Sibutramine : review of its cardiovascular risk-benefit profile

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SUMMARY

Sibutramine is a combined norepinephrine and serotonin reuptake inhibitor used as an antiobesity agent to reduce appetite and promote weight loss in combination with diet and exercise. At a daily dose of 10-20 mg, it was initially considered to have a good safety profile as it does not induce primary pulmonary hypertension or adverse effects on cardiac valves, in contrast to what was previously reported with some other anti-obesity agents. However, it exerts

contrasted effects on cardiovascular risk factors. On the one hand, sibutramine may have antiatherogenic activities as it improves insulin resistance, glucose metabolism, dyslipidaemia and inflammation markers, most of these effects resulting from weight loss rather than from an intrinsic effect of the compound. On the other hand, because of its specific mode of action, sibutramine exerts a peripheral sympathomimetic effect, which induces a moderate increase in heart rate and attenuates the reduction in blood pressure attributable to weight loss or even slightly increases blood pressure. It may also prolong QT interval, an effect that could induce arrhythmias. Because of these complex effects, it is difficult to conclude what might be the final impact of sibutramine on cardiovascular outcome. Sibutramine was shown to exert favourable effects on some surrogate cardiovascular endpoints such as reduction of left ventricular hypertrophy and improvement of endothelial dysfunction. A good cardiovascular safety profile was demonstrated in numerous 1-2 year controlled trials, in both diabetic and nondiabetic well-selected patients, as well as in several observational studies. However, since 2002, several cardiovascular adverse events (hypertension, tachycardia, arrhythmias, myocardial infarction) were reported in sibutramine-treated patients. This led to a contraindication of the use of this anti-obesity agent in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias. The « Sibutramine Cardiovascular and Diabetes Outcome Study » (SCOUT) was designed to prospectively evaluate the efficacy/safety ratio of sibutramine in a high risk population. The efficacy/safety results of the first 6-week lead-in open period of treatment with sibutramine 10 mg/day were reassuring in 10,742 overweight/obese high risk subjects (97% had cardiovascular disease, 88% hypertension and 84% type 2 diabetes). However, the recently reported final results of SCOUT showed that long-term (5 years) treatment with sibutramine (10-15 mg/day) exposed subjects with pre-existing cardiovascular disease to a significantly increased risk for nonfatal myocardial infarction and nonfatal stroke, but not cardiovascular death or all cause mortality. Because the benefit of sibutramine as a weight-loss aid seems not outweigh the cardiovascular risks, the European Medicines Agency recommended the suspension of marketing authorisations for sibutramine across the European Union. The Food and Drug Administration stated that the drug should carry a "black box" warning due to an increased risk of stroke and heart attack in patients with a history of cardiovascular disease. In conclusion, concern still persists about the safety profile of sibutramine concerning cardiovascular outcome and the drug should not be prescribed in overweight/obese patients with a high cardiovascular risk profile.

Obesity is epidemic and considered as a major health problem, as its prevalence continuously rises worldwide.[1] Obesity is a major cause of morbidity and mortality, predominantly through cardiovascular diseases (CVD).[2,3] The metabolic consequences of obesity, more particularly abdominal obesity associated with increased visceral adipose tissue, include atherogenic dyslipidaemia,[4] impaired glucose metabolism,[5] hypertension[6] and silent inflammation,[7] all CVD risk factors.[8,9] Obesity has a major impact on CVD, such as heart failure, coronary heart disease, sudden cardiac death, and atrial fibrillation, and is associated with reduced overall survival.[2,3] Weight loss is considered to be the initial step that helps to prevent or to control the clinical consequences of obesity.[10,11] However, the current state of weight reduction in the prevention and treatment of CVD remains controversial.[10,12] One of the common health consequences of abdominal obesity is type 2 diabetes mellitus (T2DM) and antiobesity management is a prerequisite in preventing diabetes and treating diabetic patients.[5,13,14] Weight reduction in obese persons will improve hyperglycaemia and will reduce all of the CVD risk factors associated with T2DM. However, no long-term, large-scale study of intentional weight loss with medical means has been adequately powered to examine CVD endpoints in individuals with or without diabetes.[15]

The initial clinical strategy for weight loss is lifestyle modification involving a combination of diet, exercise, and behaviour change.[16,17] However, it is difficult for many to achieve and maintain weight loss solely through this approach. Pharmacological therapy can be offered to obese patients who have failed to achieve their weight loss goals through diet and exercise alone.[18-21] It should be considered for those with body mass index (BMI) > 30 kg/m² or BMI > 27 kg/m² with obesity-related risk factors or disease. Among the drugs still available for the clinician, only two compounds, orlistat and sibutramine, have been approved to treat obesity long term.[22] Although >5% of placebo-subtracted weight loss maintained over 1 year is the primary efficacy endpoint for anti-obesity agents, an associated reduction in CVD risk factors is considered as an important secondary endpoint that may help for grant approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMEA).[23,24] Safety aspects are also critical in this indication essentially because antiobesity agents are known to be associated with adverse events and several of them have been withdrawn from the market because of serious safety problems. [25-28]

