TAYSIDE PRESCRIBER

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In this issue:

SMC Advice Issued March 2004

Alteplase (Actilyse®) - acute ischaemic stroke

SMC recommendation

Advice: following a full submission.
Alteplase (rt-PA) (Actilyse) is accepted for restricted use within NHS Scotland for the treatment of acute ischaemic stroke.
Alteplase is licensed in the UK for the early treatment of acute ischaemic stroke, but there are potentially fatal risks incurred in using this treatment. The use of alteplase is therefore confined to specialist centres with adequate resources and appropriate expertise. It is associated with an increased risk of intracerebral haemorrhage including fatal haemorrhage and must be used strictly in accordance with detailed protocols specifying the availability of appropriate expertise and resources, including computerised tomography or magnetic resonance imaging in order to exclude haemorrhagic stroke. Treatment centres must participate in the post-marketing surveillance study SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study) designed to determine whether alteplase is as safe and beneficial in routine clinical practice as has been shown in the clinical trial setting.
Further details of SITS-MOST are available from www.acutestroke.org

Tayside recommendation

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

Points for consideration:

- Alteplase is the first thrombolytic licensed in the UK for the treatment of acute ischaemic stroke. It is also indicated for the treatment of acute MI and acute massive pulmonary embolism with haemodynamic instability.
- The above SMC advice relates only to treatment post stroke.
- Alteplase, administered up to three hours after ischaemic stroke, significantly reduces the proportion of patients dead or dependent at three months.
- Treatment with alteplase must be started within three hours of the onset of stroke symptoms. Haemorrhagic stroke must be excluded prior to treatment hence the requirement for rapid access to CT or MRI scans.
- Treatment with alteplase is associated with an increased risk of intracerebral haemorrhage.
- Questions remain concerning the duration of the therapeutic time window and the clinical or radiological

Continued over

Alteplase continued

features which identify the patients most likely to be benefited or (harmed), the age of the patient, and when and whether anti-thrombotic treatment may be safely used around the time of thrombolysis.

- The main financial impact associated with alteplase is the requirement to upgrade staffing and diagnostic facilities within stroke units. Reduction in the proportion of dependent patients should reduce the requirement for long-term nursing care.
- Ninewells stroke centre is registered with SITS-MOST.

Anastrozole (Arimidex®) - ER positive early invasive breast cancer in post-menopausal women

SMC recommendation

Advice: following a full submission
Anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland for the adjunctive treatment of early breast cancer in post-menopausal women with oestrogen-receptor positive disease who cannot take tamoxifen because of the presence of thrombophillic disorders or a past history of venous thromboembolic events, endometrial malignancy or undiagnosed vaginal bleeding. Treatment with anastrozole should be initiated by oncologists.
Tamoxifen continues to be the first line treatment for early breast cancer where it is not contra-indicated for the reasons above.

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Anastrozole is also licensed for the treatment of advanced breast cancer in post-menopausal women.
- The above SMC advice relates only to adjunctive treatment of post-menopausal women with oestrogen receptor (ER) positive early invasive breast cancer.
- The evidence to support the use of anastrozole in early breast cancer comes from an ongoing adjuvant clinical development programme: Arimidex, Tamoxifen Alone or in Combination (ATAC) trial. This trial shows that anastrozole significantly delays disease progression, by an absolute difference of 2-3% compared to tamoxifen. A formal analysis of survival is as yet unavailable.
- Data from the ATAC trial shows that, compared to tamoxifen, fractures and musculoskeletal disorders are more common with anastrozole, whilst the incidence of hot flushes, vaginal bleeding and discharge, ischaemic cerebrovascular events and venous thromboembolic events is greater with tamoxifen.
- The price of anastrozole is considerably higher than tamoxifen (£83 for 28 days anastrozole treatment versus £2 for generic tamoxifen).
- **Anastrozole is recommended locally for the adjunctive treatment of post-menopausal women with ER positive early invasive breast cancer:**
  - **with a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), or**
  - **who develop endometrial cancer or symptomatic polyps whilst receiving tamoxifen, or**
  - **who develop DVT or PE whilst receiving tamoxifen**
- The recommended duration of treatment for early breast cancer is five years.
- Patients who develop endometrial abnormalities or thromboembolic disease whilst receiving tamoxifen should be referred to oncology.

