



11 October 2010

Dear Healthcare Professional

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SUSPENSION OF SALES OF SIBUTRAMINE

The Health Sciences Authority (HSA) would like to update healthcare professionals on its regulatory decision to suspend the sales of sibutramine products following a benefit-risk assessment, which took into consideration the findings from the Sibutramine Cardiovascular Outcomes (SCOUT) study, use of the product in the local context and developments in other international jurisdictions. The Vigilance Branch (VB), HSA, had consulted with its Pharmacovigilance Advisory Committee (PVAC) and a panel of external experts before arriving at this regulatory decision.

2 Sibutramine is licensed in Singapore since 2001 for use as an adjunctive therapy to diet and exercise for obese patients with a body mass index (BMI) $\geq 30\text{kg/m}^2$, or for overweight patients with a BMI $\geq 27\text{kg/m}^2$ with other obesity-related risk factors such as Type 2 diabetes mellitus (DM) or dyslipidaemia. It is marketed under 4 different brands in Singapore: Reductil® (Abbott), Ectiva® (Abbott), Reduxade® (Abbott) and Slenfig® (Apotheca Marketing Pte Ltd).

HSA's Review of the SCOUT Study

3 The SCOUT study was a randomised, double-blind, placebo-controlled, multi-centre study conducted in approximately 10,000 patients aged ≥ 55 who were obese or overweight and had a history of cardiovascular (CV) disease and/or type 2 diabetes with at least one other CV risk factor treated over a six year period. The study results showed that there was a 16% increase in the risk of a primary outcome event of nonfatal myocardial infarction (MI), nonfatal stroke, resuscitated cardiac arrest and CV death in the sibutramine group as compared with the placebo group (HR: 1.16; 1.03 -1.31; $p=0.02$). This was driven primarily by increase in rates of nonfatal MI and nonfatal stroke seen in the sibutramine group. A review of the serious adverse events also showed that there were significantly more reports of myocardial ischaemia and ischaemic stroke in subjects taking sibutramine as compared to placebo.

4 The weight loss achieved in the SCOUT study was modest. At the end of 12 months, the mean weight loss achieved with sibutramine was up to 2.4kg more than placebo (4.3kg with sibutramine vs 1.9kg with placebo). After 12 months of treatment, no additional mean weight loss was achieved and it was not clear if the effect on weight loss could be maintained when sibutramine was stopped.

International Regulatory Actions Taken

(A) US Food and Drug Administration (FDA)

5 Recently, in October 2010, the US FDA recommended against the continued use of sibutramine following deliberations of its Advisory Committee meeting in September 2010. The agency concluded that the risk for an adverse CV event from sibutramine in the population studied outweighed any benefit from the modest weight loss observed with the drug. In a subgroup analyses conducted on 3 predefined CV risk groups: (1) type 2 DM only; (2) a history of CV disease only; (3) a history of CV disease and type 2 DM, it was shown that the magnitude of risk for major CV events across the 3 subgroups were not statistically significantly different. Abbott Laboratories has agreed to voluntarily withdraw the drug from the US market.

(B) European Medicines Agency (EMA)

6 The Committee for Medicinal Products for Human Use (CHMP) conducted a safety review of sibutramine, including the preliminary results of the SCOUT study earlier this year and concluded that the benefit-risk profile of sibutramine was no longer favourable. A suspension of sibutramine across the European Union (EU) was recommended and this recommendation was adopted by the European Commission in August 2010. The marketing authorisation of the product has been suspended throughout Europe until additional data becomes available on a patient population, whereby the benefit would outweigh its risks.

Local Situation

7 HSA has been closely monitoring the safety profile, concerns and developments involving sibutramine following the release of the preliminary SCOUT results. In January 2010, HSA updated healthcare professionals (HCPs) on the CV risks associated with the use of sibutramine and advised HCPs not to prescribe the drug to patients with a history of CV disease. This message was reinforced in April 2010 when it was published in the HSA Adverse Drug Reaction News Bulletin, which was distributed to all HCPs.

8 As of 11 October 2010, VB has received three non-serious CV-related adverse reaction reports associated with the use of sibutramine describing sudden chest pain, palpitations, tachycardia, mild chest discomfort and elevated blood pressure. All three patients have recovered following the discontinuation of sibutramine.


HSA's Assessment and Recommendations

9 The availability of the SCOUT study results has added to the knowledge about sibutramine and has demonstrated that the increased CV risk of sibutramine outweighed the modest efficacy seen. While it was noted that majority of the patients in the SCOUT study should not normally be given sibutramine, as it is contraindicated in patients with a history of CV disease, it was considered that an increased risk could also apply to patients for whom sibutramine can be prescribed because obese and overweight patients are likely to be at risk of CV disease. It was also not shown that there was a reasonable benefit to offset the attributable risk for CV events.

10 Based on these findings and the overall assessment, HSA has concluded that the benefits of sibutramine do not outweigh their risks and has recommended that the sales of sibutramine be suspended. This suspension will remain in place until the company can provide sufficient data to identify a group of patients for whom sibutramine's benefits clearly outweigh its risks.

11 In view of the cessation of marketing of sibutramine in Singapore with immediate effect, healthcare professionals are advised to stop prescribing sibutramine, to review the therapy of existing patients who have been prescribed sibutramine and to consider suitable alternatives where appropriate. Please feel free to contact Ms Christine Ho at Tel: 6866-1064 or email: Christine_ho@hsa.gov.sg should you have any queries on the above information. For other matters pertaining to the respective products, please contact Abbott Laboratories (S) Pte Ltd at Tel: 6277-6335 (Ms Cheah Sin Yun) and Apotheca Marketing Pte Ltd at Tel: 6760-3588 (Mr Suryo Kartawinata).

Yours sincerely



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