10. QUESTION 10

The PMS studies show very low rates for suicide and suicide attempts. An explanation of these results is required.

Response

In GSK's response of 01 September 2003, nine large scale Post-Marketing Surveillance (PMS) studies conducted locally by GSK Germany (seven studies) and GSK Belgium (two studies), and involving a total of over 19,000 adult patients were assessed. All of these studies evaluated the safety and efficacy of paroxetine in the treatment of depressive disorders, with the size of the individual study populations ranging from 974 to 4,024 patients. A total of 27 suicide-related events were identified from the listings of reported adverse events across the nine studies (four completed suicides, sixteen suicide attempts, four reports of suicidal ideation, one report of increased suicidality and two reports of an increased suicidal tendency). The 27 events came from seven of the nine studies.

Further review of the adverse event data has shown that the overall reporting rate of adverse events from the PMS studies was low in comparison to rates one would expect from a randomised clinical study (between 3.3% and 35% of patients experienced an adverse event in the PMS studies, with a mean reporting rate of 12.1%). This factor could account for the low rates of suicide-related events seen across the nine studies. Both psychiatrists and non-psychiatrists (including General Practitioners) were involved in recruiting patients into the studies, however, the majority of patients were recruited by the non-psychiatrists (between 81% and 93% of patients). It is noteworthy that, data from several of the studies suggests that the reporting rate of adverse events was approximately two-fold higher for those patients recruited by the psychiatrists compared to the non-psychiatrists. Therefore, the fact that non-psychiatrists recruited most patients to the studies may have contributed to the overall low reporting rates of adverse events.

It should also be noted that since GSK's initial response, further review of the efficacy measures used in the studies has shown that in two of the seven German studies (involving a total of 5525 patients) data on suicidal thoughts/behaviour was collected as a measure of efficacy. In both of these studies patients were classified using the DSM diagnosis of major or minor depression which is dependent upon disease duration and the presence of a number of symptoms. The presence and severity of these symptoms (including thoughts of death and suicidality/suicidal behaviour) were documented at baseline and after six and twelve weeks. At baseline, 2932 (53%) of the 5525 patients experienced thoughts of death, whilst 1295 (23%) of the patients experienced suicidality. The majority of patients in the studies showed an improvement in these symptoms, however, a small number of patients did experience a deterioration in symptoms over the course of the two studies with 1.1% of those patients with baseline thoughts of death, and 1.1% of those patients with baseline suicidality showing a deterioration in symptoms at six weeks, and 3.0% of patients with no thoughts of death at baseline and 1.3% of patients with no suicidality at baseline showing a deterioration over six weeks. However, only nine suicidal events were reported as adverse events in these two studies. In a further

two of the German studies (involving 1103 and 974 patients) a measure of baseline suicidality was documented (13% and 28% of patients respectively, had a degree of baseline suicidality), however, changes in the symptoms of suicidality over the course of the study were not recorded within the study reports. There were no suicide-related events reported as adverse events in these two studies. In the remaining five studies the suicidality of patients at baseline and throughout the study was not documented within the study reports. A total of 18 suicide-related events were documented as adverse events across these five studies.

Overall Conclusion

In conclusion, the very low rates of reporting of suicide and suicide attempts from the PMS studies may be a reflection of the overall low rate of reporting of adverse events in these studies. Even taking into account the additional data from these studies where suicidality was assessed formally as an efficacy measure, the rate of emergence of suicide-related behaviour during paroxetine therapy remains low.