Cilostazol (Pletal®) – intermittent claudication

SMC recommendation

Advice: following a full submission.
Cilostazol (Pletal®) is not recommended within NHS Scotland for the treatment of intermittent claudication. It improves maximal and pain-free-walking distances more than placebo, but has limited effects on quality of life assessments. There are concerns about clinical effectiveness, including potential for several major drug interactions including with antiplatelet therapy, which is recommended by the Scottish Intercollegiate Guideline Network (SIGN) for patients with peripheral vascular disease. The economic case for this product has not been proven and it is substantially more expensive than its competitors. *Continued over*

Cilostazol continued

Tayside recommendation

Not recommended

Points for consideration:

- Cilostazol is a reversible phosphodiesterase III inhibitor with antiplatelet vasodilatory and anti-thrombotic effects, licensed for the treatment of intermittent claudication in patients without rest pain or evidence of tissue necrosis.
- The antiplatelet effect of cilostazol could result in interaction with antiplatelet agents eg low-dose aspirin. The SPC advises that the daily dose of aspirin should not exceed 80mg. Cilostazol is metabolised by cytochrome CYP3A4 and CYP2C19 isoenzymes, concomitant administration with drugs which inhibit these enzymes (eg cimetidine, diltiazem, erythromycin, ketoconazole, lansoprazole, omeprazole and protease inhibitors) is contraindicated.
- No comparative data versus naftidrofuryl are available.
- Cilostazol is priced considerably higher than naftidrofuryl (£460 per patient per year for cilostazol 100mg bd versus £99 for naftidrofuryl 100mg tds).
- Peripheral vasodilators are generally considered to be of limited benefit.
- SIGN guideline No. 27 "Drug therapy for peripheral vascular disease" recommends that all patients with intermittent claudication should receive low-dose aspirin as long-term prophylaxis against cardiovascular events. It is noted that naftidrofuryl may improve the symptoms of patients suffering moderate disease, but its effect on disease outcome is unknown.
- Cilostazol is not stocked by the hospital pharmacy.

Clopidogrel (Plavix®) – acute coronary syndrome (ACS)

SMC recommendation

Advice: following a full submission
Clopidogrel (Plavix®) is accepted for restricted use within NHS Scotland for the treatment of acute coronary syndrome (without ST-segment elevation) in combination with aspirin. It should be initiated only during an inpatient stay and only in patients in whom a diagnosis of acute coronary syndrome is confirmed with ECG changes or raised cardiac enzymes/markers. The maximum benefit appears within 3 months of starting treatment and the available information suggests that there is loss of benefit on stopping treatment. Benefits are greatest in patients with a high Thrombosis in Myocardial Infarction (TIMI) risk score (5-7).

Tayside recommendation

Recommended within specialist treatment pathway

Points for consideration:

- Clopidogrel is an antiplatelet agent initially licensed for the prevention of atherothrombotic events in patients suffering from MI, ischaemic stroke, or established peripheral vascular disease. Its licence was extended in September 2002 to include the prevention of atherothrombotic events in patients with non-ST segment elevation acute coronary syndrome (ACS) in combination with aspirin.
- The above SMC advice relates only to the ACS indication.
- The CURE study shows that clopidogrel administered with aspirin, over an average period of nine months, significantly reduces the frequency of cardiovascular events compared to aspirin alone, in patients with acute coronary syndrome without ST-segment elevation.
- The addition of clopidogrel to aspirin increases the risk of bleeding which remains throughout the course of treatment.
- Local guidance within the Tayside Area Prescribing Guide (TAPG) recommends that treatment is reviewed at three months and is not continued beyond 12 months. Thereafter patients should receive aspirin monotherapy for ongoing treatment. Practices should therefore ensure that patients are reviewed, and therapy discontinued as appropriate.
- There is currently no evidence to support the use of the clopidogrel/aspirin combination in ST elevation MI.
- Refer to Tayside Prescriber, Issue No. 86, Nov 2001 for further information on the CURE study.