Sibutramine is one of the few established and well-proven agents for obesity and may be considered effective in the management of patients requiring pharmacotherapy as part of the multi-modal approach to weight-loss.[29-32] Though this serotonin-norepinephrine reuptake inhibitor was originally evaluated for possible use as an antidepressant, its research development was redirected to evaluate it as an anorexiant.[33] The pharmacological mechanisms by which sibutramine exerts its weight loss effect are likely due to a combination of reduced appetite, feelings of satiety, and possibly the induction of thermogenesis. Its efficacy for inducing an initial weight loss and the subsequent maintenance of the weight loss is well proven in short- and long-term clinical trials of up to 2 years duration.[34,35] Indirect comparisons suggest that sibutramine is slightly more effective than orlistat for promoting weight loss and weight maintenance, both in diabetic and non-diabetic patients.[35-37] Nevertheless, mean weight loss reported in many studies only achieved 5-10 % of initial body weight, with large interindividual differences (good

and poor responders). Sibutramine was also shown to improve atherogenic dyslipidaemia, part of this effect possibly occurring beyond weight loss.[38,39] Several randomised clinical trials were performed in overweight/obese patients with T2DM demonstrating the potential of sibutramine to improve glucose control.[36,40] In general, sibutramine has been well tolerated,[41,42] with no induction of primary pulmonary hypertension[43] or adverse effects on cardiac valves[44,45], in contrast to what was previously reported with fenfluramine and dexfenfluramine[25,26]. However, its action on the sympathetic nervous system has linked sibutramine to blood pressure (BP) and heart rate (HR) elevations[46,47]. This raises the possibility of increased CVD risk despite the favourable weight reducing effect of the drug[48]. For that reason, sibutramine's use is contraindicated in patients with uncontrolled hypertension, coronary heart disease, cardiac dysrhythmias, congestive heart failure, or stroke.[41,42,49,50]

This review article discusses the perceived benefits and risks of sibutramine and focuses on cardiovascular safety and outcome in overweight/obese patients with or without T2DM. To identify relevant articles concerning sibutramine and cardiovascular outcomes, an extensive literature search of MEDLINE was performed from January 1998 to April 2010, with any of the following key-words "cardiovascular", "safety", "efficacy", "outcome", and "adverse event" combined with the key-word "sibutramine" No language restrictions were imposed. In addition, reference lists of original studies, narrative reviews, and previous systematic reviews were examined. Furthermore, the FDA and EMEA statements concerning sibutramine were also checked. We will successively consider 1) the contrasted effects of sibutramine on metabolic and cardiovascular risk factors; 2) the effects of sibutramine on some surrogate cardiovascular endpoints; 3) case reports of cardiovascular adverse events and safety profile of sibutramine in observational studies; and 4) the initial and late results from the « Sibutramine Cardiovascular and Diabetes Outcome Study » (SCOUT), a large prospective trial specifically designed to study the cardiovascular safety and efficacy of sibutramine. Overall recent observations concerning the safety profile of sibutramine led to further important limitations of the use of this anti-obesity agent in US and its (temporary ?) suspension in Europe.

Effects of sibutramine on metabolic risk profile

Lipids

Abdominal obesity is associated with atherogenic dyslipidaemia, which is part of the metabolic syndrome.[4] In most trials sibutramine exerted favourable effects on lipids, especially on high density lipoprotein (HDL) cholesterol and triglycerides, as well as on the total:HDL cholesterol ratio.[51] Most beneficial effects observed with sibutramine appear to result from the drug-induced weight loss. However, in the STORM ("Sibutramine Trial of Obesity Reduction and Maintenance") trial, sibutramine treatment was associated with an impressive increase in HDL cholesterol levels : overall increases were 20.7% with sibutramine versus 11.7% with placebo (p<0.001).[38] In two recent meta-analyses, however, it was evident that the effect of the drug on HDL cholesterol was not so important. HDL cholesterol levels increased by 2.53%[52] and 0.04 mmol/l[53] more with sibutramine than with placebo and these rather modest changes were essentially attributable to the weight loss.

Similar results were obtained in patients with T2DM. According to a meta-analysis of 8 placebo-controlled trials,

sibutramine benefits were seen in plasma triglycerides and HDL, without significant variations in serum total and LDL cholesterol.[40]

Insulin resistance and glucose metabolism

Insulin resistance coexists very often with central obesity and weight loss may ameliorate this condition and associated metabolic disorders.[5] Several studies reported that sibutramine improves insulin resistance parameters including fasting plasma insulin levels, homeostasis model assessment (HOMA) index, and serum free fatty acids concentrations.[54] Most of them, however, demonstrated that the improvement in insulin resistance by the drug is dependent on weight reduction *per se*[32, 52]. Until now, a direct action of sibutramine on insulin sensitivity is not proven. Furthermore, the sympathomimetic activity related to the mechanism of action of the drug (see below) may be counteractive regarding insulin sensitivity.[36]

