

# Early West Nile Case May Bode Ill for Far West

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LOS ANGELES — The first human case of West Nile virus infection this year was diagnosed in Los Angeles in early February, perhaps setting the stage for an early and virulent season for the far western United States.

“Since West Nile virus was [first] detected in 1999, we’ve seen a lengthening period of transmission,” said Ned Hayes,

M.D., of the Centers for Disease Control and Prevention’s Division of Vector-Borne Infectious Diseases in Fort Collins, Colo.

As the virus has spread south and west across the United States, new “ecological dynamics” have influenced transmission patterns, he explained.

A wetter than normal winter in California and the Southwest may suit mosquitoes well, meaning physicians will need to be especially alert to possible cases of the now reportable disease.

The Los Angeles County Department of Health Services announced an infection in an older man in east Los Angeles County on Feb. 8. As of mid-February, state and federal health officials had not completed confirmatory tests on the case.

Symptoms of West Nile infection include fever, headache, fatigue, body aches, skin rash, and swollen lymph nodes.

More serious manifestations of West Nile encephalitis or meningitis include neck stiffness, stupor, disorientation, coma,

tremors, convulsions, muscle weakness, and a paralysis that can resemble polio.

“It doesn’t matter whether we’ve had one case or five; if you see encephalitis or meningitis, you look for West Nile virus,” said Laurence Mascola, M.D., chief of the acute communicable disease control unit of Los Angeles County.

The first bird carrying the virus was found in mid-January, whereas no bird evidence was confirmed in California until the end of March in 2004. Twelve birds in eight counties had been found to have the virus by mid-February. “It’s pretty much all up and down the state,” said Robert Miller, a spokesman for the California Department of Health Services in Sacramento.

Birds are an important player in the transmission cycle of West Nile virus and are carefully tracked, although mosquitoes are the direct vectors infecting humans.

California and the Southwest, where the

disease struck hardest in 2004, have warmer climates than the northeastern states, where the virus first took hold in the United States. Mosquito vectors also differ, with *Culex pipiens* most common in the Northeast and *C. tarsalis* and *C. quinquefasciatus* often the culprits in the West.

*C. tarsalis* was a common vector in Colorado, where West Nile virus infected almost 3,000 people in 2003, killing 63. “It’s a very efficient vector. It avidly bites humans and also bites birds, and it seems to transmit the virus very well.”

Dr. Hayes urged physicians to test for West Nile virus and report cases to their state health departments, which notify the CDC. “We have no way of knowing what’s happening [in terms of transmission patterns] unless practicing physicians report their cases,” he said in an interview.

A special online registry for physicians reporting pregnant patients infected with the virus has been established by the CDC at its Web site, www.cdc.gov. Additionally the CDC is organizing a voluntary birth outcome registry.

West Nile virus infected 2,470 people in 40 states in 2004, resulting in 88 deaths. The highest number of cases was in 2003, when 9,862 infections and 264 deaths were reported. States have been variably affected over time. For example, Nebraska had 1,942 cases in 2003 but just 49 in 2004.

Though some have speculated that disease patterns may reflect herd immunity, Dr. Hayes discounted that theory. He said that even in the most concentrated “hot zones,” antibodies have been detected in just 3%-5% of the population.

On the other hand, changes in weather, bird migration and infection patterns, mosquito abatement, and basic prevention strategies such as wearing mosquito repellent, may change human infection rates over time.

## MIRAPEX\* Tablets

brand of pramipexole dihydrochloride tablets

Brief Summary of Prescribing Information.

### INDICATIONS AND USAGE

Treatment of the signs and symptoms of idiopathic Parkinson’s disease.

### CONTRAINDICATIONS

Demonstrated hypersensitivity to the drug or its ingredients.

