) – metastatic bone disease (MBD) associated with breast cancer

SMC recommendation

Advice: following a full submission.

Ibandronic acid is accepted for use within NHS Scotland for the prevention of skeletal events (pathological fractures, bone complications requiring radiotherapy or surgery) in patients with breast cancer and bone metastases.

It reduces the rate of skeletal events consisting of a composite of vertebral fractures, pathological non-vertebral fractures and the need for radiotherapy or surgery to deal with bone complications. It can be given both by the oral or intravenous route.

Tayside recommendation

Not currently recommended – pending specialist treatment pathway

Points for consideration:

- Ibandronic acid is the only bisphosphonate licensed for MBD that is available in both intravenous (IV) and oral formulations. It is not licensed for the treatment of MBD associated with any other type of cancer eg prostate or multiple myeloma.
- In the key clinical study, ibandronic acid reduced the risk of skeletal events (SEs) by 38%. Reduced need for radiotherapy accounted for a large part of this reduction.
- Direct comparative data versus other bisphosphonates are currently lacking. Indirect comparison indicates that ibandronic acid is at least as effective as other IV bisphosphonates (zoledronic acid or pamidronate) in reducing SE risk. (Such indirect comparisons are limited by differences in study design, definition of SEs and patient inclusion criteria.)
- Ibandronic acid infusion is priced slightly below zoledronic acid and above generic pamidronate (see box above). Oral ibandronic acid is more expensive than clodronate (£195 per 28 days treatment with ibandronate 50mg daily versus £162 for clodronate 1.6g daily).
- Compared to oral clodronate, ibandronic acid tablets are smaller and require less frequent and less complex administration.
- Generic pamidronate infusion and oral clodronate are used locally for the treatment of MDB associated with breast cancer.
- **The place of ibandronate in the local treatment of MBD associated with breast cancer, and in relation to pamidronate and clodronate, is being addressed as part of a wider bisphosphonate guideline currently under development by oncologists.**
- Ibandronic acid is not currently stocked by the hospital pharmacy.

Oxycodone (OxyNorm®) injection – moderate to severe pain in cancer patients

SMC recommendation

Advice: following a full submission.

Oxycodone (OxyNorm®) injection is accepted for restricted use within NHS Scotland only for the treatment of moderate to severe pain in patients with cancer.

Use of this drug should be restricted to patients who have difficulty in tolerating morphine or diamorphine therapy. Limited data indicate that it provides analgesia similar to parenteral morphine at similar doses.

However, there are no comparative data with diamorphine, the opioid recommended by Scottish Intercollegiate Guidelines Network (SIGN) for patients with cancer who require parenteral opioids.

Oxycodone is more expensive than diamorphine and the economic case for this product replacing the other products has not been clearly demonstrated.

Other indications for this medicine, treatment of moderate to severe post-operative pain and severe pain requiring the use of strong opioid, have yet to be considered by the Scottish Medicines Consortium. Advice on these indications will be made after the relevant submissions have been made by the licence holder.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- The above SMC advice only relates to the use of oxycodone injection in cancer pain.
- Oxycodone is an agonist at kappa, mu and delta opioid receptors in the brain and spinal cord. It appears to have an adverse effect profile similar to other opioids, although there may be inter-individual variations in response.

Continued over

Oxycodone inj continued

- Relative efficacy and safety of parenteral oxycodone versus diamorphine are unknown.
- At roughly equivalent doses, oxycodone injection costs more than diamorphine (£1-£28 per day for oxycodone versus £1-£6 for diamorphine).
- Diamorphine has the advantage that it can be reconstituted into more concentrated solutions than oxycodone allowing higher opioid doses to be delivered subcutaneously. Knowledge of the stability of mixtures of diamorphine and various adjuvant drugs also exists.
- Diamorphine is the parenteral opioid of first-choice for the treatment of cancer pain (including patients progressing from oral oxycodone).
- **Locally, oxycodone injection is recommended as an alternative parenteral opioid for the treatment of cancer pain in patients unable to tolerate diamorphine.**
- Oxycodone injection is not currently recommended for the treatment of non-cancer pain, ie moderate to severe post-operative pain or severe pain requiring the use of strong opioid.
- National advice on the management of cancer pain is available in the SIGN Guideline “[Control of pain in patients with cancer](#)”. Local advice is available within [Pain Guidance Notes](#) in the Tayside Area Prescribing Guide (TAPG) and the recently issued Tayside Palliative Care Guidelines.

Sumatriptan fast disintegrating tablets (Imigran Radis[®]) - migraine

SMC recommendation

Advice: following an abbreviated submission.

