

Herceptin Approved for Early-Stage Breast Cancer

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The Food and Drug Administration granted expanded approval to the drug Herceptin. The biologic therapy was approved for use as an adjuvant in combination with doxorubicin, cyclophosphamide, and paclitaxel for treatment of early HER-2 node-positive breast cancer.

Herceptin (trastuzumab), manufactured by Genentech Inc., was first approved by the

FDA in 1998 for metastatic breast cancer. The latest approval is based on results from two phase III studies led by the National Surgical Adjuvant Breast and Bowel Project and the North Central Cancer Treatment Group, in collaboration with several National Cancer Institute cooperative groups.

In those studies, 87% of women treated with Herceptin plus the other chemotherapeutics were disease free after 3.5 years, compared with 71% of those treated with the combination minus Her-

ceptin (N. Engl. J. Med. 2005;353:1673-84).

"For women with early-stage HER-2-positive breast cancer, the addition of Herceptin to chemotherapy reduces the relative risk of breast cancer recurrence by approximately half," Dr. Edward Romond, a professor of medicine in hematology/oncology at the University of Kentucky, Lexington, said in a statement provided by Genentech.

About 212,000 women in the United States will be diagnosed with breast can-

cer this year. Of those, 25% percent will have HER-2-positive disease.

The approval "is especially good news for women who have breast cancer caused by excessive amounts of HER-2 protein because this cancer typically has a poor prognosis," Dr. Steven Galson, director of the FDA's Center for Drug Evaluation and Research, said in a statement.

Genentech markets Herceptin in the United States. Roche has licensed Herceptin outside of the United States. ■

Mirapex® (pramipexole dihydrochloride)

0.125 mg, 0.25 mg, 0.5 mg, 1 mg, and 1.5 mg tablets

INDICATIONS AND USAGE

Parkinson's Disease: MIRAPEX tablets are indicated for the treatment of the signs and symptoms of idiopathic Parkinson's disease.

Restless Legs Syndrome: MIRAPEX tablets are indicated for the treatment of moderate-to-severe primary Restless Legs Syndrome (RLS).

CONTRAINDICATIONS: MIRAPEX tablets are contraindicated in patients who have demonstrated hypersensitivity to the drug or its ingredients.

WARNINGS: Falling Asleep During Activities of Daily Living

Patients treated with Mirapex® (pramipexole dihydrochloride) 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 tablets, 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 had been reported as late as one year after the initiation of treatment.

Somnolence is a common occurrence in patients receiving MIRAPEX tablets at doses above 1.5 mg/day (0.5 mg TID) for Parkinson's disease. In controlled clinical trials in RLS, patients treated with MIRAPEX tablets at doses of 0.25-0.75 mg once a day, the incidence of somnolence was 6% compared to an incidence of 3% for placebo-treated patients (see ADVERSE EVENTS). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing 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 tablets, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with MIRAPEX tablets 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 tablets should ordinarily be discontinued. If a decision is made to continue MIRAPEX tablets, 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: Dopamine agonists, in clinical studies and clinical experience, appear to impair the systemic regulation of blood pressure, with resulting orthostatic hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to an orthostatic challenge. For these reasons, both Parkinson's disease patients and RLS patients being treated with dopaminergic agonists ordinarily require careful monitoring for signs and symptoms of orthostatic hypotension, especially during dose escalation, and should be informed of this risk (see PRECAUTIONS, Information for Patients).

In clinical trials of pramipexole, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to Mirapex® (pramipexole dihydrochloride) tablets than among those assigned to placebo. This result, especially with the higher doses used in Parkinson's disease, is clearly unexpected in light of the previous experience with the risks of dopamine agonist therapy. While this finding could reflect a unique property of pramipexole, it might also be explained by the conditions of the study and the nature of the population enrolled in the clinical trials. Patients were very carefully titrated, and patients with active cardiovascular disease or significant orthostatic hypotension at baseline were excluded. Also, clinical trials in patients with RLS did not incorporate orthostatic challenges with intensive blood pressure monitoring done in close temporal proximity to dosing.