### WARNINGS

**Falling Asleep During Activities of Daily Living:** Patients treated with MIRAPEX have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on MIRAPEX, some perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as one year after the initiation of treatment. Somnolence is a common occurrence in patients receiving MIRAPEX at doses above 1.5 mg/day. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities. Before initiating treatment with MIRAPEX, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX, such as concomitant sedating medications, the presence of sleep disorders, and concomitant medications that increase pramipexole plasma levels (e.g., cimetidine—see PRECAUTIONS, Drug Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc.), MIRAPEX should be discontinued. If a decision is made to continue MIRAPEX, patients should be advised to not drive and to avoid other potentially dangerous activities. While dose reduction clearly reduces the degree of somnolence, there is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

**Symptomatic hypotension:** Carefully monitor Parkinson’s disease patients treated with dopaminergic agents for signs and symptoms of orthostatic hypotension, especially during dose escalation, and inform them of this risk (see PRECAUTIONS, Information for Patients). Despite clear orthostatic effects in normal volunteers, clinically significant orthostatic hypotension in clinical trials was not more frequent among those taking MIRAPEX Tablets than among those taking placebo. While this unexpected finding could reflect a unique property of pramipexole, it might also be due to study conditions and the nature of the clinical trial populations. Patients were carefully titrated, and those with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded.

**Hallucinations:** In three double-blind, placebo-controlled trials in early Parkinson’s disease, hallucinations were observed in 9% (35/388) of patients on MIRAPEX compared with 2.6% (6/235) of patients on placebo. In four double-blind, placebo-controlled trials in advanced Parkinson’s disease where patients received MIRAPEX and concomitant levodopa, hallucinations were observed in 16.5% (42/253) of patients on MIRAPEX compared with 3.8% (10/264) of patients on placebo. Hallucinations caused treatment discontinuation in 3.1% of early Parkinson’s disease patients and 2.7% of advanced Parkinson’s disease patients compared with about 0.4% of placebo patients in both populations. Age appears to increase the risk of hallucinations attributable to pramipexole. In early Parkinson’s disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients <65 years and 6.8 times greater than placebo in patients >65 years. In advanced Parkinson’s disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients <65 years and 5.2 times greater than placebo in patients >65 years.

### PRECAUTIONS

**Rhabdomyolysis:** A single case occurred in a 49-year-old man with advanced Parkinson’s disease treated with MIRAPEX Tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). Symptoms resolved with medication discontinuation.

**Renal:** Exercise caution when prescribing MIRAPEX to patients with renal insufficiency (see full Prescribing Information, DOSAGE AND ADMINISTRATION).

**Dyskinesia:** MIRAPEX may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Levodopa dose reduction may ameliorate this side effect.

**Retinal pathology in albino rats:** Pathologic changes (degeneration and loss of photoreceptor cells) were observed in the retina of albino rats in the 2-year carcinogenicity study. While retinal degeneration was not diagnosed in pigmented rats treated for 2 years, a thinning in the outer nuclear layer of the retina was slightly greater in rats given drug compared with controls. No similar changes were seen in albino mice, monkeys, and minipigs. The potential significance of this effect in humans has not been established but cannot be disregarded, because disruption of a mechanism that is universally present in vertebrates (i.e., disk shedding) may be involved (see full Prescribing Information, ANIMAL TOXICOLOGY).

### Events Reported With Dopaminergic Therapy

Although the events listed below have not been reported in pramipexole clinical trials, they are associated with the use of other dopaminergic drugs. The expected incidence of these events, however, is so low that even if pramipexole caused these events at rates similar to those attributable to other dopaminergic therapies, it would be unlikely that even a single case would have occurred in a cohort of the size exposed to pramipexole in studies to date.

**Withdrawal-emergent hyperreflexia and confusion:** A symptom complex resembling the neuroleptic malignant syndrome characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability, with no other obvious etiology, has been reported with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy.

**Fibrotic complications:** Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve with drug discontinuation, complete resolution does not always occur.

Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, nonergot-derived dopamine agonists can cause them is unknown.

**Information for patients:** Instruct patients to take MIRAPEX only as prescribed. Alert patients to the potential sedating effects associated with MIRAPEX, including somnolence and the possibility of falling asleep while engaged in activities of daily living. Since somnolence is a frequent adverse event with potentially serious consequences, patients should neither drive a car nor engage in other potentially dangerous activities until they have gained sufficient experience with MIRAPEX to gauge whether or not it affects their mental and/or motor performance adversely. Advise patients that if increased somnolence or new episodes of falling asleep during activities of daily living (e.g., watching television, passenger in a car, etc.) are experienced at any time during treatment, they should not drive or participate in potentially dangerous activities until they have contacted their physician.

