

# Rising Premiums Found to Shrink Medicaid Rolls

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Senior Writer

NASHVILLE, TENN. — Proposals to increase cost sharing for Medicaid beneficiaries could reduce enrollment in the program, according to the preliminary results of a study presented at the annual conference of the National Academy for State Health Policy.

Genevieve Kenney, principal research associate at The Urban Institute, and her col-

leagues examined the impact of increases in premiums in the State Children's Health Insurance Program (SCHIP) as a way to inform policy changes under Medicaid.

More than 30 states have premiums for some children whose incomes are above the federal poverty level. No existing Medicaid program charges premiums for children below poverty, Ms. Kenney said.

However, proposals, such as one from the National Governors' Association, would permit states to charge up to \$480

annually per child to low-income families.

The research, which was funded by the David and Lucile Packard Foundation, looked at enrollment and disenrollment patterns in three states that increased premiums in 2003—Kansas, Kentucky, and New Hampshire.

SCHIP officials in Kansas increased premiums from \$10 to \$30 per family in February 2003 for families between 151% and 175% of the federal poverty level. The state then decreased the premiums to \$20

in July 2003. For families between 176% and 200% of poverty, the premium was increased from \$15 to \$45 and then decreased to \$30.

The total caseload growth rate 6 months before the premium increase in Kansas was 14.6%. Six months after the increase the growth rate had fallen to -4.2%, Ms. Kenney reported. Although there was an initial drop in enrollment, the caseload picked up over time, and there has been healthy growth, she said.

The results were similar in New Hampshire where SCHIP officials increased the premiums from \$20 to \$25 per child in January 2003 for families between 185% and 249% of poverty. For families between 250% and 300% of poverty, the premium was increased from \$40 to \$45.

But in Kentucky, which instituted a premium for the first time, the decline in caseload was more dramatic. Officials there initiated a \$20 premium for families between 151% and 200% of poverty in December 2003. Six months before the change, the total caseload growth rate was -0.2%. Six months after the new premium was instituted, the growth rate fell to -17.4%. The premium increases there also had a stronger disenrollment effect than in the other two states.

These findings add to a growing body of evidence that increased premiums appear to reduce enrollment and increase disenrollment, Ms. Kenney said, though the impact is different among subgroups.

The largest effects were among new premiums as imposed, especially on lower-income beneficiaries, Ms. Kenney said. ■

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**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 acute participation (e.g., conversations, eating, etc.), MIRAPEX should ordinarily 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 agonists 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, and although orthostatic hypotension in clinical trials was not more frequent among those taking MIRAPEX Tablets than among those taking placebo, 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% (9/235) 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% (43/260) 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 6.0 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). **DOSE AND ADMINISTRATION**

**Dyskinesia:** MIRAPEX may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Levodopa dose reduction may alleviate 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. No retinal changes were seen in albino mice, monkeys, and dogs. 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 hyperpyrexia 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 pramipexole. The risk of 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, nonergoline-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 has not been observed in patients 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**  
**Carbidopa/levodopa:** Carbidopa/levodopa did not influence pramipexole pharmacokinetics in healthy volunteers. Pramipexole did not alter the extent of absorption (AUC) or the elimination of carbidopa/levodopa, although it caused an increase in levodopa  $C_{max}$  by about 40% and a decrease in  $T_{max}$  from 2.5 to 0.5 hours.

**Sedation:** Sedation 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 quinone) decreases oral pramipexole clearance by about 20%, while those secreted by anionic transport (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) 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 *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 later 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 taken 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.

**Pediatric use:** Safety and efficacy have not been established.

**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 6.5 hours to 12 hours. In clinical studies, 38.2% of patients were ≥65 years. There were no apparent differences in efficacy or safety between older and younger patients, except that the relative risk of hallucinations 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 early 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%) that were more frequent in the group treated with MIRAPEX were nausea, dizziness, somnolence, insomnia, constipation, asthenia, 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 in patients with early Parkinson's disease.

By 21% of patients treated with MIRAPEX and were more frequent than 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 frequencies cannot be compared with figures obtained from other clinical investigations. However, the cited figures do provide some basis for estimating the relative contribution of drug and nongdrug 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 in 21% 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 (cont)		
Asthenia	14	12	Dizziness	25	24
General edema	5	3	Somnolence	22	9
Melasma	2	1	Insomnia	17	12
Reaction unlabelable	2	1	Hallucinations	9	3
Fever	1	0	Confusion	4	1
			Amnesia	4	2
Digestive System			Dysphagia	2	1
Nausea	28	18	Hypertension	2	0
Constipation	14	6	Alkathisia	2	1
Anorexia	4	2	Thinking abnormalities	2	0
Dysphagia	2	0	Decreased libido	1	0
			Myoclonus	1	0
Metabolic & Nutritional System			Special Senses		
Peripheral edema	5	4	Vision 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 disorder, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritus, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tremor, diplopia, and taste perversion. 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 tid to 6 mg tid: postural hypotension, nausea, constipation, somnolence, and amnesia. The frequency of these events was generally 2-fold greater than placebo for pramipexole doses greater than 3 mg tid. 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, gait abnormality, hypertension, dry mouth, amnesia, 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 16% of 264 patients who received placebo and concomitant levodopa. Events most commonly causing treatment discontinuation for MIRAPEX and placebo, respectively, were hallucinations (2.7% 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 frequencies cannot be compared with figures obtained from other clinical investigations. However, the cited figures do provide some basis for estimating the relative contribution of drug and nongdrug 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 in 21% 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	7	7
General edema	4	3	Gait abnormalities	7	5
Chest pain	3	2	Hypertonia	7	6
Melasma	3	2	Amnesia	6	4
			Alkathisia	3	2
Cardiovascular System			Thinking abnormalities	3	2
Postural hypotension	53	49	Paranoid reaction	2	0
			Delusions	1	0
Digestive System			Sleep disorders	1	0
Constipation	10	9			
Dry mouth	7	3	Respiratory System		
			Dyspnea	4	3
Metabolic & Nutritional System			Rhinitis	3	1
Peripheral edema	2	1	Pneumonia	2	0
Increased creatine PK	1	0			
			Skin & Appendages		
Musculoskeletal System			Skin disorders	2	1
Arthritis	3	1			
Twitching	2	0	Special Senses		
Buritis	2	0	Accommodation abnormalities	4	2
Myasthenia	1	0	Vision abnormalities	3	1
			Diplopia	1	0
Nervous System			Urogenital System		
Dyskinesia	47	31	Urinary frequency	6	3
Extrapyramidal syndrome	28	26	Urinary tract infection	4	3
Insomnia	27	22	Urinary incontinence	2	1
Dizziness	26	25			
Hallucinations	17	4			
Dream abnormalities	11	10			
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, paresthesia, hypertension, increased saliva, tooth disorder, apathy, hypotension, sweating, vasodilation, vomiting, increased cough, nervousness, pruritus, hyposthesia, 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 clinical trials in early 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:** color blindness, eye pain, and glaucoma. **Urogenital System:** urinary tract infection.

**Other events:** 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 reactions 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 kinds), headache, hypotension (including postural and orthostatic), libido disorders, syncope, and tachycardia.

**DRUG**