Hallucinations: In the three double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving MIRAPEX tablets, compared with 2.6% (6 of 235) of patients receiving placebo. In the four double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received MIRAPEX tablets and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving MIRAPEX tablets compared with 3.8% (10 of 264) of patients receiving placebo. Hallucinations were of sufficient severity to cause discontinuation of treatment in 3.1% of the early Parkinson's disease patients and 2.7% of the 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 the early Parkinson's disease patients, the risk of hallucinations was 1.9 times greater than placebo in patients younger than 65 years and 6.8 times greater than placebo in patients older than 65 years. In the advanced Parkinson's disease patients, the risk of hallucinations was 3.5 times greater than placebo in patients younger than 65 years and 5.2 times greater than placebo in patients older than 65 years.

In the RLS clinical program, one pramipexole-treated patient (of 889) reported hallucinations; this patient discontinued treatment and the symptoms resolved.

PRECAUTIONS

Rhabdomyolysis: A single case of rhabdomyolysis occurred in a 49-year-old male with advanced Parkinson's disease treated with MIRAPEX tablets. The patient was hospitalized with an elevated CPK (10,631 IU/L). The symptoms resolved with discontinuation of the medication. **Renal:** Since pramipexole is eliminated through the kidneys, caution should be exercised when prescribing Mirapex® (pramipexole dihydrochloride) tablets to patients with renal insufficiency (see DOSAGE AND ADMINISTRATION in full Prescribing Information). **Dyskinesia:** MIRAPEX tablets may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate preexisting dyskinesia. Decreasing the dose of levodopa 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. Evaluation of the retinas of albino mice, monkeys, and minipigs did not reveal similar changes. 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 ANIMAL TOXICOLOGY).

Events Reported with Dopaminergic Therapy: Although the events enumerated below may not have been reported in association with the use of pramipexole in its development program, 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:** Although not reported with pramipexole in the clinical development program, 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 in association with rapid dose reduction, withdrawal of, or changes in antiparkinsonian therapy. **Fibrotic Complications:** Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, and pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agonists. While these complications may resolve when the drug is discontinued, 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.

A small number of reports have been received of possible fibrotic complications, including peritoneal fibrosis, pleural fibrosis, and pulmonary fibrosis in the post-marketing experience for Mirapex® (pramipexole dihydrochloride) tablets. While the evidence is not sufficient to establish a causal relationship between MIRAPEX tablets and these fibrotic complications, a contribution of MIRAPEX tablets cannot be completely ruled out in rare cases. **Melanoma:** Some epidemiologic studies have shown that patients with Parkinson's disease have a higher risk (perhaps 2- to 4-fold higher) of developing melanoma than the general population. Whether the observed increased risk was due to Parkinson's disease or other factors, such as drugs used to treat Parkinson's disease, was unclear. MIRAPEX tablets are one of the dopamine agonists used to treat Parkinson's disease. Although MIRAPEX tablets have not been associated with an increased risk of melanoma specifically, its potential role as a risk factor has not been systematically studied. Patients using MIRAPEX tablets for any indication should be made aware of these results and should undergo periodic dermatologic screening.

Impulse Control/Compulsive Behaviors: Cases of pathological gambling, hypersexuality, and compulsive eating (including binge eating) have been reported in patients treated with dopamine agonist therapy, including pramipexole therapy. As described in the literature, such behaviors are generally reversible upon dose reduction or treatment discontinuation.

Rebound and Augmentation in RLS: Reports in the literature indicate treatment of RLS with dopaminergic medications can result in a shifting of symptoms to the early morning hours, referred to as rebound. Rebound was not reported in the clinical trials of MIRAPEX tablets but the trials were generally not of sufficient duration to capture this phenomenon. Augmentation has also been described during therapy for RLS. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. In a controlled trial of MIRAPEX tablets for RLS, approximately 20% of both the Mirapex- and placebo-treated patients reported at least a 2-hour earlier onset of symptoms during the day by the end of 3 months of treatment. The frequency and severity of augmentation and/or rebound after longer-term use of MIRAPEX tablets and the appropriate management of these events have not been adequately evaluated in controlled clinical trials.

Information for Patients (also see Patient Package Insert): Patients should be instructed to take MIRAPEX tablets only as prescribed.

