This multinational, randomized, double-blind study was specifically designed to prospectively compare the onset of antidepressant efficacy of mirtazapine orally disintegrating tablets and sertraline at dosages commonly used in clinical practice. A total of 345 patients with major depressive episode (DSM-IV) received mirtazapine (30-45 mg/d) or sertraline (50-150 mg/d) for 8 weeks. Mirtazapine was administered in the newly developed fast dissolving, orally disintegrating tablet formulation. Assessments were performed at baseline and on days 4, 7, 10, 14, 28, 42, and 56. The primary efficacy variable (mean absolute change from baseline in the Hamilton Depression Rating Scale [HAMD] total score [17 items]) showed that mirtazapine was significantly (P ≤ 0.05) more effective than sertraline in reducing HAMD scores and improving remission rates. Both treatments were well tolerated. In addition, mirtazapine had a greater effect than sertraline on sexual functioning. In conclusion, this first prospective onset of action study using the orally disintegrating tablet formulation indicates that mirtazapine has a faster onset of therapeutic effect than sertraline. The orally disintegrating tablet formulation of mirtazapine used in this study is known to enhance the convenience and compliance by the patient.