PRAMIROL (Pramipexole)

Available as tablets: 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 1.5 mg.

(1) Indications (for elderly):

- Treatment-resistant depression (investigational use)
- Treatment of the signs and symptoms of idiopathic Parkinson's disease

(2) Recent trials:

Abstract 1

Pramipexole in treatment-resistant depression: An extended follow-up

Paolo Cassano, Lorenzo Lattanzi, Federico Soldani, S.M., Serena Navari, et al.
Depression and Anxiety 2004;20:131-138.

We evaluated the long-term antidepressant safety and response of adjunctive pramipexole, a D2-D3 dopamine agonist, in the course of drug-resistant depression. Twenty-three patients with treatment-resistant major depressive episode (MDE) were followed up after a 16-week pramipexole add-on trial. Pramipexole was added to current treatment with TCA or SSRI, at increasing doses from 0.375-1.500 mg/day. The LIFE scale was administered at baseline of the acute trial, at Weeks 16, 32, and 48. Patients were analyzed for sustained remission (score=<2 at LIFE for at least 8 weeks) and recurrence (after remission score >=3 at LIFE for at least 2 weeks) of depression. Of 23 patients, 12 had major depression and 11 had bipolar depression (16 women; mean age=52.8 years). Mean age of onset and median duration of current MDE were 35.1 years and 6 months, respectively; all subjects had at least two prior MDEs. Mean pramipexole dose was 0.990 mg/day. Median duration of follow-up was 28 weeks. Mean baseline MADRS and CGI-S scores were 33.7±8.4 (*sd*) and 4.6±0.8, respectively. Median time to sustained remission from baseline was 10 weeks and overall 60.9% (14/23) of subjects recovered within Week 22. Recurrence of depression occurred in 35.7% (5/14) of remitters after Week 24 and within Week 28 from remission. Although there were no sleep attacks, two cases of hypomania and one case of psychotic mania occurred at Weeks 22, 24, and 30, respectively. **Pramipexole augmentation of antidepressant treatment was relatively safe and presumably effective in the long-term course of treatment resistant depression.**

Abstract 2

Pramipexole Augmentation in the Treatment of Unipolar and Bipolar Depression: A Retrospective Chart Review

Jonathan Sporn, S. Nassir Ghaemi, Marnie R. Sambur, Meridith A. Rankin, et al.
Annals of Clinical Psychiatry 2000; 12 (3):137 – 140.

Objective: To assess the effectiveness and safety of pramipexole as an adjunctive medication in refractory bipolar and unipolar depression in a naturalistic setting.

Methods: Retrospective chart review by psychiatrists on staff at a university hospital identified all patients who had received pramipexole. Response was based on moderate to marked improvement in the Clinical Global Impression-Improvement (CGIT) scale.

Results: Pramipexole (mean dose 0.70 mg/d, mean duration 24.4 weeks) was effective in 6/12 (50.0%) of patients with bipolar depression, and 8/20 (40%) of patients with unipolar depression, mean duration of follow-up of 24.4 weeks. One case of transient hypomania was noted. Eight patients discontinued pramipexole due to lack of response and four due to side effects.

Conclusions: **Pramipexole, used as an adjunct to antidepressants or mood stabilizers, appeared to be effective and safe in the treatment of unipolar and bipolar depression.** These uncontrolled, retrospective, naturalistic pilot data require confirmation by controlled research before conclusions can be made

Abstract 3

Pramipexole in treatment-resistant depression: a 16-week naturalistic study.

Lattanzi L, Dell'Osso L, Cassano P, Pini S, et al.
Bipolar Disord 2002: 4: 307–314.

Objective: To assess the antidepressant efficacy and tolerability of adjunctive pramipexole, a D_2–D_3 dopamine agonist, in patients with drug-resistant depression.

Methods: The study sample consisted of in-patients with major depressive episode, according to the DSM-IV, and drug resistance. Pramipexole was added to antidepressant treatment with TCA or SSRI, at increasing doses from 0.375 to 1.0 mg/day. Two independent response criteria were adopted: a >50% reduction of the Montgomery–Asberg Depressive Rating Scale (MADRS) total score and a score of 1 or 2 on the Clinical Global Impression scale (CGI-I) at endpoint. Side-effects were assessed by the Dosage Record Treatment Emergent Symptom Scale (DOTES).