Patients should be alerted to the potential sedating effects associated with MIRAPEX tablets, 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® (pramipexole dihydrochloride) tablets to gauge whether or not it affects their mental and/or motor performance adversely. Patients should be advised that if increased

Brief Summary of Prescribing Information

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 tablets and when taking concomitant medications that increase plasma levels of pramipexole (e.g., cimetidine).

Patients should be informed that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease. In clinical trials, patients with RLS treated with pramipexole rarely reported hallucinations.

Patients and caregivers should be informed that impulse control disorders/compulsive behaviors may occur while taking medicines to treat Parkinson's disease or RLS, including MIRAPEX tablets. These include pathological gambling, hypersexuality, and compulsive eating (including binge eating). If such behaviors are observed with MIRAPEX tablets, dose reduction or treatment discontinuation should be considered.

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, patients should be cautioned 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 with MIRAPEX tablets.

Because the teratogenic potential of pramipexole has not been completely established in laboratory animals, and because experience in humans is limited, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy (see PRECAUTIONS, Pregnancy).

Because of the possibility that pramipexole may be excreted in breast milk, patients should be advised to notify their physicians if they intend to breast-feed or are breast-feeding an infant.

If patients develop nausea, they should be advised that taking MIRAPEX tablets with food may reduce the occurrence of nausea.

Laboratory Tests: During the development of MIRAPEX tablets, 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 in his or her care.

Drug Interactions: *Carbidopa/levodopa:* Carbidopa/levodopa did not influence the pharmacokinetics of pramipexole in healthy volunteers (N=10). 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. *Selegiline:* In healthy volunteers (N=11), selegiline did not influence the pharmacokinetics of pramipexole. *Amantadine:* Population pharmacokinetic analyses suggest that amantadine may slightly decrease the oral clearance of pramipexole. *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 (N=12). *Probenecid:* Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transporter, did not noticeably influence pramipexole pharmacokinetics (N=12). *Other drugs eliminated via renal secretion:* Population pharmacokinetic analysis suggests that coadministration of drugs that are secreted by the cationic transport system (e.g., cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine) decreases the oral clearance of pramipexole by about 20%, while those secreted by the anionic transport system (e.g., cephalosporins, penicillins, indomethacin, hydrochlorothiazide, and chlorpropamide) are likely to have little effect on the oral clearance of pramipexole. *CYP interactions:* Inhibitors of cytochrome P450 enzymes would not be expected to affect pramipexole elimination because pramipexole is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole does not inhibit CYP enzymes CYP1A2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent K_i of 30 μM, indicating that pramipexole will not inhibit CYP enzymes at plasma concentrations observed following the clinical dose of 4.5 mg/day (1.5 mg TID). *Dopamine antagonists:* Since pramipexole is a dopamine agonist, it is possible that dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthenes) or metoclopramide, may diminish the effectiveness of Mirapex® (pramipexole dihydrochloride) tablets.

Drug/Laboratory Test Interactions: There are no known interactions between MIRAPEX tablets and laboratory tests.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Two-year carcinogenicity studies with pramipexole have been conducted in mice and rats. Pramipexole was administered in the diet to C57BL/6J mice at doses of 0.3, 2, and 10 mg/kg/day [0.3, 2.2, and 11 times the Maximum Recommended Human Dose (MRHD) (MRHD of 1.5 mg TID on a mg/m² basis)]. Pramipexole was administered in the diet to Wistar rats at 0.3, 2, and 8 mg/kg/day (plasma AUCs were 0.3, 2.5, and 12.5 times the AUC in humans at the MRHD). No significant increases in tumors occurred in either species. Pramipexole was not mutagenic or clastogenic in a battery of assays, including 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, pramipexole at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis), prolonged estrus cycles and inhibited implantation. These effects were associated with reductions in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pregnancy: Teratogenic Effect: Pregnancy Category C: When pramipexole was given to female rats throughout pregnancy, implantation was inhibited at a dose of 2.5 mg/kg/day (5 times the MRHD on a mg/m² basis). Administration of 1.5 mg/kg/day of pramipexole to pregnant rats during the period of organogenesis (gestation days 7 through 16) resulted in a high incidence of total resorption of embryos. The plasma AUC in rats at this dose was 4 times the AUC in humans at the MRHD. These findings are thought to be due to the prolactin-lowering effect of pramipexole, 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, the teratogenic potential of pramipexole could not be adequately evaluated. There was no evidence of adverse effects on embryo-fetal development following administration of up to 10 mg/kg/day to pregnant rabbits during organogenesis (plasma AUC was 71 times that in humans at the MRHD). Postnatal growth was inhibited in the offspring of rats treated with 0.5 mg/kg/day (approximately equivalent to the MRHD on a mg/m² basis) or greater during the latter part of pregnancy and throughout lactation.