Sibutramine may help improve glucose control because it is conductive to weight loss but does not seem to exert glucose-lowering effects per se in patients with T2DM.[36] In a comprehensive meta-analysis of clinical studies on the effects of sibutramine on weight loss and glycaemic control in obese subjects with T2DM, eight placebo-controlled, double-blind, randomised trials of sibutramine were identified.[40] After sibutramine treatment (10-20 mg/day), the reduction in body weight, waist circumference, fasting blood glucose and glycated haemoglobin (HbA$_{1c}$) levels were significantly greater after sibutramine treatment than in the placebo group. Mean changes in basal blood glucose showed a small but significant variation (-0.17 [95% CI 0.03–0.32]; $P = 0.0187$), whereas the overall effect size on HbA$_{1c}$ was -0.28% (-0.13 to -0.42; $P = 0.0002$), with some heterogeneity ($P = 0.0104$) among the studies. In fact, the improvement in blood glucose control with sibutramine was generally less impressive in terms of reduction in HbA$_{1c}$ levels as compared with orlistat, despite a trend for a greater weight loss with sibutramine than with orlistat.[35,36] These discrepancies may result from intrinsic beneficial effects of orlistat on insulin sensitivity beyond weight loss because of an additional favourable lipid effect and/or from deleterious direct effects of sibutramine on insulin sensitivity, possibly via the sympathomimetic activity of the drug (see below).

Other risk factors

Elevated serum uric acid levels are frequently present in obese patients and might be associated with increased vascular risk. In some studies, sibutramine lowered serum uric acid levels and this reduction was proportional to weight loss.[32]

Overweight and obese patients frequently have elevated levels of inflammatory markers and inflammation plays an important role in the pathogenesis of atherosclerosis.[7] Sibutramine reduced high sensitivity C-reactive protein (hsCRP) levels in some studies[55] but not in others.[32] In an open-label study, sibutramine along with diet and exercise reduced the serum levels of the pro-inflammatory cytokines tumor necrosis factor α (TNFα) and interleukin 6 (IL-6) and increased the serum levels of the anti-inflammatory cytokine IL-10.[56] These anti-inflammatory effects most probably result from weight loss rather than from sibutramine treatment, but might contribute to a better CVD

risk profile.[32]

Finally, sibutramine seems to favourably influence adipocytokines; it reduced serum leptin and resistin levels and increased adiponectin levels.[51] In a non-blinded observational 6-month study comparing sibutramine with orlistat, the sibutramine group had modest mean body weight and waist circumference reductions, which were associated with a significant decrease in serum resistin, leptin, and CRP levels, and a significant rise in serum adiponectin concentrations. Although these effects were associated with improvements in insulin resistance and metabolic risk factors,[55,56] their impact on the overall CVD risk remains unknown. Again, most of these hormonal effects may be attributed to sibutramine-induced weight loss than to a direct action of the pharmacological agent. Thus, overall sibutramine exerts favourable effects on metabolic and inflammatory parameters, which may result in a beneficial effect on CVD risk. However, this favourable impact might be counterbalanced by some unwanted effects on BP and HR because of the sympathomimetic activity of sibutramine, leading to concern about cardiovascular outcome (Figure 1).

Sibutramine and sympathetic nervous system

Blood pressure

Weight loss is recommended in all major guidelines for antihypertensive therapy. However, the relation between sibutramine and BP was considered as a therapeutic dilemma.[57] Indeed, because of its mode of action, sibutramine treatment could somewhat dampen the classically observed reduction in arterial BP resulting from weight loss as shown in several meta-analyses.[50,53,58-60]

In a meta-analysis of 21 double-blind, randomised controlled trials of sibutramine, modest increases in systolic and diastolic BP were observed in patients treated with sibitramine as compared to placebo.[58] These results were confirmed in another meta-analysis of seven long-term studies.[53] Compared with placebo, sibutramine modestly increased systolic BP by 1.7 mm Hg (0.1 to 3.3 mm Hg) and diastolic BP by 2.4 mm Hg (1.5 to 3.3 mm Hg). A recent meta-analysis compared long-term changes in BP following orlistat and sibutramine treatment.[60] In contrast to orlistat, sibutramine caused significant elevations in diastolic BP [1.7 (0.7, 2.6) mmHg], while the overall systolic BP effect was near null [0.5 (-1.1, 2.1) mmHg]. A slightly higher diastolic BP elevation by sibutramine was observed in persons with T2DM [2.4; (0.6, 4.1) mmHg].[60] A total of eight trials (three orlistat and five sibutramine) with information on 1391 individuals was included in another meta-analysis.[61] The mean decrease in weight between the sibutramine and control groups was 5.32 kg and there was little evidence that sibutramine treatment was associated with adverse effects on CVD risk factors. However, this requires verification from large trials with longer follow-up such as SCOUT (see below). Furthermore, additional analysis in at risk patients deserved further attention, more particularly patients with essential hypertension and patients with T2DM for whom BP control is particularly important.

A systematic review and meta-analysis was performed in patients with essential hypertension.[59] Patients assigned to weight loss diets, orlistat, or sibutramine reduced their body weight more effectively than did patients in the usual care/placebo groups. Reduction of BP was higher in patients treated with weight loss diets or orlistat than with sibutramine. In fact, systolic BP increased with sibutramine treatment (weighed mean difference, 3.2 mm Hg). Thus, although sibutramine treatment reduced body weight, it did not lower BP in contrast to diet alone or orlistat. In a meta-analysis in patients with T2DM,[40] eight trials did not report differences in systolic BP between the sibutramine and the placebo but showed a weak increase in diastolic BP in the sibutramine group.