Because of possible additive effects, caution should be advised when patients are taking other sedating medications or alcohol in combination with MIRAPEX and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine). Inform patients that hallucinations can occur and that the elderly are at a higher risk than younger patients. Patients may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, fainting or blackouts, and, sometimes, sweating. Hypotension may occur more frequently during initial therapy. Accordingly, caution patients against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment. Because the teratogenic potential of pramipexole is not completely established, and because experience in humans is limited, advise patients to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy). Because pramipexole may be excreted in breast milk, advise patients to notify their physicians if they intend to breast-feed or are breast-feeding an infant. Advise patients who develop nausea that taking MIRAPEX with food may reduce the occurrence of nausea.

**Laboratory tests:** During the development program, no systematic abnormalities on routine laboratory testing were noted. Therefore, no specific guidance is offered regarding routine monitoring; the practitioner retains responsibility for determining how best to monitor the patient.

### Drug Interactions

**Cardiopa/levodopa:** Cardiopa/levodopa did not influence pramipexole pharmacokinetics in healthy volunteers. Pramipexole did not alter the extent of absorption (AUC) or the elimination of cardiopa/levodopa, although it caused an increase in levodopa C<sub>max</sub> by about 40% and a decrease in T<sub>1/2</sub> from 2.5 to 0.5 hours.

**Sellepine:** Sellepine did not influence pramipexole pharmacokinetics in healthy volunteers.

**Amantadine:** Population pharmacokinetic analysis suggests that amantadine is unlikely to alter oral pramipexole clearance.

**Cimetidine:** Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, caused a 50% increase in pramipexole AUC and a 40% increase in half-life.

**Probenecid:** Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics.

**Other drugs eliminated via renal secretion:** Population pharmacokinetic analysis suggests that coadministration of drugs secreted by cationic transport (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinolone) decreases oral pramipexole clearance by about 20%, while those secreted by anionic transport (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpromazine) are likely to have little effect on oral pramipexole clearance.

**CYP interactions:** Cytochrome P450 enzyme inhibitors are not expected to affect pramipexole elimination, because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Studies indicate that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

**Dopamine antagonists:** Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of MIRAPEX. Drug/laboratory test interactions: No known interactions.

**Carcinogenesis, mutagenesis, fertility impairment:** Two-year pramipexole carcinogenicity studies were conducted in mice and rats. Pramipexole was fed to C57BL/6J mice at doses 0.3, 2.2, and 11 times the highest recommended human dose (1.5 mg tid) on a mg/m<sup>2</sup> basis and to Wistar rats at doses resulting in plasma AUCs equal to 0.3, 2.5, and 12.5 times the AUC in humans receiving 1.5 mg tid. No significant increases in tumors occurred in either species. Pramipexole was not mutagenic or clastogenic in the *in vitro* Ames assay, V79 gene mutation assay for HGPRT mutants, chromosomal aberration assay in Chinese hamster ovary cells, and *in vivo* mouse micronucleus assay. In rat fertility studies, a pramipexole dose 5.4 times the highest human dose on a mg/m<sup>2</sup> basis prolonged estrus cycles and inhibited implantation. These effects were associated with reduced serum prolactin levels, a hormone necessary for implantation and maintenance of early pregnancy in rats.

