NOVARTIS

Novartis Ireland Ltd
Beech House
Beech Hill Office
Campus
Clonskeagh
Dublin 4

Re: Ritalin® 10mg Tablets, Ritalin® LA 20mg prolonged-release capsules, Ritalin® LA 30mg prolonged-release capsules, Ritalin® LA 40mg prolonged-release capsules*:

Update of Product Information with Important Safety Information

September 2006

Dear Healthcare Professional

Following a recent safety review and subsequent discussions with the Irish Medicines Board, Novartis would like to inform you of important safety data and consequently of updated product information for the Ritalin range.

In April 2006, Novartis revised the core labelling of its ADHD products. Changes to the **prescribing information for Ritalin and Ritalin LA has been approved by the Irish Medicines Board.**

The product information for **Ritalin** has recently been updated to include the following information:

- Addition of a warning regarding use of stimulants in patients with structural cardiac abnormalities
- Addition of a warning regarding the use of Ritalin in patients with severe hypertension and other cardiovascular conditions
- Addition of a warning regarding misuse of stimulants

The Summary of Product Characteristics (SmPC) has been changed as follows:

Section 4.4 Special warnings and special precautions for use:

- ***Pre-existing Structural Cardiac Abnormalities:*** *Sudden death has been reported in association with the use of stimulants of the central nervous system at usual doses in children with structural cardiac abnormalities. A causal relationship with stimulant products has not been established since some structural cardiac abnormalities alone may carry an increased risk of sudden death. Stimulant products generally should not be used in patients with known structural cardiac abnormalities.*
- ***Cardiovascular Conditions:*** *Ritalin generally should not be used in patients with severe hypertension. Ritalin increases heart rate and systolic and diastolic blood pressure. Therefore, caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction. Cardiac arrhythmia and severe angina pectoris are contraindicated.*
- ***Misuse and Cardiovascular Events:*** *Misuse of stimulants of the central nervous system may be associated with sudden death and other serious cardiovascular adverse events.*

* Ritalin LA 40mg not currently on Irish Market

Background to Regulatory Action.

In April 2006 Novartis presented the IMB with data to support a variation application to update the product information for Ritalin. This consisted of a cumulative review of Novartis safety data with a data lock point up to 21st February 2006 with the adverse term sudden cardiovascular death or ventricular arrhythmia cases where a pre-existing structural cardiac abnormality may have been present.

This safety signal originally generated at the Canadian Regulatory authority when a number of cases of sudden death were reported with amphetamine (not licensed in Ireland) and methylphenidate use. This triggered a wider review by the FDA and Novartis.
The Novartis review retrieved 7 cases from the database with 6 of the 7 being under the age of 18 years. The table below is a line listing of the reports

(1) Cases with Pre-existing structural abnormalities

Age and Dose	ADE	Time to onset	Confounders Other Risk Factors
15 M. Unknown	Cardiomegaly Cardiac disorder, Circulatory Collapse Sudden Death	Years	Cardiomegaly. Cardiac defect at autopsy. Possible hx of other recreational drugs
10 Male Unknown	Cardiac Arrest (fatal)	Unknown	At Autopsy "Congenital malformation capable of causing transient ischaemia and arrhythmia"
7 Male 45mg	Death	Unknown	Prem birth at 34 wks gestation. Hearth murmur. Autopsy revealed left ventricular fibrosis with injury due to perinatal hypoxia
12 male 20mg	Cardiomyopathy	313days	Sudden death. Autopsy showed idiopathic cardiomyopathy. The child was taking Ritalin SR*. Whether the cardiomyopathy existed prior to Ritalin use is unknown
13male Unknown	Cardiomegaly. Tricuspid Valve disease, Cardiac arrhythmia. Death	Unknown	Patient receiving Ritalin died during football practice. Autopsy revealed heart was hypertrophied and enlarged with anomalies of tricuspid valve, and another anatomic variation. Cause of death is felt to be cardiac arrhythmia resulting from anatomic cardiac abnormalities. Methylphenidate is present at a level expected from therapeutic dosage.
17male 30mg	Ventricular Arrhythmia (Non-fatal event)	2100 days	Right Ventricular Dysplasia
58 female 5mg	Cardiac Arrest	44 Days	Hx of cardiac transplant

(2) Cardiovascular Conditions

The Novartis review of its Ritalin safety database for sudden death, myocardial infarction and cerebrovascular accident did not generate a signal. While these events did occur the rate was low. There is no causal support to add sudden death or MI into the SPC.

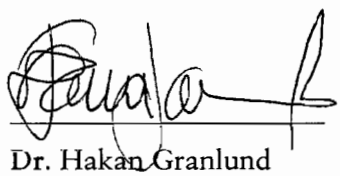
(3) Hypertension

Ritalin is a sympathomimetic medication with the documented adverse event of increasing blood pressure in some individuals. Given the acute risk and potential consequences of exacerbation of an already elevated blood pressure in severely hypertensive patients, Ritalin should not be recommended for these patients.

The patient information leaflet for Ritalin® and Ritalin® LA has also been updated to reflect this new information all will be avialable in the coming months. Please contact Novartis at 01-2601255 if you have any questions.

Finaly, all health care professionals are advised to report suspected adverse reactions to the company and/or the IMB, in the usual way.

Yours sincerely,



Dr. Hakan Granlund
Medical Director
Novartis Ireland Limited