Hypertension, if adequately treated and frequently monitored, is not an absolute contraindication for the prescription of sibutramine.[62] An antihypertensive combination therapy regimen with angiotensin-converting enzyme inhibitors and calcium channel blockers was shown to be more advantageous than a beta-blocker/diuretic-based regimen in supporting the weight-reducing actions and concomitant metabolic changes induced by sibutramine in obese hypertensive patients.[63] Sibutramine treatment is unlikely to elicit a critical increase in BP even in hypertensive patients, although an effect on CVD outcome could not be totally excluded in some individuals. In patients who experience a clinically significant and sustained increase in BP, the drug should probably be discontinued.

Heart rate

Increased HR is another side effect of sibutramine and was observed in most studies. In a first meta-analysis of 29 trials of various durations, weight loss with sibutramine was associated with modest increases in HR compared to placebo.[34] The effect of sibutramine, 10 to 20 mg/day, on HR was statistically homogeneous among the 11 trials with complete data : the summary mean difference in HR was 3.76 beats/min (95% CI, 2.70-4.82 beats/min). Another meta-analysis focusing on ten long-term (one year or longer) trials reported an increase in HR by 4.5 beats/min in sibutramine-treated patients.[53] In a meta-analysis of 8 trials in patients with T2DM[40], recording of HR showed that sibutramine produced a small increase relative to placebo, either between groups or within groups over time. In the general population, elevated HR is associated with increased vascular risk[64], but it is not clear whether the sibutramine-induced increase in HR is also harmful.

Autonomic nervous system

The effects of sibutramine on the autonomic nervous system are complex as the drug might have opposing effects on peripheral and central sympathetic activity.[65] Experimental studies in healthy subjects with and without metoprolol suggested that the cardiovascular effect of sibutramine results from a complex interaction of peripheral and central nervous system effects. The inhibitory clonidine-like action of sibutramine on the central nervous system attenuates the peripheral stimulatory effect.[66] Similar results were obtained in obese hypertensive patients. Resting BP tends to increase with sibutramine, whereas BP during sympathetic stimulation and low frequency BP oscillations are decreased.[67] These paradoxical changes suggest a combination of peripheral and central nervous

system mechanisms. These conclusions have been confirmed by direct measurements of muscle sympathetic nerve activity in sibutramine-treated patients. Indeed, sibutramine treatment in obese subjects profoundly and selectively reduces sympathetic nerve traffic at rest and attenuates the responsiveness to sympathetic stimuli such as a cold pressor test.[68] Open-label chronic sibutramine treatment in obese subjects decreased muscle sympathetic nerve activity assessed by microneurography and increased diastolic BP and HR.[69] Interestingly, the BP response to sibutramine treatment was related to initial muscle sympathetic nerve activity so that subjects with higher activity exhibited a smaller increase or even a decrease in BP. The phenomenon might be explained by a sustained reduction in central sympathetic activity with sibutramine treatment, which may counteract the peripheral sympathomimetic effect of sibutramine. These observations may also explain the between-subject variability of BP response to sibutramine treatment. Indeed, it has been shown that the higher the patient's sympathetic tone, the more it is dampened by sibutramine,[68] and the more likely it is that the blood pressure will be unaffected or even decreased by the drug.[69] Thus, the initial vasoconstrictor sympathetic tone may be crucial for the outcome at least in terms of blood pressure.

In an experimental study in healthy volunteers, using sequential pharmacological blockade by intravenous administration of atropine and esmolol, sibutramine has been shown to produce significant increase in sympathetic control, but no change in parasympathetic control.[70] Respective changes in parasympathetic and sympathetic activities were assessed by analyzing time domain HR variability, QT dynamicity, and spectral components on ambulatory electrocardiographs after a 6-month diet plus sibutramine (10 or 20 mg/day) weight loss programme.[71] At 6 months, low frequencies (LF, mainly related to the sympathetic nervous system) significantly decreased, whereas high frequencies (HF) were higher than the initial value.

Thus, because of these complex effects of sibutramine on the sympathetic nervous system[65] together with the pleiotropic effects of moderate weight loss, it is difficult to conclude what might be the final impact of sibutramine on CVD outcome.

Effects of sibutramine on cardiovascular surrogate endpoints

Contrary to previous plasma biomarkers considered as CVD risk factors, vascular imaging data[72] or functional tests[73] can provide information on atherosclerosis as a continuous variable, since the disease process of the vascular wall itself is assessed.[72] Only a few studies have investigated the effects of sibutramine on CVD surrogate endpoints.