Results: Thirty-seven patients were enrolled. Of these, 16 had unipolar depression and 21 had bipolar depression. Six patients dropped out in the first week. Of the 31 patients included in the analyses, 19 completed the 16-week follow-up. Mean maximal dose of pramipexole was 0.95 mg/day. Mean scores on MADRS decreased from 33.3 ± 8.4 at baseline to 13.9 ± 11.5 at endpoint ($p < 0.001$) and the CGI-S decreased from 4.6 ± 0.8 at

baseline to 2.8 ± 1.3 at endpoint ($p < 0.001$). At endpoint, 67.7% (21/31) of patients were responders on MADRS and 74.2% on CGI-I. Of the 37 patients enrolled, 10 discontinued pramipexole because of adverse events.

Conclusions: These preliminary data suggest that **pramipexole adjunction to antidepressant treatment may be effective and well tolerated in patients with resistant major depression**

Abstract 4

Pramipexole in psychiatry: a systematic review of the literature.

Aiken CB.
J Clin Psychiatry. 2007 Aug;68(8):1230-6.

OBJECTIVE: To assess the risks and benefits of pramipexole in psychiatric populations. DATA SOURCES: A PubMed search was performed using the keywords pramipexole and ropinirole, which identified 500 articles.

STUDY SELECTION: All clinical studies in psychiatric populations were included in the primary review (24 articles). Studies involving other populations were then reviewed to evaluate potential risks and benefits not identified in the psychiatric studies.

DATA EXTRACTION: Effect sizes were calculated from controlled studies. Rates of intolerable side effects and manic switching were estimated by pooled analysis of controlled and uncontrolled studies.

DATA SYNTHESIS: Pramipexole has a large effect size (0.6-1.1) in the treatment of both bipolar and unipolar depression with a low short-term rate of manic switching in bipolar patients (1% mania, 5% hypomania). The pooled discontinuation rate for all reasons was 9%. Pramipexole is neuroprotective and exerts beneficial effects on sleep architecture. Pramipexole is associated with 3 rare but serious side effects: sleep attacks, which have only occurred in Parkinson's disease; compulsive behaviors and pathologic gambling, which have occurred in Parkinson's disease and restless legs syndrome; and psychosis, which has occurred in both psychiatric and neurologic populations.

CONCLUSIONS: Pramipexole is an important therapeutic option for treatment-resistant bipolar and unipolar depression; further studies are warranted to evaluate its safety in psychiatric patients.

(3) Dosage in elderly:

PRAMIROL (pramipexole dihydrochloride) tablets should be titrated gradually in all patients. The dosage should be increased to achieve a maximum therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and

dry mouth. Dosage should be initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension.

Pramipexole clearance decreases with age as the half-life and clearance are about 40% longer and 30% lower, respectively, in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years). This difference is most likely due to the well known reduction in renal function with age, since pramipexole clearance is correlated with renal function, as measured by creatinine clearance.

Dosing in Patients with Normal Renal Function

Initial Treatment

Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. A suggested ascending dosage schedule that was used in clinical studies is shown in the following table:

Table: Ascending Dosage Schedule of PRAMIROL tablets for Parkinson's Disease

Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 TID	0.375
2	0.25 TID	0.75
3	0.5 TID	1.50
4	0.75 TID	2.25
5	1 TID	3.0
6	1.25 TID	3.75
7	1.5 TID	4.50

Maintenance Treatment

PRAMIROL (pramipexole dihydrochloride) tablets are effective and well tolerated over a dosage range of 1.5 to 4.5 mg/day administered in equally divided doses three times per day with or without concomitant levodopa (approximately 800 mg/day).

When PRAMIROL tablets are used in combination with levodopa, a reduction of the levodopa dosage should be considered. In a controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

Dosing in Patients with Renal Impairment

Table: Pramipexole Dosage in Parkinson’s Disease Patients with Renal Impairment

Renal Status	Starting Dose (mg)	Maximum Dose (mg)
Normal to mild impairment (creatinine Cl > 60 mL/min)	0.125 TID	1.5 TID
Moderate impairment (creatinine Cl = 35 to 59 mL/min)	0.125 BID	1.5 BID
Severe impairment (creatinine Cl = 15 to 34 mL/min)	0.125 QD	1.5 QD

Very severe impairment (creatinine Cl < 15 mL/min and hemodialysis patients): The use of PRAMIROL tablets has not been adequately studied in this group of patients.

Discontinuation of Treatment
It is recommended that PRAMIROL tablets be discontinued over a period of 1 week.

(4) Common side effects:

Pramipexole may cause nausea, dizziness, sleepiness, difficulty falling asleep, involuntary movement, constipation and hallucinations (seeing, hearing, feeling, or tasting something that isn't there). It may lead to low blood pressure when you sit up or stand quickly, muscle weakness and confusion. Pramipexole may cause you to fall asleep without any warning, even while doing normal daily activities, such as driving.