IRISH MEDICINES BOARD

# Drug Safety NEWSLETTER

29th EDITION

## Prograf and Advagraf (Tacrolimus): Risk of serious medication errors

### Prograf and Advagraf are not interchangeable and should not be substituted without careful therapeutic monitoring

**Prograf Capsules (0.5mg/1mg/5g)**
Prograf is indicated for prophylaxis of transplant rejection in allograft recipients of a liver, kidney, or heart, and for treatment of allograft rejection that is resistant to treatment with other immunosuppressants. It is an **immediate-release** formulation intended for twice-daily dosing (based on patient weight), once in the morning and once in the evening

**Advagraf Prolonged-Release Capsules (0.5mg/1mg/5mg)**
Advagraf is indicated for prophylaxis of transplant rejection in allograft **adult** recipients of a liver or kidney, and for treatment of allograft rejection in **adults** who are resistant to treatment with other immunosuppressants. It is a **prolonged-release** formulation for once-daily administration (based on patient weight), in the morning.

**Reports of serious medication errors**
Medication errors with Advagraf and Prograf have been reported across the EU, with just one case notified in Ireland to date. The reported errors have been associated with prescribing, dispensing and administration, due to confusion between the products and their dosing regimens.

These errors have in some cases resulted in patients being dosed incorrectly, and some have led to adverse reactions which could be a consequence of either under or over exposure to tacrolimus including biopsy-confirmed acute rejection of transplanted organs.

**Communication and Regulatory Action**
Following identification of this issue, the IMB and the marketing authorisation holder (Astellas) communicated with healthcare professionals to inform them of the occurrence of medication errors and to highlight the need for caution when dispensing, administering and prescribing these products.

Temporary changes have been made to the outer packaging of Advagraf to highlight the once-daily dose regimen and further changes to the labelling are planned to come into effect by April 2009.

The IMB wishes to emphasise that Prograf and Advagraf are not interchangeable without careful therapeutic monitoring.

- Substitution should be made only under the close supervision of a transplant specialist and special care should be taken to ensure that patients switched from one product to another fully understand the changed dosing regimen.
- The indications for Advagraf and Prograf are not identical (see above) and Advagraf is only authorised for use in adults.
- Particular care should be taken in prescribing, dispensing and administering these products to ensure the correct dosage regimen.
- Prescribers, pharmacists, and patients should be fully aware of the brand being prescribed and the associated correct dose regimen.
- The likelihood of errors will be reduced if tacrolimus is prescribed by brand, either as Advagraf or Prograf, as is routinely the case for other products with a narrow therapeutic index.

Drug Safety – February 2009 – Issue Number 29

IRISH MEDICINES BOARD

Correspondence/Comments should be sent to the

Pharmacovigilance Section, Irish Medicines Board,
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Tel: 676 4971-7 Fax: 676 2517

## Ezetimibe (Ezetrol/Inegy): Updates from studies on possible increased risk of cancer

Ezetimibe is a lipid lowering agent which selectively inhibits the absorption of cholesterol from the small intestine. As monotherapy (Ezetrol) ezetimibe is indicated for patients with high cholesterol where a statin is considered inappropriate or is not tolerated. Ezetimibe is also available as a combination product with simvastatin (Inegy) for patients whose cholesterol is not controlled with a statin alone.

### SEAS study

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study[1] compared Simvastatin and ezetimibe with placebo to determine whether intensive lipid-lowering improved clinical outcomes in 1873 patients with mild to moderate asymptomatic aortic stenosis. The SEAS study investigated the effect of an "aggressive" lipid lowering treatment with the fixed combination of ezitimibe (10mg) plus simvastatin (40 mg) to reduce the risk of composite major cardio-vascular events (e.g. cardiovascular death, aortic valve replacement surgery, CHF), aortic valve events, and ischemic cardio-vascular events. Patients were followed up for an average of 4·35 years. The study failed to show a benefit of the fixed combination of ezetimibe/simvastatin as used in the SEAS study with regards to the pre-defined primary and secondary endpoints. Treatment with simvastatin and ezetimibe had no effect on the primary endpoint of major cardiovascular events (hazard ratio [HR] 0·96 [95% CI 0·83–1·12]), despite reducing serum LDL-cholesterol levels by approximately 50%. Overall mortality did not differ between the two treatment groups.