Left ventricular hypertrophy

Left ventricular hypertrophy is associated with increased vascular and all cause mortality in hypertensive patients and in the general population, and regression of left ventricular hypertrophy with antihypertensive treatment

reduces vascular risk.[74] Left ventricular hypertrophy appears to be more prevalent in obese patients than in subjects with normal weight regardless of the presence of hypertension. In obese patients, sibutramine (10–20 mg/day for 3–6 months) reduced left ventricular mass whereas no significant change was observed in the placebo group.[75,76] This reduction correlated with the decrease in body weight.[76] Thus, combined to hypocaloric diet, sibutramine-associated weight reduction in obese individuals has positive effect on reduction of BP and contributes to reduce left ventricular mass, the hallmark of markers of preclinical CVD and most powerful predictor of adverse outcome.[47]

Endothelial dysfunction

Endothelial dysfunction might represent an early stage of the atherosclerotic process and may be used as an endpoint in CVD studies.[73] Non-invasive techniques such as flow-mediated vasodilation of the brachial artery and strain-gauge venous plethysmography of the forearm have been developed. Endothelium dysfunction is frequently present in obese patients and correlates with the degree of abdominal obesity.[8] In obese patients with coronary heart disease, sibutramine (10 mg/day for four months) improved endothelial function. This correlated with the decrease in hs-CRP levels but not with the change in body weight.[77]

Carotid intima-media thickness

Epidemiological and clinical trial evidence have made carotid intima-media thickness (IMT) a validated and accepted marker for generalized atherosclerosis burden and vascular disease risk.[78] To our knowledge, no clinical study has investigated the influence of sibutramine on this surrogate endpoint of CVD.

Sibutramine and reports of CVD adverse events

- Early concern in 2002

Soon after its launch, sibutramine was associated with several adverse effects, which has given rise to a debate that still endures today. In March 2002, sibutramine was temporarily withdrawn from the Italian market on the basis of 47 adverse event reports (primarily tachycardia, hypertension and arrhythmias) and 2 deaths from CVD causes received between April and December 2001 in that country.[79] The EMEA has begun a comprehensive risk-benefit assessment of the drug, which remained on the market in several European countries, including the United Kingdom, where 215 reports of 411 adverse reactions (including 95 serious reactions and 2 deaths) have been reported, and in France, where 99 adverse events have been reported (including 10 serious adverse events but no deaths). Between February 1998 and September 2001 the FDA received reports of 397 adverse events, including 143 cardiac arrhythmias and 29 deaths (19 due to cardiovascular causes). Nineteen of the deaths in the United States were from cardiovascular causes; 10 involved people under 50 years of age, and 3 involved women under 30. In Canada

reports of 28 adverse events (no deaths) in patients using sibutramine were received between December 2000 and February 2002.[80] However, a worldwide review of efficacy and safety data has shown that the overall risk/benefit profile of sibutramine remains favourable.[79] Nevertheless, since that time, sibutramine is contraindicated in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias.[2]

- **Safety profile in randomised controlled trials**

The safety profile of sibutramine was generally considered as excellent in randomised controlled trials, which mostly recruited patients who fulfilled the indications and contraindications of sibutramine use.[29,30,42] In placebo-controlled studies, the risk ratio for discontinuation due to adverse events was not significantly elevated for sibutramine (0.98, 0.68-1.41), in contrast to what was observed with rimonabant and orlistat.[81] This safe profile of sibutramine may be explained by the strict inclusion-exclusion criteria used in such controlled trials, in contrast to what may be observed in clinical practice.[82]

In a previous benefit-risk assessment of sibutramine published in Drug Safety in 2003, the safety profile of the drug was summarized as followed.[41] The most commonly reported adverse effects of sibutramine are headache, constipation and nausea. Certain adverse events associated with the nervous system, including dizziness, dry mouth and insomnia, are reported by > 5% of patients receiving sibutramine. Increases in blood pressure and heart rate were possible adverse effects that require regular monitoring especially in obese hypertensive patients. Neither left-sided cardiac valve disease nor primary pulmonary hypertension was associated with the use of sibutramine. The assessment of the benefit-risk profile of sibutramine remained positive, although the product must be kept under regular review.

- **Safety profile in observational studies**

Observational cohort studies were conducted using prescription-event monitoring to examine the safety profiles of sibutramine compared to orlistat.[83] The cohort comprised 12,336 patients (approximately 80% were female) prescribed sibutramine, with a median age of 45 years. The most common reason for stopping sibutramine was hypertension (203 patients; 1.6%). Clinical events significantly associated with taking sibutramine included palpitation, besides central nervous system effects, nausea/vomiting and sweating. The efficacy and tolerability of sibutramine (10-15 mg/day) in 2,225 overweight or obese patients with CVD risk factors were examined in a 12-week, open-label, observational trial carried out in primary care settings in Poland.[84] The study population included patients in general good health and with controlled hypertension (41%), T2DM (15%), hyperlipidaemia (45%), and who were chronic tobacco users (smokers) (37%). Mean systolic and diastolic BP and HR decreased from baseline to week 12. Overall, sibutramine was well tolerated in these obese adults with a range of CVD risk factors.

During routine analysis of adverse drug reaction (ADR) reports related to sibutramine centrally collected and analyzed by the German Federal Institute for Drugs and Medical Devices, descriptions of its label*-inconsistent use

(*European Summary of Product Characteristics (SmPC) were repeatedly observed.[85] Out of a total of 104 identified reports of adverse drug reactions considered as suitable for further analysis, 35 reports (34 %) contained information indicative of label-inconsistent use. The observed percentage of adverse drug reaction reports, indicating a label-inconsistent use of sibutramine, is considered a signal for a therapeutic risk. There is strong evidence supporting the usefulness of the correct use of sibutramine in the management of obesity. A Swedish study investigated how sibutramine was prescribed in relation to the approved indications.[86] About half of the patients were not treated in accordance with the approved indications and a fourth (28 %) of the patients prescribed sibutramine had one or several contraindications to the drug. Prescribing of sibutramine to patients with contraindications is a serious health hazard.