**Pregnancy:** Pregnancy Category C. Pramipexole given to female rats throughout pregnancy inhibited implantation at a dose 5.4 times the highest human dose on a mg/m<sup>2</sup> basis. Pregnant rats given pramipexole during the period of organogenesis (gestation days 7 through 16) at a dose resulting in a plasma AUC 4.3 times the AUC in humans receiving 1.5 mg tid resulted in a high incidence of total resorption of embryos. These findings are probably due to pramipexole’s prolactin-lowering effect, since prolactin is necessary for implantation and maintenance of early pregnancy in rats (but not rabbits or humans). Because of pregnancy disruption and early embryonic loss in these studies, pramipexole’s teratogenic potential could not be adequately evaluated. In pregnant rabbits given pramipexole during organogenesis, there was no evidence of adverse effects on embryo-fetal development following administration of doses resulting in a plasma AUC 7.1 times the AUC in humans receiving 1.5 mg tid. Postnatal growth was inhibited in the offspring of rats treated with a dose approximately equivalent to the highest human dose on a mg/m<sup>2</sup> basis or greater during latter pregnancy and throughout lactation. Pramipexole was not studied in human pregnancy. Because animal reproduction studies are not always predictive of human response, use pramipexole during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

**Nursing mothers:** A single-dose, radio-labeled study showed that drug-related materials were excreted into breast milk of lactating rats. Radioactivity concentrations in milk were three to six times higher than plasma concentrations at equivalent time points. Other studies have shown that pramipexole inhibits prolactin secretion in humans and rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because pramipexole may cause potentially serious adverse reactions in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

**Geriatric use:** Pramipexole total oral clearance was approximately 30% lower in subjects >65 years compared with younger subjects because of a decline in pramipexole renal clearance due to an age-related reduction in renal function. This resulted in an increase in elimination half-life from approximately 8.5 hours to 12 hours. In clinical studies, 38.7% of patients were >65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the risk of hallucination associated with MIRAPEX was increased in the elderly.

### ADVERSE REACTIONS

Patients with either early or advanced Parkinson’s disease were enrolled in clinical trials. Apart from disease severity and duration, the two populations differed in use of concomitant levodopa. Patients with advanced disease did not receive concomitant levodopa during treatment with pramipexole; those with advanced Parkinson’s disease all received concomitant levodopa. Because these two populations may have differential risks for various adverse events, data are presented separately by population. Because all premarketing controlled trials used a titration design, confounding time and dose, it is impossible to adequately evaluate effects of dose on incidence of adverse events.

#### Early Parkinson’s Disease

In three double-blind, placebo-controlled trials of patients with early Parkinson’s disease, the most commonly observed adverse events (≥5%) were more frequent in the group treated with MIRAPEX Tablets than placebo: nausea, dizziness, somnolence, insomnia, constipation, and hallucinations. In double-blind, placebo-controlled trials, approximately 12% of 388 patients treated with MIRAPEX discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. Adverse events most commonly causing discontinuation for MIRAPEX and placebo, respectively, were hallucinations (3.1% vs 0.4%), dizziness (2.1% vs 1%), somnolence (1.6% vs 0%), extrapyramidal syndrome (1.6% vs 6.4%), headache (1.3% vs 0%), confusion (1.0% vs 0%), and nausea (2.1% vs 0.4%).

**Adverse-event incidence in controlled clinical studies in early Parkinson’s disease:** Table 1 lists treatment-emergent adverse events (≥5%) that were more frequent in the group treated with MIRAPEX than placebo. The incidence of these events was generally similar to that reported in the placebo group. Adverse-event intensity was usually mild or moderate. These figures cannot be used to predict adverse-event incidence in usual medical practice where patient characteristics and other factors differ from those in clinical studies. Similarly, the cited figures do not compare with figures obtained from other clinical investigations. However, the cited figures do provide some basis for estimating the relative contribution of drug and nongroup factors to the adverse-event incidence rate in the population studied.