Imigran Radis[®] film-coated tablets are accepted for use within NHS Scotland for acute relief of migraine attacks, with or without aura, provided there is a clear diagnosis of migraine. They offer a fast disintegrating oral formulation of sumatriptan succinate. No increased cost is associated with this product compared to prescribing conventional Imigran[®] tablets.

Tayside recommendation

Not recommended – pending formulary decision

Points for consideration:

- As with standard release sumatriptan, fast disintegrating tablets should be swallowed whole with water.
- Local [formulary](#) choices of oral 5HT₁ agonists include sumatriptan and rizatriptan standard release tablets and rizatriptan oral lyophilisate (wafers).
- The Imigran[®] patent is likely to expire in 2006.
- Advice on the management of migraine is available in the [Pain Guidance Notes](#) within the TAPG.
- **The place of Imigran Radis[®] in relation to other 5HT₁ agonist preparations used in the management of migraine will be addressed by the Formulary Committee. Prescribers are advised to await the formulary decision.**

Pimecrolimus Update

The National Institute for Clinical Excellence (NICE) has recently published [guidance on the use of topical tacrolimus and pimecrolimus for atopic eczema](#). The NICE appraisal defines very specific circumstances for the use of pimecrolimus as a **second-line** treatment as follows:

- Pimecrolimus is recommended as an option for the second-line treatment of **moderate** atopic eczema on the face and neck in children aged 2 to 16 years that has not been controlled by topical corticosteroids, where there is a serious risk of important adverse effects from further topical corticosteroid use, particularly irreversible skin atrophy.
- Pimecrolimus should only be initiated by physicians with a special interest and experience in dermatology.

Note that pimecrolimus is **not recommended** for the treatment of **mild** atopic eczema or as a **first-line** treatment for atopic eczema of any severity.

Tayside recommendation

Not currently recommended – pending specialist treatment pathway

- **A local protocol defining the place of topical pimecrolimus in the treatment of moderate atopic dermatitis, and in relation to topical tacrolimus, is under development by dermatologists.**

Atazanavir Update

The September SMC advice for atazanavir was deferred to the ASD Anti-Infectives Committee for consideration of its place in the management of HIV. See below for final decision:

Tayside recommendation

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

- Atazanavir is restricted to the HIV clinic for the treatment of HIV in patients who have developed elevated lipid levels on existing boosted PI regimens.

Forthcoming SMC Advice

Gastro-intestinal system
Creon micro (Creon [®])
Beclometasone Dipropionate 5mg
Cardiovascular system
Candesartan (Amias [®])
Eplerenone (Inspra [®])
Nicotinic acid (Niaspan [®]) <i>Resubmission</i>
Losartan (Cozaar [®])
Respiratory
Ciclesonide (Alvesco [®])
Central nervous system
Methylphenidate (Equasym XL [®])
Atomoxetine (Strattera [®])
Aprepitant (Emend [®])
Paracetamol infusion (Perfalgan [®])
Tramadol (Tramacet [®])
Galantamine (Reminyl XL [®])
Pregabalin (Lyrica [®])
Infections
Mycophenolate (Myfortic [®])
Ertapenem (Invanz [®])
Voriconazole (VFEND [®])
Lamivudine OD (Epivir [®]) & Abacavir OD (Kivexa [®])
Fosamprenavir (Telzir [®])
Caspofungin acetate (Cancidas [®])
Abacavir (Ziagen [®])

Endocrine system
Strontium ranelate (Protelos [®])
Testosterone buccal SR (Striant SR [®])
Somatropin (Norditropin SimpleXx [®])
Premique [®] low dose
Rosiglitazone/Metformin (Avandamet [®])
Metformin hydrochloride (Glucophage SR [®])
Insulin detemir (Levemir [®])
Obstetrics, gynaecology & urinary tract disorders
Solifenacin (Vesicare [®])
Malignant disease & immunosuppression
Letrozole (Femara [®])
Rituximab (MabThera [®])
Gliadel wafer
Docetaxel (Taxotere [®])
Cetuximab (Erbix [®])
Darbepoetin alfa (Aranesp [®])
Oxaliplatin (Eloxatin [®])
Gemcitabine (Gemzar [®])
Ibritumomab (Zevalin [®])
Nutrition & blood
Miglustat (Zavesca [®])
Laronidase (Aldurazyme [®]) <i>Resubmission</i>
Lanthanum carbonate (Fosrenol)
Musculoskeletal & joint diseases
Lumiracoxib (Prexige [®])
Skin
Vaniga 11.5% Cream (Vaniga [®])
Efalizumab (Raptiva [®])
Anaesthesia
Etomidate-lipuro (Etomidate [®] - Lipuro)

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

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