A long-term open-label extension study of subjects from the two short-term efficacy studies was also using the alkaline hematin methodology) were treated with 3900 mg/day for up to 5 days during each cycle. The types and severity of adverse events in these two long-term open-label trials were similar to those observed in the double-blind, placebo-controlled studies although the percentage of subjects reporting adverse events was higher. The number of subjects with at least one adverse event was 208 (89.7%) with LYSTEDA versus 122 (87.8%) with placebo in the 6-cycle study. In the 12-cycle study, adverse events occurred in 226 (87.8%) of LYSTEDA-treated subjects compared to 130 (87.8%) of placebo-treated subjects. More LYSTEDA-treated subjects (N=232) than placebo-treated subjects (N=157) discontinued treatment due to adverse events (23.4% versus 14.8%).

In the 6-cycle study, the rate in the LYSTEDA group was 2.4% as compared to 4.1% in the placebo group. Across the studies, the combined exposure to 3900 mg/day LYSTEDA was 947 cycles and the intrinsic risk of thrombosis or thromboembolism (e.g., thrombogenic valvular disease, thrombogenic arterial plaque) was 0.003. Women using hormonal contraception were excluded from the trials. The rates of discontinuation observed in this study were similar to those observed in prior studies. The risk of thrombosis may be increased with the concomitant use of hormonal contraceptives. There have been US postmarketing reports of thrombotic events in women using LYSTEDA concomitantly with hormonal contraceptives. There are no clinical trial data on the risk of thrombotic events with the concomitant use of LYSTEDA and hormonal contraceptives. There have been reports of venous and arterial thrombotic events in women who have used LYSTEDA concurrently with combined hormonal contraceptives. It is unknown whether combined hormonal contraceptives may affect the efficiency of both LYSTEDA and tissue plasminogen activators. Therefore, exercises caution when using LYSTEDA concomitantly with combined hormonal contraceptives.

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