Table 1.—Treatment-Emergent Adverse-Event\* Incidence in Double-Blind, Placebo-Controlled Trials in Early Parkinson’s Disease (Events ≥1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	MIRAPEX N=388	Placebo N=235	Body System/Adverse Event	MIRAPEX N=388	Placebo N=235
Body as a Whole			Nervous System		
Asthenia	14	12	Dizziness	25	24
General edema	5	3	Somnolence	22	9
Malaise	2	1	Insomnia	17	12
Reaction unevaluable	2	1	Hallucinations	9	3
Fever	1	0	Confusion	4	1
Digestive System			Anorexia	4	2
Nausea	28	18	Hyposthesia	3	1
Constipation	14	6	Dystonia	2	1
Anorexia	4	2	Thinking abnormalities	2	0
Dysphagia	2	0	Decreased libido	1	0
			Mycoduria	1	0
Metabolic & Nutritional System			Special Senses		
Peripheral edema	5	4	Visual abnormalities	3	0
Decreased weight	2	0	Urogenital System		
			Impotence	2	1

\*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

Other events reported by ≥1% of patients treated with MIRAPEX but reported equally or more frequently in the placebo group were infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertension, depression, abdominal pain, anxiety, dyspepsia, flatulence, diarrhea, rash, ataxia, dry mouth, extrapyramidal syndrome, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gag abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, parosmia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions. In a fixed-dose study in early Parkinson’s disease, occurrence of the following events increased in frequency as the dose increased over the range from 1.5 mg/day to 6 mg/day: postural hypotension, nausea, constipation, somnolence, and anorexia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg/day. The incidence of somnolence with pramipexole at a dose of 1.5 mg/day was comparable to that reported for placebo.

#### Advanced Parkinson’s Disease

In four double-blind, placebo-controlled trials of patients with advanced Parkinson’s disease, the most commonly observed adverse events (≥5%) that were more frequent in the group treated with MIRAPEX and concomitant levodopa were postural (orthostatic) hypotension, dyskinesia, extrapyramidal syndrome, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, confusion, constipation, asthenia, somnolence, dystonia, gag abnormalities, hypertension, dry mouth, anorexia, and urinary frequency. Approximately 12% of 260 patients with advanced Parkinson’s disease who received MIRAPEX and concomitant levodopa in double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 264 patients who received placebo and concomitant levodopa. Events most commonly causing treatment discontinuation for MIRAPEX and placebo, respectively, were hallucinations (1.7% vs 0.4%), dyskinesia (1.9% vs 0.8%), extrapyramidal syndrome (1.5% vs 4.9%), dizziness (1.2% vs 1.5%), confusion (1.2% vs 2.3%), and postural (orthostatic) hypotension (2.3% vs 1.1%).

**Adverse-event incidence in controlled clinical studies in advanced Parkinson’s disease:** Table 2 lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies that were reported by ≥1% of patients treated with MIRAPEX and were more frequent than in the placebo group. In these studies, MIRAPEX or placebo was administered to patients who were also receiving concomitant levodopa. Adverse-event intensity was usually mild or moderate. These figures cannot be used to predict adverse-event incidence in usual medical practice where patient characteristics and other factors differ from those in clinical studies. Similarly, the cited figures do not compare with figures obtained from other clinical investigations. However, the cited figures do provide some basis for estimating the relative contribution of drug and nongroup factors to the adverse-event incidence rate in the population studied.

Table 2.—Treatment-Emergent Adverse-Event\* Incidence in Double-Blind, Placebo-Controlled Trials in Advanced Parkinson’s Disease (Events ≥1% of Patients Treated With MIRAPEX and Numerically More Frequent Than in the Placebo Group)

Body System/Adverse Event	MIRAPEX N=260	Placebo N=264	Body System/Adverse Event	MIRAPEX N=260	Placebo N=264
Body as a Whole			Nervous System (cont)		
Accidental injury	17	15	Somnolence	9	6
Asthenia	10	8	Dystonia	8	7
General edema	4	3	Gag abnormalities	7	5
Chest pain	3	2	Hypertonia	7	6
Malaise	3	2	Anorexia	6	4
Cardiovascular System			Weight loss	3	2
Postural hypotension	53	49	Thinking abnormalities	3	2
			Paranoid reaction	2	0
Digestive System			Delusions	1	0
Constipation	10	9	Sleep disorders	1	0
Dry mouth	7	3			
Metabolic & Nutritional System			Respiratory System		
Peripheral edema	2	1	Dyspnea	4	3
Increased creatine PK	1	0	Rhinitis	3	1
			Pneumonia	2	0
Musculoskeletal System			Skin & Appendages		
Arthritis	3	1	Skin disorders	2	1
Twitching	2	0			
Bursitis	2	0	Special Senses		
Myasthenia	1	0	Accommodation abnormalities	4	2
			Vision abnormalities	3	1
Nervous System			Diplopia	1	0
Dyskinesia	47	31	Urogenital System		
Extrapyramidal syndrome	28	26	Urinary frequency	6	3
Insomnia	27	22	Urinary tract infection	4	3
Dizziness	26	25	Urinary incontinence	2	1
Hallucinations	17	4			
Dream abnormalities	11	7			
Confusion	10	7			

