Overview of Relevant Sildenafil Data

Absence of Adverse Outcomes Potentially Related to QT Prolongation - 5 Years of Post-Marketing Experience

EXECUTIVE SUMMARY

There is no pre-clinical or clinical data to support a clinically relevant effect of sildenafil on ion channels or action potential duration. There is no evidence from an extensive clinical trial database after analysis of the QT/QTc interval data, or adverse events, to suggest there is any risk of proarrhythmia. In general, the frequency of 'drug induced' torsade de pointes is sufficiently low such that any conclusion that 'a drug' is safe should be reserved until post-marketing surveillance data have been reviewed[1]. It is only in the post-marketing environment that sufficient numbers of patients with predisposing medical conditions and concomitant drug therapy will be exposed to a new drug. Sildenafil has now had over five years of post-marketing exposure with more than 20 million men treated worldwide, and there have been no reports of QTc prolongation or torsade de pointes in which sildenafil has been implicated as a possible cause. Together these data would confirm that in clinical practice, sildenafil does not cause prolongation of the QTc interval nor does it cause torsade de pointes.

The following post-marketing data is summarised which confirms the absence of any sildenafil induced cases of QTc prolongation or torsade de pointes in the five years that it has been available. The relevant pre-clinical and new clinical data is summarised and confirms the lack of any clinically meaningful effect on cardiac repolarization, or proarrhythmic signal, associated with sildenafil use.

- No case of QTc prolongation or torsade de pointes has been identified in a review of post-marketing surveillance data in which sildenafil was implicated and no cases have been identified in which adverse events were suggestive of drug induced torsade de pointes. Indeed, there were no cases of torsade de pointes and

only one case of 'QT increase', occuring in a diabetic male, which was noted after starting Cisapride (a drug known to prolong QTc) for gastroparesis. He had been taking sildenafil for two years prior to this with no reported adverse events. Pfizer's early alert safety database was reviewed for all relevant adverse event terms through 31 December 2002. At the time of this report, there were more than 20 million men treated with sildenafil worldwide.

- The published independent non-clinical data consistently demonstrate the lack of a prolonging effect on cardiac repolarization by sildenafil up to the highest concentration tested (0.9μM). Shortening of QT and QTc is the only effect that has been observed *in vivo* at unbound plasma concentrations estimated to reach 2.2μM. Data presented in the original NDA similarly failed to show a direct effect of sildenafil on the QT interval at concentrations up to 1.8μM. At concentrations greatly in excess of these levels, *in vitro* studies suggest that sildenafil may block calcium channels and has the potential to affect I_{Kr}, the IC_{50} values being 27.2μM and greater than 30μM, respectively. Importantly, and to place these findings into clinical perspective, the unbound C_{max} plasma concentrations associated with 25, 50 and 100mg oral doses of sildenafil to patients are 7.1, 13.2 and 27.6nM, respectively. The concentrations represented in the above non-clinical studies are approximately 30 (0.9μM), 80 (2.2μM) and 1000 (30μM) times the maximum unbound drug concentrations in clinical practice.

- The QT/QTc data from the relevant sildenafil phase 1/2/3 studies provides no evidence that sildenafil, administered at doses up to 800mg, prolongs the QT/QTc interval. Furthermore, three independent studies have reported no effect of sildenafil on QTc in healthy volunteers and patients with cardiac disease. Additionally, a search of the clinical trial database for adverse event terms suggestive of QTc prolongation or ventricular arrhythmia has not revealed anything that would indicate a signal of an adverse effect due to sildenafil.

- A Prescription Event Monitoring study of over 26,000 men followed for over 42,000 person-years has been conducted. One case of "ventricular fibrillation" was reported, without any additional information or confirmatory data. This case was also reported to the UK regulatory authority and would be included in the Pfizer early alert safety database. The frequency of cardiovascular events in this study was no higher than that of the general population of UK men of the same age range.

- Since approval by the Cardio-Renal division of the FDA in March 1998, sildenafil has been extensively researched. The incidence of myocardial infarction and all cause mortality is no different between sildenafil and placebo from clinical trials. Pfizer and independent researchers around the world have performed pre-clinical and clinical studies in a number of different cardiovascular and other indications. This has resulted in approximately two hundred publications to date from which a comprehensive picture of overall cardiovascular safety has been built and from which no signal for torsade de pointes has been generated.

- Due to the differences in chemical structure, pharmacokinetics and pharmacodynamics amongst drugs of any one class, it is appropriate that the individual safety record of each member of any particular drug class is established through clinical and post-marketing surveillance.

REFERENCE

1. Haverkamp W, Breithardt G, Camm AJ et al. The potential for QT prolongation and proarrhythmia by non-antiarrhythmic drugs: Clinical and regulatory implications. *European Heart Journal* (2000)21:1216-1231