An unexpected finding was a higher number of cancer related deaths in the ezetimibe/simvastatin arm compared to the placebo arm (39 vs. 23 cases). Newly incident cancers (of mixed origin) were recorded for 101 (10·7%) patients in the treated group versus 65 (7%) patients in the placebo group (HR 1·55 [1·13–2·12], p=0·01). Presently there is no conclusive explanation for this finding. No specific pattern of the type of malignancies has been observed in the study. Pre-clinical data for ezetimibe on carcinogenicity or mutagenicity have not raised concern in this respect, and possible carcinogenicity of statins has been previously reviewed and it was considered that this concern could not be substantiated [2]

The SEAS study is limited by its relatively small size and short duration, and it was not powered to detect comparatively infrequent and long-term side-effects.

### Meta-analysis of SHARP and IMPROVE-IT trials

There are also two large ongoing clinical studies with ezetimibe/simvastatin, which have been meta-analysed:[3] the Study of Heart and Renal Protection (SHARP; n=9264, average follow-up 2·7 years) and the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT; n=11353, average follow-up 1 year). Together these trials provide about four-times more information on cancer incidence than does the SEAS trial and more than four-times the number of patient-years of follow-up. In this meta-analysis, no excess cancer incidence was observed in groups given ezetimibe. Furthermore, there was no clustering of cancer site; the specific sites most affected in the SEAS study were not similarly affected in the SHARP and IMPROVE-IT studies; and no increase in relative risk was noted with increasing follow-up. The authors conclude that there is no credible evidence for an adverse effect of ezetimibe on cancer.

### Advice for healthcare professionals:

The available data have been considered at EU level by the CHMP Pharmacovigilance Working Party, who consider that the data currently available are insufficient to draw any conclusions about the effect of ezetimibe on cancer. Further assessment of this issue will be necessary when the final results of the two large ongoing studies are available.


1 Rossebo AB, et al. *N Engl J Med* 2008; **359**: 1343–56.
2 Baigent C. *Lancet* 2005; **366**: 1267–78.
3 Peto R, et al. *N Engl J Med* 2008; **359**: 1357–66

## Inhaled anticholinergics: Publications on risk of death or stroke

Tiotropium (Spiriva) and ipratropium (Atrovent) are muscarinic receptor antagonists, which are licensed for the treatment of symptoms of chronic obstructive pulmonary disease (COPD). In September 2008 an article was published in JAMA, in which the authors concluded that inhaled anticholinergics (tiotropium bromide, ipratropium bromide) are associated with a significantly increased risk of cardio-vascular death, myocardial infarction (MI) or stroke among patients with COPD.(1) In the same month a publication in the Annals of Internal Medicine reported increased adjusted odds ratios (OR) for all cause mortality for ipratropium. Ipratropium was also associated with an increased number of cardiovascular deaths.(2) However, there were limitations in the methods of these studies. Furthermore, a 4-year placebo-controlled randomised double-blind trial of 5993 patients with COPD (the UPLIFT study)(3) concluded that tiotropium was associated with a non-significantly decreased risk of all-cause mortality, myocardial infarction, or stroke compared with placebo. These conflicting findings currently make it difficult to draw firm conclusions on the risk of all-cause mortality, cardiovascular death, or stroke associated with inhaled anticholinergics. Additional analyses are needed to further evaluate any possible increased risk. Patients with COPD who use tiotropium should be reminded not to exceed the recommended once-daily dose of Spiriva.


