actavis
think smart medicine

1st June, 2011

Important Safety Information on
restrictions regarding Quinine Sulphate's use for nocturnal leg cramps
and consequential inclusion in the product information of the associated risks

Summary

This letter is to inform about the important amendments to quinine's product information in order to maintain a favorable risk: benefit balance in the treatment of nocturnal leg cramps.
Quinine is not a routine treatment for nocturnal leg cramps, and should only be considered under the following restrictions:

- **Restrictions in indications:**
  Quinine Sulphate should be used in the treatment and prevention of nocturnal leg cramps in adults and the elderly **only when cramps cause regular disruption of sleep**. Before use for nocturnal leg cramps, the risks (including significant adverse effects and interactions), should be carefully considered relative to the potential benefits.
- **High-risk patient subsets**:
  The risks associated with Quinine Sulphate are particularly high in **the elderly**. Quinine Sulphate should be used only when cramps are very painful or frequent, when other treatable causes of cramps have been ruled out, and when non-pharmacological measures have been unsuccessful. Quinine Sulphate should not be used to treat cramps during **pregnancy**.
- **Restrictions in dosage**:
  The recommended dose for the treatment and prevention of nocturnal leg cramps in adults (including elderly) is **300 mg at bedtime, not to be exceeded**.
- **Treatment duration restrictions**:
  Patients should be monitored closely during the early stages of treatment for adverse effects. After an initial **trial of 4 weeks** (the usual latency until response occurs), treatment should be stopped if there is no benefit. The benefit of treatment should also be **reassessed every approximately three months** by temporarily interrupting it.

Further information on the safety concern

The Irish Medicines Board and MHRA Therapeutic Review Group (in agreement with the Commission on Human Medicines and its Pharmacovigilance Expert Advisory Group) have reviewed the safety and efficacy of quinine tablets in the treatment of nocturnal leg cramps. They have determined restrictions in indications and warnings regarding the increased potential for serious undesirable effects, especially in specific subsets of patients or when co-administered with other interacting drugs.

Main safety risks associated with quinine use for nocturnal leg cramps are:

- **Unpredictable serious and life-threatening thrombocytopenia**
  This is thought to be an idiosyncratic hypersensitivity reaction. Quinine Sulphate should not be prescribed or administered to patients who have previously experienced any adverse reaction to Quinine Sulphate, including that in tonic water or other beverages. Patients should be instructed to stop treatment and consult a physician if signs of thrombocytopenia such as unexplained bruising or bleeding occur.

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- **Cinchonism** (especially if coadministered with quinidine)
  Is generally more severe in overdose (with possibly serious, irreversible side effects including blindness and death), but may also occur in normal therapeutic doses. Patients should be warned not to exceed the prescribed dose and treatment for night cramps should be stopped if symptoms of cinchonism emerge (tinnitus, impaired hearing, headache, nausea, and disturbed vision).

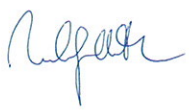
- **Increased Quinine Sulphate toxicity from interaction with concurrently administered drugs, including warfarin and the potent CYP3A4 inhibitors**, like cimetidine, azole antifungal drugs and HIV protease inhibitors. Care should also be taken when Quinine Sulphate is used in combination with antiarrhythmics, terfenadine or other CYP3A4 substrates, especially **those causing prolongation of the QT interval** (including amiodarone, moxifloxacin, pimozide, thioridazine and halofantrine – co-therapy that can increase the risk of ventricular arrhythmias).

Please consult the Summaries of Product Characteristics and Patient Information Leaflets for further safety information.

The information in this letter has been agreed with the IMB.

Call for reporting
For better monitoring of the overall safety profile, please remember to report suspected adverse reactions to IMB using a Yellow Card obtained either from the IMB, or electronically via the website at www.imb.ie.
Communication information
Should there be any questions or need for additional information, please contact the Actavis Ireland Medical Information and Regulatory Affairs Department at the following e-mail address: **plrp-ireland@actavis.com** and telephone number: **021 4619040**.

Kind regards,



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