PRODUCT MONOGRAPH

[Pr] TEVA-PRAMIPEXOLE

pramipexole dihydrochloride monohydrate tablets

0.25 mg, 0.5 mg, 1 mg, 1.5 mg Tablets

Antiparkinsonian agent / Dopamine Agonist

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
M1B 2K9

Date of Revision:
September 20, 2017

Submission Control No.: 209411

Table of Contents

PrTEVA-PRAMIPEXOLE

pramipexole dihydrochloride monohydrate tablets

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	All Non-medicinal ingredients
oral	Tablet 0.25 mg, 0.5 mg, 1 mg and 1.5 mg	Colloidal Silicon Dioxide, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate.

INDICATIONS AND CLINICAL USE

Adults
TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) is indicated for

- treatment of the signs and symptoms of idiopathic Parkinson's disease. TEVA-PRAMIPEXOLE may be used both as early therapy, without concomitant levodopa, and as an adjunct to levodopa.

Geriatrics (> 65 years of age): The majority of pramipexole (88%) is cleared via renal secretion. Due to age-related reduction in renal function, the elderly have a slower clearance of pramipexole (approximately 25 - 30% lower).The efficacy and safety appear to be unaffected, except the relative risk of hallucination is higher (See WARNINGS AND PRECAUTIONS, **Special Populations, Geriatrics**).

Pediatrics: The safety and efficacy of pramipexole dihydrochloride have not been established in children less than 18 years of age, therefore pramipexole dihydrochloride is not recommended in this patient population.

CONTRAINDICATIONS

- TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) is contraindicated in patients who have demonstrated hypersensitivity to pramipexole or the excipients of the drug product (see DOSAGE FORMS, COMPOSITION AND PACKAGING).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Sudden Onset of Sleep and Somnolence
Patients receiving treatment with pramipexole dihydrochloride and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which sometimes resulted in accidents. Although some of the patients reported somnolence while on pramipexole dihydrochloride, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event

Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician.

Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e g., operating machines). Substituting other dopamine agonists may not alleviate these symptoms, as episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking these products.

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.

Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness.

The following Warnings and Precautions are listed in alphabetical order.

Carcinogenesis and Mutagenesis
For animal data, see Part II: TOXICOLOGY
Two-year carcinogenicity studies have been conducted with pramipexole in mice and rats. In rats, pramipexole was administered in the diet, at doses of 0.3, 2 and 8 mg/kg/day. The highest dose corresponded to 12.5 times the highest recommended clinical dose (1.5 mg t.i.d) based on comparative AUC values. No significant increases in tumours occurred.

Testicular Leydig cell adenomas were found in male rats as follows: 13 of 50 control group A males, 9 of 60 control group B males, 17 of 50 males given 0.3 mg/kg/day, 22 of 50 males given 2 mg/kg/day, and 22 of 50 males given 8 mg/kg/day. Leydig cell hyperplasia and increased numbers

of adenomas are attributed to pramipexole-induced decreases in serum prolactin levels, causing a down-regulation of Leydig cell luteinizing hormone (LH) receptors and a compensatory elevation of LH secretion by the pituitary gland. The endocrine mechanisms believed to be involved in rats are not relevant to humans.

In mice, pramipexole was administered in the diet, at doses of 0.3, 2 and 10 mg/kg/day. The highest dose corresponded to 11 times the highest recommended clinical dose on a mg/m^2 basis. No significant increases in tumours occurred.

Pramipexole was not mutagenic in a battery of in vitro and in vivo assays including the Ames assay and the in vivo mouse micronucleus assay.

Cardiovascular

Postural Hypotension
In case of severe cardiovascular disease, care should be taken. Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting postural (orthostatic) hypotension, especially during dose escalation. Postural (orthostatic) hypotension has been observed in patients treated with pramipexole dihydrochloride. Therefore, patients should be carefully monitored for signs and symptoms of orthostatic hypotension especially during dose escalation (see DOSAGE AND ADMINISTRATION) and should be informed of this risk (see CONSUMER INFORMATION).

In clinical trials of pramipexole dihydrochloride, however, and despite clear orthostatic effects in normal volunteers, the reported incidence of clinically significant orthostatic hypotension was not greater among those assigned to pramipexole dihydrochloride than among those assigned to placebo. This result 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 dihydrochloride, 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.

Connective Tissue

Fibrotic Complications
Although not reported with pramipexole in the clinical development program, cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. 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 postmarketing experience for

pramipexole dihydrochloride. While the evidence is not sufficient to establish a causal relationship between pramipexole dihydrochloride and these fibrotic complications, a contribution of pramipexole dihydrochloride cannot be completely ruled out in rare cases.

Dependence/Tolerance
Pramipexole dihydrochloride has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. However, in a rat model on cocaine self-administration, pramipexole dihydrochloride had little or no effect.