There are no studies of pramipexole in human pregnancy. Because animal reproduction studies are not always predictive of human response, pramipexole should be used 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 the breast milk of lactating rats. Concentrations of radioactivity in milk were three to six times higher than concentrations in plasma at equivalent time points.

Other studies have shown that pramipexole treatment resulted in an inhibition of 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 of the potential for serious adverse reactions in nursing infants from pramipexole, a decision should be made as to whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: The safety and efficacy of Mirapex® (pramipexole dihydrochloride) tablets in pediatric patients has not been established.

Geriatric Use: Pramipexole total oral clearance was approximately 30% lower in subjects older than 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 with Parkinson's disease patients, 38.7% of patients were older than 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 the use of MIRAPEX tablets was increased in the elderly. In clinical studies with RLS patients, 22% of patients were at least 65 years old. There were no apparent differences in efficacy or safety between older and younger patients.

ADVERSE EVENTS

Parkinson's Disease: During the premarketing development of pramipexole, patients with either early or advanced Parkinson's disease were enrolled in clinical trials. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole; those with advanced Parkinson's disease all received concomitant levodopa treatment. Because these two populations may have differential risks for various adverse events, this section will, in general, present adverse-event data for these two populations separately.

Because the controlled trials performed during premarketing development all used a titration design, with a resultant confounding of time and dose, it was impossible to adequately evaluate the effects of dose on the incidence of adverse events. **Early Parkinson's Disease:** In the three double-blind, placebo-controlled trials of patients with early Parkinson's disease, the most commonly observed adverse events (>5%) that were numerically more frequent in the group treated with MIRAPEX tablets were nausea, dizziness, somnolence, insomnia, constipation, asthenia, and hallucinations. Approximately 12% of 388 patients with early Parkinson's disease and treated with MIRAPEX tablets who participated in the double-blind, placebo-controlled trials discontinued treatment due to adverse events compared with 11% of 235 patients who received placebo. The adverse events most commonly causing discontinuation of treatment were related to the nervous system (hallucinations [3.1% on MIRAPEX tablets vs 0.4% on placebo]; dizziness [2.1% on MIRAPEX tablets vs 1% on placebo]; somnolence [1.6% on MIRAPEX tablets vs 0% on placebo]; extrapyramidal syndrome [1.6% on MIRAPEX tablets vs 6.4% on placebo]; headache and confusion [1.3% and 1.0%, respectively, on Mirapex® (pramipexole dihydrochloride) tablets vs 0% on placebo]; and gastrointestinal system [nausea [2.1% on MIRAPEX tablets vs 0.4% on placebo]).

Adverse-event Incidence in Controlled Clinical Studies in Early Parkinson's Disease: This section lists treatment-emergent adverse events that occurred in the double-blind, placebo-controlled studies in early Parkinson's disease that were reported by 1% or more of patients treated with MIRAPEX tablets and were numerically more frequent than in the placebo group. In these studies, patients did not receive concomitant levodopa. Adverse events were usually mild or moderate in intensity.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse-event incidence rate in the population studied.

Treatment-emergent adverse events are listed by body system in order of decreasing incidence for MIRAPEX tablets (N=388) vs placebo (N=235), respectively. **Body as a whole:** asthenia (14% vs 12%), general edema (5% vs 3%), malaise (2% vs 1%), reaction unevaluable (2% vs 1%), fever (1% vs 0%). **Digestive system:** nausea (28% vs 18%), constipation (14% vs