1 Singh S, et al. *JAMA* 2008; **300**: 1439–50.
2 Lee TA, et al. *Ann Intern Med* 2008; **149**: 380–90.
3 Tashkin DP, et al. *N Engl J Med* 2008; **359**: 1543


## Ibuprofen and low dose aspirin: Interaction potential

Low dose aspirin has been shown to be protective against cardiovascular disease by irreversibly inhibiting the isoenzyme cyclooxygenase-1 (COX-1) leading to impaired platelet aggregation. The non-selective NSAIDs also inhibit COX-1 but bind reversibly to the active site on the isoenzyme and most do not inhibit the isoenzyme completely throughout the dosing interval. The potential for competitive interaction between aspirin and non-selective NSAIDs therefore exists with the cardioprotective effects of aspirin potentially reduced by co-administration with NSAIDs. Based on available data it appears that for immediate release formulations of aspirin, such interaction may occur if ibuprofen is taken concomitantly, or within 8 hours before, or within 30 minutes after intake of low-dose aspirin. In light of ex vivo data demonstrating pharmacological interaction between ibuprofen and low dose aspirin, it has been agreed that the product information should be updated to reflect these data, as outlined below.

**Summary of Product Characteristics**

***Section 4.5 Interaction with other medicinal products and other forms of Interaction***
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use (see section 5.1).

***Section 5.1 Pharmacodynamic properties***
Experimental data suggest that ibuprofen may inhibit the effect of low dose aspirin on platelet aggregation when they are dosed concomitantly. In one study, when a single dose of ibuprofen 400mg was taken within 8 h before or within 30 min after immediate release aspirin dosing (81mg), a decreased effect of ASA on the formation of thromboxane or platelet aggregation occurred. However, the limitations of these data and the uncertainties regarding extrapolation of ex vivo data to the clinical situation imply that no firm conclusions can be made for regular

ibuprofen use, and no clinically relevant effect is considered to be likely for occasional ibuprofen use.

***Package Leaflet (PL)***
**Can you take <*Product Name*> with other medicines?**
Some medicines that are anti-coagulants (i.e. thin blood/prevent clotting e.g. aspirin/ acetylsalicylic acid, warfarin, ticlopidine), some medicines that reduce high blood pressure (ACE-inhibitors such as captopril, beta-blockers such as atenolol, or angiotensin-II receptor antagonists such as losartan), and other medicines may affect or be affected by treatment with ibuprofen. You should therefore always seek the advice of a healthcare professional before you use ibuprofen with other medicines.

## Antiepileptic Medicines: Risk of suicidal thoughts and behaviour

Recently completed European and US reviews of antiepileptic medicines have concluded that these medicines may be associated with a small risk of suicidal thoughts and behaviour.

The EU review assessed clinical trial data, spontaneous adverse reaction reports received after marketing, and literature reports of suicidal thoughts and behaviour associated with antiepileptic medicines. On the basis of the available evidence it is not possible to determine whether the risk of suicidal thoughts and behaviour differs between antiepileptic medicines. Furthermore, the mechanism by which antiepileptic medicines may increase the risk of a patient having suicidal thoughts and behaviour is not known. As a result of this review, the product information for all antiepileptic medicines is being updated to reflect the currently available information for the potential risk of suicidal thoughts and behaviour, as outlined below.

**Summary of Product Characteristics**
*'Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo controlled trials of anti-epileptic drugs has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for <drug substance>. Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge."*

**Package Leaflet**
*'A small number of people being treated with anti-epileptics such as << drug substance >> have had thoughts of harming or killing themselves. If at any time you have these thoughts, immediately contact your doctor.'*

**Key information for Healthcare Professionals:**

- Treatment with antiepileptic medicines is associated with a small risk of suicidal thoughts and behaviour; available data suggest that the increased risk applies to all anti-epileptic medicines and may be seen as early as 1 week after starting treatment.
- Patients should be monitored for signs of depression or suicidal thoughts and behaviour throughout treatment, and should be referred for appropriate treatment if necessary.
- Patients and caregivers should be advised to be alert to any mood changes, distressing thoughts, or feelings about suicide or harming themselves at any point during treatment. Patients should be advised to seek medical advice if they develop such thoughts.



IRISH MEDICINES BOARD

Correspondence/Comments should be sent to the

Pharmacovigilance Section, Irish Medicines Board,
Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Tel: 676 4971-7 Fax: 676 2517