An observational prospective cohort study evaluated the risk of fatal and non-fatal cardiovascular adverse events in a general population of New Zealand who were prescribed sibutramine in 'real-life' use.[87] Sibutramine postmarketing safety was monitored by the New Zealand Intensive Medicines Monitoring Programme (IMMP) between February 2001 and March 2004. The rate of death from a cardiovascular event in the overall cohort was 0.07 per 100 treatment-years sibutramine exposure and the rate of death from all causes was 0.13 per 100 treatment-years sibutramine exposure. The latter level was considered lower than that reported in other overweight/obese populations. However, an important limitation of this study is that there was no direct comparator group because New Zealand national statistics available for the general population are stratified by age and sex, but not by bodyweight or body mass index. [88] Follow-up questionnaires were also sent to doctors for patients with a first prescription of sibutramine. In the latter intensively followed-up cohort, the most frequent nonfatal cardiovascular events were hypertension, palpitations, hypotensive events and tachycardia, all of which are known adverse events associated with sibutramine therapy.

- **Recent case reports of arrhythmia or acute myocardial infarction**

Acute cardiovascular events either malignant arrhythmias or acute coronary syndromes, including myocardial infarction, have been reported during the last few years in patients treated with sibutramine (Figure 2, Figure 3). A case series suggested that sibutramine may be associated with QT prolongation and related dysrhythmias. Further studies are required, but sibutramine should be avoided in patients with long QT syndrome and in patients taking other medicines that may prolong the QT interval.[89] Another paper reported on a probable association between sibutramine and QT interval prolongation leading to ventricular fibrillation and cardiac arrest in a 51-year-old woman with obesity but no other relevant past medical history or cardiac risk factors.[90] In vitro studies demonstrated that sibutramine preferentially inhibits the hERG potassium channel, in a concentration-dependent manner, an effect that may contribute to prolong the cardiac action potential duration associated with long QT syndrome.[91] Therefore sibutramine should be avoided by patients with high susceptibility for cardiac arrhythmia. Furthermore, clinicians prescribing sibutramine should monitor their patients for ECG abnormalities and be cautious in coprescribing drugs known to prolong the QT interval (eg, certain antipsychotics,

antidepressants, and antiarrhythmic agents).

Several recent brief reports described the occurrence of acute myocardial infarction or acute coronary syndrome in young individuals receiving sibutramine.[92-95] Although it is practically impossible to demonstrate a causal relation, the patient's age, the absence of any attendant CVD risk factors and/or the negative results of the other studies (including coronary angiography), together with the coincidence between the start of drug treatment for obesity, led to the conclusion that the use of sibutramine was probably responsible for the myocardial infarction, possibly as the result of coronary vasospasm. In another report, sibutramine was also considered as a possible cause of a reversible cardiomyopathy.[96]

It remains unknown whether these isolated acute cardiovascular events occurred in susceptible subjects because of different pharmacokinetics of sibutramine. This deserves further investigation. Indeed, recent studies demonstrated the presence of polymorphisms that may influence the metabolism of sibutramine and consequently expose the individuals to higher plasma concentrations of the parent drug or its main metabolite than expected. Studies performed in Asian populations showed that CYP2C19 genotype substantially affects the pharmacokinetics of sibutramine (poor metabolizers had plasma sibutramine levels almost 2.5 higher than extensive metabolizers)[97] and that the CYP2B6*6 allele may be associated with a lower metabolic clearance of the M1 metabolite of sibutramine.[98] Further pharmacogenetic studies should be performed to more deeply investigate the potential influence of such polymorphisms on individual sibutramine safety profile. It has been suggested that genotyping (or phenotyping) of genetically polymorphic drug-metabolizing enzymes might be beneficial for drug safety or therapeutic outcome.[99]

-        **Safety profile in case of overdose or abuse**

In an observational retrospective case series from the California Poison Control System database between January 1998 and August 1, 2008, a total of 62 cases of sibutramine overdose or abuse were identified.[100] Of the patients who did experience adverse effects, cardiovascular side effects were the most common. In particular, tachycardia (nine patients, 14.5%) was the most notable, followed by chest pain (four patients, 6.5%). Sibutramine ingestion resulted in no serious CV effects or deaths, but the apparent maximal dose ingested was only 75 mg.

Sibutramine Cardiovascular and Diabetes Outcome Study (SCOUT)

There is no direct evidence that sibutramine reduces obesity-associated morbidity or mortality.[10] Moreover, as already mentioned, there are uncertainties about the cardiovascular safety of sibutramine. Therefore, a long-term large-scale prospective trial (« Sibutramine Cardiovascular and Diabetes Outcome Study » or SCOUT) has been designed to determine whether weight management with a novel lifestyle intervention plus either sibutramine (10-15

mg/day) or placebo in cardiovascular high-risk overweight and obese patients can impact upon CVD endpoints.[101] To be eligible for inclusion, the patients should meet the following key criteria : BMI 27-45 kg/m² or BMI 25-27 kg/m² with a waist circumference of ≥ 102 cm in males or ≥ 88 cm in females; history of documented coronary artery disease, cerebrovascular disease, or peripheral arterial occlusive disease or with type 2 diabetes wit at least one other risk factor. Exclusion criteria included heart failure symptoms (> NYHA class II), blood pressure > 160/> 100 mmHg, pulse > 100 bpm, scheduled cardiac surgery or coronary angioplasty, recent (> 3 months) myocardial infarction, stroke or transient ischemic attack. The primary endpoint of the trial included a composite of myocardial infarction, stroke, resuscitated cardiac arrest, and cardiovascular death.[101]

