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Direct healthcare professional communication

IMPORTANT SAFETY INFORMATION

Re: Medication Errors involving Prograf Capsules and Advagraf Prolonged Release Capsules

Prograf 0.5mg hard capsules	PA 1241/14/1
Prograf 1mg hard capsules	PA 1241/14/2
Prograf 5mg hard capsules	PA 1241/14/3
Prograf 5mg/ml concentrate for solution for infusion	PA 1241/14/4
Advagraf 0.5mg Prolonged Release Capsules	EU/1/07/387/001, 2, 9
Advagraf 1mg Prolonged Release Capsules	EU/1/07/387/003, 4, 5, 6
Advagraf 5mg Prolonged Release Capsules	EU/1/07/387/007, 8, 10

Dear Healthcare Professional,

Astellas wishes to draw your attention to a series of cases of medication errors involving Prograf and Advagraf. Both of these medicines contain the immunosuppressant tacrolimus, but are given according to different dosing schedules.

The medication errors have resulted in patients being dosed incorrectly. This has caused serious adverse reactions, including biopsy-confirmed acute rejection of transplanted organs and toxicity due to overexposure.

It is important to note the correct use of these medicines:

- **Prograf is an immediate-release formulation that must be taken twice a day, once in the morning and once in the evening.**
- **Advagraf is a prolonged-release formulation that must be taken once a day in the morning.**

Prograf and Advagraf are not interchangeable without careful therapeutic monitoring. Substitution should only be made under the close supervision of a transplant specialist.

Particular care should be taken in prescribing the correct brand of tacrolimus, i.e. either Prograf or Advagraf. Prescribers, pharmacists and patients need to be fully aware of the brand being prescribed and the associated dosing regimen.

Changes to product information and labelling to reduce errors

In order to reduce the frequency of medication errors, Astellas is planning to undertake the following corrective actions. These measures have been agreed with EU regulatory authorities, including the Irish Medicines Board (IMB) and the EMEA:

- Advagraf will be supplied in an over-labelled outer package, including the words 'once daily' in a larger font. This is an interim measure that will take effect as of 12 December 2008.

- Advagraf will be supplied in a new outer package, including the words 'once daily and 'prolonged-release hard capsules' in a larger font. This will take effect as of 1 April 2009.

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- The summary of product characteristics (SPC) and package leaflet for Advagraf and Prograf will be updated to include special warnings and precautions. The new product information will be made available as of March 2009.

If you require further information, please contact Astellas Medical Information on 01 4671555 or by e-mail to irishdrugsafety@ie.astellas.com.

Healthcare professionals should continue to report medication errors and suspected adverse reactions to Astellas Pharma by phone at (01) 4671555 or fax at (01) 4671550 and additionally to the Pharmacovigilance Unit of the Irish Medicines Board using the "on-line reporting" section of the IMB website at www.imb.ie or by post to Pharmacovigilance Unit, Irish Medicines Board, Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2.

Yours faithfully

Dr Greg Hays,
Medical Director,
Astellas Pharma Co., Ltd.

Willem Jan Atsma, MD, MSCE, MFPM
Senior Director Drug Safety and Pharmacovigilance
European Qualified Person for Pharmacovigilance
Astellas Pharma Europe B.V.

1st December 2008