An open-label, multicentre clinical trial to determine the levodopa dose-sparing capacity of pramipexole in patients with idiopathic Parkinson’s disease

M. M. Pinter¹, A. W. F. Rutgers², and E. Hebenstreit³, on behalf of the study centers

¹Ludwig-Boltzmann-Institute for Restorative Neurology and Neuromodulation, Neurological Hospital Maria Theresien Schloessel, Vienna, Austria
²Department of Neurology, Martini Ziekenhuis, Groningen, The Netherlands
³Boehringer Ingelheim Austria GmbH, Vienna, Austria

Received November 11, 1999; accepted April 7, 2000

Summary. Ninety-three patients with idiopathic Parkinson’s disease (PD) entered a 12 week open-label, baseline controlled, multicentre study. The study was designed to determine the levodopa sparing effect of pramipexole as add-on treatment in PD while maintaining an optimal clinical improvement in motor performance. The overall reduction in adjusted levodopa dose was the primary endpoint. Unified Parkinson’s Disease Rating Scale (UPDRS) subscores as well as motor fluctuations, frequency and severity of dyskinesia (assessed by patient diaries) were secondary endpoints.

Pramipexole permitted a median reduction of adjusted levodopa by 40% while maintaining or improving the UPDRS scores in 61 patients (per protocol [PP] analysis). The intent-to-treat (ITT) analysis (90 patients) similarly revealed a median reduction of 40%. An anticipated short-term levodopa dose reduction as substantiated by 95% confidence interval calculations lies within a range of 35% to 50%. If unadjusted levodopa doses were considered, a median reduction of 42% (PP) or 43% (ITT) was achieved. 47% patients (ITT) had a levodopa dose reduction (adjusted) of more than 40% while maintaining or improving their level of efficacy, and 72.2% had a reduction of at least 20%. Motor fluctuations improved compared to baseline according to patient diaries and UPDRS part IV.

These findings suggest that pramipexole can markedly reduce the daily levodopa dosage without deterioration of motor response and support that this new selective D2/D3 receptor agonist also improves later levodopa-associated motor complications.

Keywords: Parkinson’s disease, pramipexole, levodopa dose-sparing capacity.
Pramipexole – recently registered for the treatment of patients with early and advanced Parkinson’s disease (PD) – is a potent and selective non ergot dopamine receptor agonist that exerts highest affinity for the D₂ receptor sites. This synthetic amino-benzathiazol derivative appears to have preferential binding specificity for the D₃ receptor of the D₂ receptor family (Piercey et al., 1995; Mierau et al., 1995). Pramipexole shows linear, predictable pharmacokinetic properties with a plasma concentration increase in a dose-dependent fashion; a peak plasma concentration occurring between 1 to 3 hours, a half life ranging from 8 to 12 hours and a bioavailability greater than 90%. Pramipexol undergoes minimal metabolism being excreted virtually unchanged (Wright et al., 1997).

Clinical studies in patients with early and advanced PD have shown that pramipexole possesses full agonist efficacy (Molho et al., 1995; Guttman et al., 1997; Lieberman et al., 1997; Parkinson Study Group, 1997; Shannon et al., 1997; Pinter et al., 1999). Primary aim of these double-blind, placebo-controlled trials was to assess efficacy, tolerability and safety of pramipexole treatment, either as monotherapy in early PD or as adjunct to levodopa (LD) plus decarboxylase inhibitor in advanced PD. Overall, results indicate that pramipexole is safe, well tolerated, and effective in improving PD signs as well as long-term treatment complications in advanced PD patients, if present. The adverse event profile disclosed a high tolerability. The most important adverse events under pramipexole were nausea, constipation, somnolence, and visual hallucinations in early PD patients (Parkinson Study Group, 1997; Shannon et al., 1997) whereas dyskinesia, vivid dreams and hallucinations occurred more frequently in advanced PD patients (Guttman et al., 1997; Lieberman et al., 1997; Pinter et al., 1999).

Levodopa plus decarboxylase inhibitor is considered the mainstay of treatment for PD. However, long-term use of levodopa is limited by the development of motor complications which may be attributed to a combination of disease duration and severity, and the duration of levodopa therapy (Blin et al., 1988; Horstink et al., 1990; Jenner, 1995; Nutt, 1995). Regardless the concern about the theoretical possibility of contribution of levodopa to disease progression, many have advocated that levodopa therapy should be delayed in early PD until greater disability with impaired postural reflexes develops (Fahn and Bressman, 1984; Jenner, 1995; Piccoli and Riuggeri, 1995; Raijput et al., 1997), or until other drug therapies fail or are limited due to side-effects. Furthermore, levodopa should be kept to a minimum dose in advanced PD – in attempt to forestall and delay the development of long-term motor complications (Quinn, 1995; Miyawaki et al., 1997). Bearing this in mind, long-term PD treatment should be primarily guided by the goal of providing improved quality of life with maximum motor performance while limiting reversible and long-term side effects (Quinn, 1995; Lang and Lozano, 1998).

In previous double-blind, placebo-controlled trials, pramipexole permitted a reduction of levodopa dose up to 25%, but the protocols of these trials did not encourage investigators to reduce levodopa dosages to the maximum;