Early reports during the first 6 weeks of single-blind sibutramine treatment

The study had an initial single-blind, 6-week lead-in period with sibutramine plus weight management and the cardiovascular responses and weight loss were carefully examined during this period.[102-108]

A total of 10,742 subjects received treatment in the lead-in period; 97% had CVD, 88% hypertension and 84% T2DM.[102] Body weight decreased (median 2.2 kg [5th, 95th percentile changes -6.2, 0.5])and waist circumference was reduced by 2.0 cm. Systolic BP fell by 3.0 mmHg (-23.5, 12.5) and diastolic BP by 1.0 mmHg (-13.5, 10.0). HR increased by 1.5 b.p.m. (-11.0, 13.5) (all changes P < 0.001). Two consecutive increases in BP or HR of >10 mmHg/b.p.m. were observed in 4.7 and 3.5% of subjects, respectively.

Vital sign changes were assessed post hoc by initial BP categorized as normal, high-normal or hypertensive, weight change categories and current antihypertensive medication class use.[103] In hypertensive patients, BP decreases were observed during 6-week treatment with sibutramine even when body weight was unchanged. In patients with normal BP, weight loss of >5% induced decreases in systolic BP; otherwise, small increases were observed. Small HR increases were observed regardless of BP or weight change status.

Post-hoc analyses assessed anthropomorphic and vital sign responses between patients with and without diabetes (84% had a history of T2DM and additional co-morbidities).[104] Concomitant antidiabetic medication use was reported by 86% of the diabetic patients (approximately 30% required insulin-alone or in combination). In these high-risk diabetic patients, sibutramine and lifestyle modifications for 6 weeks resulted in small, but clinically relevant, median reductions in body weight, waist circumference and systolic and diastolic BP (-3.5/-1.0 mmHg) with larger BP reductions in diabetic patients who were hypertensive and/or lost the most weight (>5%). A small median increase in HR was recorded (+ 1.5 bpm.). Another post-hoc analysis investigated the influence of diabetes status at screening on changes in lipid profile during the lead-in period with lifestyle modification and sibutramine.[105 Weeke] Multivariable regression analysis showed that similar decreases in BMI resulted in smaller reductions in LDL and HDL cholesterol levels in patients with diabetes compared to those without diabetes. Patients

with hyperlipidemia and the less obese patients also had greater falls in LDL and total cholesterol concentrations during initial weight loss.

Serious adverse events, most commonly associated with the System Organ Class, Cardiac disorders, were reported by 2.7% of patients.[106] However, the majority was not considered sibutramine-related. Adverse events relating to high BP and/or HR, whether reported as adverse events leading to discontinuation, or serious adverse events were reported by less than 0.2% of patients. There were 15 (0.1%) deaths; 10 were attributed to a cardiovascular cause. Serious adverse events generally reflected sibutramine's known pharmacology or were related to cardiac disorders already present in this high-risk population. When compared with epidemiological data, overall mortality rate was considered as low and sibutramine was well tolerated in this mainly off-label population. No new safety issues were detected after a short 6-week follow up.

The responses to sibutramine during the 6-week, single-blind, lead-in period were compared between patients who conformed to the label requirements ("conformers") and those who did not ("nonconformers").[107] Of the 10,742 patients, 8.1% patients met label criteria; 91.9%, the majority with CVD and/or BP >145/90 mm Hg, were nonconformers. Conformers and nonconformers had similar reductions in body weight and waist circumference over the 6-week period. Greater BP falls and smaller HR increases were evident in nonconformers than in conformers. There was a low incidence of serious adverse events (conformers: 1.0%; nonconformers: 2.8%) and ~93% of patients in both groups completed the 6-week period.

Because elevated levels of serum uric acid are associated with an increased risk of CVD morbidity and mortality, the response of uric acid was also specifically analysed during four weeks of the lead-in period of the SCOUT trial.[108 Andersson] Uric acid concentrations at screening were significantly higher among patients with CVD compared to patients without CVD. A significant reduction in mean uric acid levels was observed in both subgroups. However, greater weight loss and diabetes were associated with smaller falls in blood uric acid levels and decreasing fasting and urinary glucose concentrations in diabetes were associated with significant reductions in mean uric acid levels. Thes results suggest that changes in renal glucose load in diabetes seem to counteract a potential uricosuric effect of sibutramine.

The SCOUT lead-in period evaluating weight management with sibutramine confirms its good tolerability and efficacy in patients who meet current label criteria. Preliminary data from high-risk patients for whom sibutramine is currently contraindicated suggest a low discontinuation rate and few serious adverse events but confirmation from the SCOUT outcome data is needed.