\*Patients may have reported multiple adverse experiences during the study or at discontinuation; thus, patients may be included in more than one category.

†Patients received concomitant levodopa.

Other events reported by ≥1% of patients treated with MIRAPEX but reported equally or more frequently in the placebo group were nausea, pain, infection, headache, depression, tremor, hypokinesia, anorexia, back pain, dyspepsia, flatulence, ataxia, flu syndrome, sinusitis, diarrhea, myalgia, abdominal pain, anxiety, rash, parosmia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hypersomnia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation disorders.

**Adverse events—relationship to age, gender, and race:** Among the treatment-emergent adverse events in patients treated with MIRAPEX, hallucination appeared to exhibit a positive relationship to age. No gender-related differences were observed. An evaluation of adverse events related to race was not possible (only 4% non-Caucasian enrollees).

**Other adverse events observed during all phase 2 and 3 clinical trials:** 1,408 individuals received MIRAPEX during all clinical trials (Parkinson’s disease and other patient populations), 648 of whom were in seven double-blind, placebo-controlled Parkinson’s disease trials. During these trials, all adverse events were recorded by the clinical investigators using their own terminology. Listed below are similar types of events, grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These events occurred in <1% of the 1,408 individuals exposed to MIRAPEX and occurred on at least two occasions (one if the event was serious). All reported events, except those already listed above, are included without regard to determination of a causal relationship to MIRAPEX. Events are listed within body-system categories in order of decreasing frequency.

**Body as a Whole:** enlarged abdomen, death, fever, and suicide attempt. **Cardiovascular System:** peripheral vascular disease, myocardial infarction, angina pectoris, atrial fibrillation, heart failure, arrhythmia, atrial arrhythmia, and pulmonary embolism. **Digestive System:** thirst.

**Musculoskeletal System:** joint disorder and myasthenia. **Nervous System:** agitation, CNS stimulation, hyperkinesia, psychosis, and convulsions. **Respiratory System:** pneumonia. **Special Senses:** cataract, eye disorder, and glaucoma. **Urogenital System:** dysuria, abnormal ejaculation, prostate cancer, hematuria, and prostate disorder. **Falling Asleep During Activities of Daily Living:** Patients treated with MIRAPEX have reported falling asleep while engaged in activities of daily living, including operation of a motor vehicle, which sometimes resulted in accidents (see boxed WARNING). **Post-Marketing Experience:** In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified during post-approval use of MIRAPEX Tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction; (2) frequency of reporting; or (3) strength of causal connection to MIRAPEX Tablets. Similar types of events were grouped into a smaller number of standardized categories using the MedDRA dictionary: accidents (including fall), compulsive behaviors (including sexual and pathological gambling), fatigue, hallucinations (all kind), headache, hypertension (including postural hypertension), libido disorders, syncope, and blackouts.

### DRUG ABUSE AND DEPENDENCE

Pramipexole is not a controlled substance. Although not systematically studied for abuse, tolerance, or physical dependence potential, pramipexole had little or no effect in a rat model of cocaine self-administration.

### OVERDOSAGE

There is no clinical experience with massive overdosage. No adverse events were reported when one patient took 11 mg/day of pramipexole for 2 days, twice to three times the protocol recommended daily dose). Blood pressure remained stable, although pulse rate increased to between 100 and 120 beats/minute. The patient withdrew from the study at the end of week 2 due to lack of efficacy. There is no known antidote for dopamine agonist overdosage. If signs of CNS stimulation are present