

for syncope, while another case did not have sufficient information for etiologic assessment. Therefore, arrhythmia is not the primary cause of syncope events in these spontaneous case reports, and atomoxetine is very unlikely to induce syncope through the mechanism of cardiac arrhythmia.

There was 1 case report diagnosed as syncope due to structural cardiac disorder. However, a short duration of atomoxetine treatment was unlikely the cause for this patient's congestive cardiomyopathy.

Of those 28 cases where the syncope type could not be categorized, 26 cases either were possibly confounded or had insufficient information for etiologic assessment. The remaining 2 cases had no apparent confounding, one of which reported positive rechallenge of atomoxetine.

Based on the clinical trial experience, it was known that during atomoxetine treatment, especially early stages of the treatment, a few patients might experience dizziness or orthostatic hypotension. During the postmarketing period, syncope adverse events have been very rarely reported. The majority of the syncope events were considered to be due to the mechanism of neurally mediated (reflex) or orthostatic hypotension, and a possible role of atomoxetine could not be ruled out in several cases. Given the presence of the biological plausibility, the MAH had added "syncope" to the spontaneous data in Section C.8 of the atomoxetine CDS as a very rarely reported adverse drug reaction.

9.8.7 CUMULATIVE REVIEW OF SPONTANEOUS ADVERSE EVENT REPORTS OF CARDIAC DISORDERS

The cumulative 40-month review of cardiac disorders is attached in Appendix 16 of this PSUR. It is summarized below:

During the 40 months post-launch of atomoxetine, from 26 November 2002 through 31 March 2006, an estimated 4,046,000 patients have been exposed to atomoxetine. Approximately 73.8% of these patients were pediatric and adolescent, and 26.2% were adults.

During this reporting period, a total of 23,132 spontaneous adverse event reports of atomoxetine, representing 58,048 adverse events, were collected by the MAH. Of these reports, 581 reports contained 656 events that were coded to the "cardiac disorders" SOC, and 847 reports contained 966 adverse events that were coded to the HLTG cardiac and vascular investigations of the "investigation" SOC.

Of all atomoxetine spontaneous reports, 789 (3.4%) reports contained adverse events of tachycardia or heart rate increased. As expected by the pharmacological property of atomoxetine, tachycardia was the most common event related to cardiac disorders reported in the spontaneous database. If taken into account the patient population exposed to atomoxetine during the reporting period, the events of tachycardia were considered "rarely reported" with a reporting rate less than 0.1%.