SAFETY STATUS FOR ANTIDIABETIC AGENT AVANDIA® (ROSIGLITAZONE)

The dispute pertaining to the safety of an antidiabetic agent, Avandia® (rosiglitazone) resurfaced following a report issued by the *United States Senate Committee on Finance* recently. Rosiglitazone is approved as an adjunct to diet and exercise for improving glycaemic control in patients with type 2 diabetes mellitus. It works by increasing the sensitivity of cells to insulin resulting in better control of blood sugar levels.

In view of the safety of this medication, the United State Food and Drug Administration (USFDA), in May 2007, had issued *Information for Healthcare Professionals* that described the potential cardiovascular risk in patients taking rosiglitazone (marketed as Avandia® as monotherapy, Avandamet® and Avandaryl® as combination products). Safety data from controlled clinical trials had shown that there is a potentially significant increase in the risk of heart attack and heart-related deaths in such patients. The USFDA has requested that the manufacturer, GlaxoSmithKline (GSK), update the prescribing information for rosiglitazone about the potential increased risk of myocardial ischaemia. The updates include a new *Boxed Warning* and changes to the *Warnings*, *Precautions* and *Indications* sections of the label. Apart from that, GSK was also requested to develop a Medication Guide for patients that provide additional information about the recommended use of rosiglitazone.

In August 2007, the USFDA had again revised the prescribing information for rosiglitazone. The updated information emphasizes that rosiglitazone may cause or exacerbate heart failure in some patients, and that initiation of rosiglitazone in patients with established New York Heart Association Class III (marked limitation in activity due to symptoms, even during less-than-ordinary activity; comfortable only at rest) or Class IV (severe limitations; experiences symptoms even while at rest) heart failure is

contraindicated. In addition, USFDA requested that close monitoring for signs and symptoms of heart failure be carried out after initiation of rosiglitazone or dose increment. If heart failure is confirmed, discontinuation or dose reduction should be considered.

In line with the action taken by USFDA, the Drug Control Authority (DCA) has requested GSK Malaysia to revise the prescribing information for all products containing rosiglitazone. Up to date, the Ministry of Health has registered 11 related products through its regulatory body, the Drug Control Authority. The products are as below:

- Avandia® (rosiglitazone) in 3 strengths:
  2mg, 4mg, 8mg
- Avandamet® (combination of rosiglitazone/metformin) in 5 strengths:
  1mg/500mg, 2mg/500mg, 4mg/500mg, 2mg/1,000mg, 4mg/1,000mg
- Avandaryl® (combination of rosiglitazone/glimipride) in 3 strengths:
  4mg/1mg, 4mg/2mg, 4mg/4mg

In the years following USFDA notifications of potential cardiovascular risk of Avandia®, seven large, prospective, randomized clinical trials, including a meta-analysis (164 clinical trials) have been conducted. None of these established a statistically significant association between Avandia® and myocardial infarction or other ischaemic cardiovascular events.

The Malaysian Adverse Drug Reaction Monitoring Program to date has received 33 reports related to the use of rosiglitazone, of which 2 reports were linked to myocardial ischaemia and heart failure. Nevertheless, these patients also suffered from other concurrent cardiovascular diseases such as hypertension, which can be contributory to the occurrence of these adverse events. Both adverse events resolved after discontinuation of rosiglitazone.

The Drug Control Authority would like to inform healthcare professionals and patients taking rosiglitazone that the current safety information available on the product

is valid and sufficient. The Drug Control Authority will continue to monitor and review any new safety information regarding this product for any further regulatory action.

Director General of Health
As DCA Chairman
Ministry of Health Malaysia

23 February 2010