

# PRAMIPEXOLE (MIRAPEX) NON-CONFIDENTIAL DISCLOSURE

## I. HISTORY AND BACKGROUND

- Pramipexole [(S)-2-amino-4,5,6,7-tetrahydro-6-(propylamino)benzo-thiazole dihydrochloride monohydrate] is a second-generation dopamine 2/3 receptor agonist. It was developed by Boehringer-Ingelheim and FDA approved for treatment of Parkinson's disease (PD) in 1997.
- Because of its benefit for restless legs syndrome (RLS) and the association of RLS with fibromyalgia (FM), dopamine agonists are considered a new treatment option for FM, a condition affecting 6-12 million Americans without an FDA approved treatment.

## II. PROFILE OF PRAMIPEXOLE

- **Neurochemistry.** Pramipexole has 7-10 times greater affinity for the D<sub>3</sub> receptor compared to D<sub>2</sub> and 17 times greater affinity compared to D<sub>4</sub>. It has milder affinity for  $\alpha_2$ -adrenergic receptors, without a significant effect at D<sub>1</sub>, D<sub>5</sub>, serotonin, acetylcholine, histamine, GABA, muscarinic, opioid,  $\alpha_1$ -adrenergic or  $\beta$ -adrenergic receptors. Although initially developed and marketed to enhance dopaminergic neurotransmission in PD, its pharmacologic effect in RSL is unknown. Its beneficial effect in FM is thought to be the result of enhanced D<sub>3</sub> mediated hippocampal dampening of autonomically induced fragmentation of stage IV, non-REM sleep.<sup>1</sup>
- **Fibromyalgia:** Investigational treatment of FM with pramipexole was first reported in 2000, and a subsequent successful open label, multicenter trial was published in 2004. In a 2005 trial, **pramipexole demonstrated the highest response rate of any FM trial to date** in terms of pain relief. Other outcomes, including fatigue, function and global assessments were also statistically improved in this single center, 14-week, double-blind, placebo controlled, fixed dose escalation study of 60 patients.<sup>2</sup>
- **Safety.** Extensive published reports of clinical trials with pramipexole indicate that it is well tolerated even in a high-risk elderly population with PD. In the FM trial, the primary adverse events were weight loss and transient, mild nausea.

## III. PATENT STATUS

- A patent describing this method of treating FM with pramipexole has been granted to Andrew J. Holman, MD in the US (2001), South Africa (2004), Singapore (2005), and Mexico (2005). Additional international applications are pending.
- Boehringer-Ingelheim holds the compound patent for pramipexole, which will expire in 2011.

## IV. LICENSING STRATEGY.

Inmedix seeks a partner to develop, market, and sell pramipexole on a worldwide basis for treatment of FM.

## V. Additional materials are available upon request. Please contact Tim Sciarrillo, CEO at [tim@inmedix.com](mailto:tim@inmedix.com) or 1-800-775-4902.

1. Wood PB. Fibromyalgia syndrome: a central role for the hippocampus- a theoretical construct. J Musculoskeletal Pain 2004;12(1):19-26.

2. Holman AJ, Myers RR. A randomized, double-blind, placebo controlled trial of pramipexole, a dopamine agonist, in patients with fibromyalgia receiving concomitant medications. Arthritis Rheum 2005;52(8):2495-2505.