Rosiglitazone (Avandia®) – type 2 diabetes mellitus

SMC recommendation

Advice: following a full submission
Rosiglitazone (Avandia®) is not recommended for use within NHS Scotland as monotherapy for type 2 diabetes mellitus patients.
It is one of two peroxisome proliferator-activated receptor-γ agonists recently marketed in the UK for this indication. In controlling blood glucose, its maximum, but not its lower dose was non-inferior to standard sulphonylurea therapy (which may not have been optimally dosed throughout the one year trial). It is substantially more expensive than both metformin and sulphonylurea therapy. The economic case for rosiglitazone as monotherapy has not been proven.

Tayside recommendation

Not recommended

Points for consideration:

- Rosiglitazone is also indicated for combination treatment in type 2 diabetes mellitus in patients with insufficient glycaemic control despite maximal tolerated doses of oral monotherapy with either metformin or a sulphonylurea:
  - in combination with metformin particularly in overweight patients
  - in combination with a sulphonylurea only in patients who show intolerance to metformin or for whom metformin is contraindicated
- The above SMC advice relates only to the recent monotherapy indication.

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

SMC recommendation

Advice: following an abbreviated submission
Rosiglitazone, metformin (Avandamet®) is accepted for use within NHS Scotland for the treatment of type 2 diabetes mellitus. It is 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. This combination product costs the same as equivalent doses of the individual constituent preparations and offers a more convenient dosing regimen, though less flexible.

Tayside recommendation

Not currently recommended – pending formulary decision

Points for consideration:

- Avandamet is available in two strength combinations: rosiglitazone 1mg/metformin 500mg and rosiglitazone 2mg/metformin 500mg.
- **The place of Avandamet® in relation to separate rosiglitazone and metformin preparations will be addressed by the Formulary Committee. Prescribers are advised to await the outcome of the formulary decision**.

Moxifloxacin Update

The October 2003 SMC recommendations for moxifloxacin were deferred to the TUH Anti-Infectives Sub-Committee for consideration of local place in the treatment of community acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB). See below for final decisions:

Tayside recommendations

- Moxifloxacin is recommended for treatment of **severe CAP in penicillin allergic patients following initial IV levofloxacin – HOSPITAL ONLY**

(Hospital prescribers should continue to use oral levofloxacin until notified that the changeover to moxifloxacin has taken place).

- Moxifloxacin is **not recommended** for the treatment of AECB.

Caspofungin Update

The Jan 2004 SMC recommendation for caspofungin in the treatment of invasive candidiasis was deferred to the TUH Anti-Infectives Sub-Committee for consideration of local place in treatment. See below for final decision:

Tayside recommendation

- Caspofungin is recommended for treatment of **fluconazole resistant invasive candidiasis intolerant or refractory to amphotericin B, on the advice of an ID Physician or Microbiologist – HOSPITAL ONLY**

Forthcoming SMC Advice

Products for which SMC advice is expected in the next quarter are listed below.

Gastro-intestinal system
Macrogol (Movicol® Paediatric Plain)
Macrogol (Idrolax®)
Cardiovascular system
Nicotinic acid modified release tablets (Niaspan®)
Valsartan/hydrochlorthiazide (Co-Diovan®)
Respiratory system
Budesonide/eformoterol (Symbicort Turbohaler®)
Central Nervous System
Quetiapine (Seroquel®)
Olanzapine (Zyprexa velotab®) *maintenance therapy*
Methylphenidate (Equasym XL®)
Lamotrigine (Lamictal®)
Botulinum type A neurotoxin (Botox®) *resubmission*
Buprenorphine patch (Transtec®)
Aripiprazole (Abilify®)

Infections
Ertapenem (Invanz®)
Endocrine system
Somatropin (Norditropin SimpleXx®)
Malignant disease & immunosuppression
Temoporfin (Foscan®)
Darbepoetin alfa (Aranesp®)
Nutrition & blood
Laronidase (Aldurazyme®)
Musculoskeletal & joint diseases
Infliximab (Remicade®)
Eye
Latanoprost (Xalatan®)
Skin
Clindamycin/benzoyl peroxide (Duac®)

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