SCOUT final results

The title of an editorial accompanying an original paper assessing cardiovascular responses to sibutramine in high-risk subjects during the 6-week lead-in period of SCOUT was the following "Sibutramine in cardiovascular disease: is SCOUT the new STORM on the horizon?"[109] It was premonitory ! The primary end-point for SCOUT was

the time-to-event analysis of the composite of primary outcome events : nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, and CVD death. The sibutramine group had a 16 % increased risk relative to the placebo group (HR = 1,162; 95% CI = 1.029-1.311; P = 0.015).[110] Results from the analysis of the individual components of the primary endpoint showed that the increased risk was primarily attributed to the treatment difference for nonfatal events of myocardial infraction and stroke. There was no apparent difference in risk for CVD death neither for all-cause mortality (Figure 3).

Subjects with pre-existing CVD on long-term treatment irrespective of weight loss had an increased risk for nonfatal myocardial infarction and nonfatal stroke but not cardiovascular death or all-cause mortality. On the basis of this trial, sibutramine should continue to be excluded from use in patients with preexisting CVD. Furthermore, when sibutramine is used in the indicated population, the decision to continue treatment should be based on weight loss achieved and blood pressure control.

Recent sibutramine limitations because of CV safety issues

The review of the EMEA's Committee for Medicinal Products for Human Use (CHMP) was initiated because data from SCOUT showed an increased risk of serious, non-fatal cardiovascular events, such as stroke or heart attack, with sibutramine compared with placebo. The CHMP noted that the use of sibutramine was not in accordance with the prescribing information for most of the patients enrolled in the SCOUT study, as sibutramine is contra-indicated in patients with known cardiovascular disease. The treatment duration in the study was also longer than normally recommended. However, because obese and overweight patients are likely to have a higher risk of cardiovascular events, the Committee was of the opinion that the data from SCOUT are relevant for the use of the medicine in clinical practice. The Committee also noted that the data from available studies show that the weight loss achieved with sibutramine is modest and may not be maintained after stopping. The CHMP concluded that the benefit of sibutramine as a weight-loss aid does not outweigh the cardiovascular risks and recommended the suspension of marketing authorisations for sibutramine across the European Union (Figure 3).[111,112]

Meantime, the FDA notified health care professionals that its review of additional data indicates an increased risk of heart attack and stroke in patients with a history of cardiovascular disease using sibutramine. Based on the serious nature of the review findings, the agency requested to add a new contraindication to the drug's label stating that sibutramine is not to be used in patients with a history of cardiovascular disease, including a history of: coronary artery disease (eg, heart attack, angina), stroke or transient ischemic attack (TIA), heart arrhythmias, congestive heart failure, peripheral arterial disease; and uncontrolled hypertension. The FDA stated that the drug should carry a "black box" warning due to an increased risk of stroke and heart attack in patients with a history of CVD (Figure 3).[111,113]

CONCLUSION

As compared to other antiobesity agents acting on the central nervous system, sibutramine was initially considered to have a good cardiovascular safety profile because it does not induce pulmonary hypertension or cardiac valve abnormalities. However, this combined norepinephrine and serotonin reuptake inhibitor exerts a sympathomimetic effect, which may lead to some increases in HR and BP. These unwanted effects may counteract the expected favourable effects resulting from weight loss such as improved insulin resistance, glucose metabolism, atherogenic dyslipidaemia and silent inflammation. Because of this contrasted profile, it is difficult to conclude what might be the final impact of sibutramine on cardiovascular outcome and the drug has given rise to a debate about its cardiovascular safety. Since 2002, several cardiovascular adverse events (among which arrhythmias due to QT prolongation and myocardial infarctions) were reported in sibutramine-treated patients. Despite the fact that it is practically impossible to demonstrate a causal relation in such case reports, sibutramine was contraindicated in patients with established coronary heart disease, previous stroke, heart failure, or cardiac arrhythmias. In SCOUT, the selected subjects with pre-existing CVD had an increased risk for nonfatal myocardial infarction and nonfatal stroke but not cardiovascular death or all-cause mortality. It should be emphasized, however, that the drug was used outside the classical indications, with a long-term treatment up to 5 years independently of weight loss in high-risk patients. Thus, on the basis of this trial, sibutramine should continue to be excluded from use in patients with prexisting CVD, as further emphasized in a recent "black box" warning requested by the FDA. Furthermore, when sibutramine is used in the indicated population, the decision to continue treatment should be based on weight loss achieved and blood pressure control. The EMEA considered that the benefit of sibutramine as a weight-loss aid does not outweigh the cardiovascular risks and recommended the suspension of marketing authorisations for sibutramine across the European Union. Thus the initial debate about cardiovascular safety of sibutramine still endures today.

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Figure 1 : Contrasted effects of sibutramine on cardiovascular risk factors raising the question of cardiovascular outcome on sibutramine treatment.

Figure 2 : Mechanisms by which sibutramine may be responsible for acute cardiovascular complications. The central/peripheral effects on blood pressure are complex, with sibutramine-induced changes depending on initial sympathetic tone and achieved weight loss. CVRF : Cardiovascular risk factor

Figure 3 : Cardiovascular outcome of sibutramine and recent decisions by the FDA and the EMEA after the results of SCOUT, a trial performed in a very high risk population. MI : Myocardial infarction.