

Studies Finally Link Tanning Beds to Melanoma

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VANCOUVER, B.C. — Two new studies presented at the Sixth World Congress on Melanoma have linked tanning bed use and melanoma.

“The year 2005 sees the first real, indisputable evidence that tanning bed use contributes to melanoma risk,” said Philippe Autier, M.D., of the Jules Bordet Institute, Brussels, the chair of the session

at which the studies were presented.

The larger of the two studies looked at tanning bed use by 106,000 Scandinavian women enrolled in a lifestyle study in the early 1990s, part of which involved a survey in which they were asked if they used tanning equipment, when, and for how long.

When the survey was repeated with a portion of the subjects 5 years after the initial one, the answers of 79% of surveys agreed completely with how the subjects

had answered before, and 96% had a high, but not exact, agreement, which suggested that the reports were very accurate, said Marit Bragelien Veierød, Ph.D., of the department of biostatistics at the University of Oslo.

With the data broken into age groups by decade, those in the 20- to 29-year age group who used tanning equipment one or more times a month had a 57% higher relative risk of melanoma, those in the 30- to 39-year age group had a 44% in-

creased risk, and those in the 40- to 49-year age group had a 69% higher risk.

By comparing all those who reported having ever used tanning equipment with those who had never used it, the study showed that there was an increased relative risk of 33% associated with tanning equipment.

In the second study, investigators compared tanning equipment use in subjects enrolled in the international Genes, Environment, and Melanoma Study who had single primary melanomas (406 cases) with those who had multiple primary melanomas (125 cases).

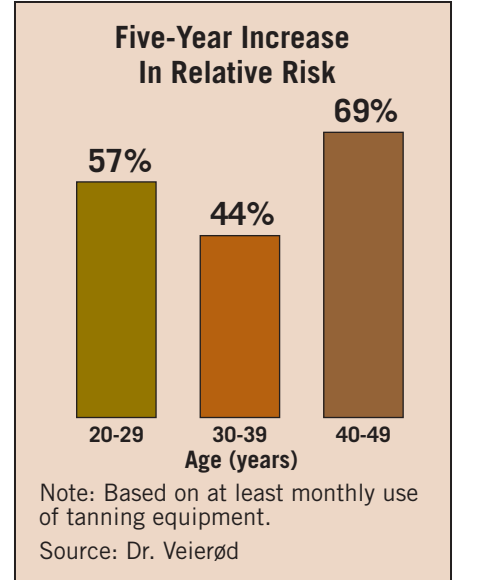
Overall, 29% of the subjects had used tanning equipment, and the mean age at initial diagnosis of melanoma in those who had used it was 10 years younger than it was those who had never used it, said Maria Chiu, of Cancer Care Ontario, in Toronto.

When adjusted for age and sex, the data indicated that tanning equipment use was associated with a higher risk of multiple melanomas, with an odds ratio of 1.68.

For those in the highest quartile of frequency of use, the odds ratio was 1.87. For those whose first exposure was before age 20 years, the odds ratio was 2.63, Ms. Chiu said.

The data indicate a strong dose response to tanning equipment use, Ms. Chiu added.

Previous studies in which investigators had attempted to associate tanning bed use with melanoma were generally inconclusive, probably because they tended to be too small to determine statistical power, the investigators and others said at the meeting.



VERBATIM

“Many of my insomniac patients tell me proudly that they aren’t using caffeine, when a good cup in the morning may be just what they need.”

Dr. Milton Erman, p. 74

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 they were not 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 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, it was not observed in clinical trials and 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% (6/235) 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 appeared 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).

DOSE 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 compared with controls. No changes were seen in albino mice, monkeys, and humans. The potential significance of this effect in human patients, the extent of which 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.

Fatolic 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
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.

Selenazine: Selenazine 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 quinine) decreases oral pramipexole clearance by about 20%, while those secreted by anionic transport (e.g., cephazolin, penicillin, 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/d).

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/d] on a mg/m² 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/d. 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/m² 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: Category C. Pramipexole given to female rats throughout pregnancy inhibited implantation at a dose 5.4 times the highest human dose on a mg/m² 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/d 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/d. Postnatal growth was inhibited in the offspring of rats treated with a dose approximately equivalent to the highest human dose on a mg/m² basis or greater during lactation 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 benefits 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.

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, 38.7% 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 hallucination associated with MIRAPEX was increased in the elderly.

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
Asthma	10	8	Dystonia	8	7
General edema	4	3	Gait abnormalities	7	5
Chest pain	3	2	Hypertonia	7	6
Melaise	3	2	Annesia	6	4
Cardiovascular System			Akathisia	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	0	Skin disorders	2	1
Twitching	2	0			
Burials	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 incontinence	4	3
Dizziness	26	25	Urinary incontinence	2	1
Hallucinations	17	4			
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 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:** conjunctivitis and glaucoma. **Urogenital System:** urinary frequency and urinary incontinence. **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, hypotension (including postural and orthostatic), fluid disorders, syncope, and arthralgia.

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
Melaise	2	1	Dystonia	17	12
Reaction unevaluable	2	1	Hallucinations	9	3
Fever	1	0	Confusion	4	1
Digestive System			Annesia	4	2
Nausea	26	18	Hyposthesia	2	1
Constipation	14	6	Dyspnea	2	0
Anorexia	4	2	Akathisia	2	0
Dysphagia	2	0	Thinking abnormalities	2	0
			Decreased libido	1	0
Metabolic & Nutritional System			Myoglobin	1	0
Peripheral edema	5	4	Special Senses		
Decreased weight	2	0	Vision abnormalities	3	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 sensations. 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 amnesia. 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, 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%), 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 nondrug factors to the adverse-event incidence rate in the population studied.

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 of pramipexole for 2 days (two 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 pramipexole overdosage. If signs of CNS stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; but efficacy in reversing overdosage effects has not been assessed. General supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring may be required.

DOSE AND ADMINISTRATION
In all clinical studies, dosage was initiated at a subtherapeutic level to avoid intolerable adverse effects and orthostatic hypotension. Gradually titrate dosage in all patients. Increase dosage to achieve a response/therapeutic effect, balanced against the principal side effects of dyskinesia, hallucinations, somnolence, and dry mouth.

Dosing in Patients With Normal Renal Function
Initial treatment: Increase dosage gradually, i.e., not more frequently than every 5 to 7 days, from a starting dose of 0.375 mg/day given in three divided doses. Refer to full Prescribing Information for the suggested ascending dosage schedule that was used in clinical studies.

Maintenance treatment: MIRAPEX Tablets were 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). In a fixed-dose study in early Parkinson’s disease patients, doses of 3 mg, 4.5 mg, and 6 mg per day of MIRAPEX were not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day. However, in the same fixed-dose study, the following adverse events were dose related: 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/day. The incidence of somnolence reported with pramipexole at a dose of 1.5 mg/day was comparable to placebo. Consider reducing levodopa dosage when MIRAPEX is used in combination. In a controlled study in advanced Parkinson’s disease, levodopa dosage was reduced by an average of 27% from baseline.

Patients with renal impairment: Dosage adjustments are recommended for patients with moderate to severe impairment (see full Prescribing Information, **DOSE AND ADMINISTRATION**). The use of MIRAPEX has not been studied in patients with severe impairment.

Treatment discontinuation: Discontinue MIRAPEX over a period of 1 week; in some studies, however, abrupt discontinuation was uneventful.

Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature]. Protect from light.

Store in a safe place out of the reach of children.

Rx only

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