Neurologic

Dyskinesia
Pramipexole dihydrochloride may potentiate the dopaminergic side effects of levodopa and may cause or exacerbate pre-existing dyskinesia. Decreasing the dose of levodopa may ameliorate this side effect.

Neuroleptic Malignant Syndrome
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 anti-Parkinsonian therapy, including pramipexole dihydrochloride. (see DOSAGE AND ADMINISTRATION for dose tapering)

Ophthalmologic

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 with pramipexole. These findings were first observed during week 76 and were dose-dependant in animals receiving 2 mg/kg/day (25/50 male rats, 10/50 female rats) and 8 mg/kg/day (44/50 male rats, 37/50 female rats). Plasma AUCs at these doses were 2.5 and 12.5 times the AUC seen in humans at the maximal recommended dose of 4.5 mg per day. Similar findings were not present in either control rats, or in rats receiving 0.3 mg/kg/day of pramipexole (0.3 times the AUC seen in humans at the 4.5 mg per day dose).

Studies demonstrated that pramipexole at very high dose (25 mg/kg/day) reduced the rate of disk shedding from the photoreceptor rod cells of the retina in albino rats; this reduction was associated with enhanced sensitivity to the damaging effects of light. In a comparative study, degeneration and loss of photoreceptor cells occurred in albino rats after 13 weeks of treatment with 25 mg/kg/day of pramipexole (54 times the highest clinical dose on an mg/m basis) and constant light (100 lux) but not in Brown-Norway rats exposed to the same dose and higher light intensities (500 lux).

The albino rats seem to be more susceptible than pigmented rats to the damaging effect of pramipexole and light. While the potential significance of this effect on humans has not been established, it cannot be excluded that human albinos (or people who suffer from albinismus oculi) might have an increased susceptibility to pramipexole compared to normally pigmented people. Therefore, such patients should take pramipexole dihydrochloride only under ophthalmological monitoring.

Psychiatric

Antipsychotic medication

Patients with psychotic disorders should be treated with dopamine agonists only if the potential benefits outweigh the risks.

It is not recommended to combine a dopamine antagonist antipsychotic medication with pramipexole unless the potential benefit outweighs the risk. Alternatives as discussed should be considered.

Behavioural changes

Patients and caregivers should be made aware that abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours) such as pathological gambling, increased libido, hypersexuality, binge eating or compulsive shopping have been reported in patients treated with dopaminergic drugs. Dose reduction/tapered discontinuation should be considered, and be performed by the treating physician in close collaboration with the patient and caregiver, based on the patient's response.

Hallucinations

Hallucinations and confusion are known side effects of treatment with dopamine agonist and levodopa. Hallucinations were more frequent when pramipexole dihydrochloride was given in combination with levodopa in patients with advanced disease than in monotherapy in patients with early disease. Patients should be aware of the fact that hallucinations (mostly visual) can occur.

In the double-blind, placebo-controlled trials in early Parkinson's disease, hallucinations were observed in 9% (35 of 388) of patients receiving pramipexole dihydrochloride, compared with 2.6% (6 of 235) of patients receiving placebo. In the double-blind, placebo-controlled trials in advanced Parkinson's disease, where patients received pramipexole dihydrochloride and concomitant levodopa, hallucinations were observed in 16.5% (43 of 260) of patients receiving pramipexole dihydrochloride 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. In patients with early Parkinson's disease, the risk of hallucinations was 1.9 times and 6.8 times greater in pramipexole dihydrochloride patients than placebo patients <65 years old, and >65 years old, respectively. In patients with advanced Parkinson`s disease, the risk of hallucinations was 3.5 times and 5.2 times greater in pramipexole dihydrochloride patients than placebo patients <65 years old, and >65 years old, respectively.

Suicidality

Patients and caregivers should be made aware of the inherent risk of suicidality in patients with Parkinson's Disease. Such risk may not resolve when disease conditions see improvement.

Renal

Since TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) is eliminated through the kidneys, caution should be exercised when prescribing TEVA-PRAMIPEXOLE to patients with renal insufficiency (see ACTION AND CLINICAL PHARMACOLOGY, pharmacokinetics and DOSAGE AND ADMINISTRATION).

Skeletal Muscular

Rhabdomyolysis
A single case of rhabdomyolysis occurred in a 49-year old male with advanced Parkinson's disease treated with pramipexole dihydrochloride. The patient was hospitalized with an elevated CPK (10.631 IU/L). The symptoms resolved with discontinuation of the medication.

Skin and Appendages

Melanoma
Epidemiological studies have shown that patients with Parkinson's disease have a higher risk (2- to approximately 6-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, is unclear.

For the reasons stated above, patients and health-care providers are advised to monitor for melanomas frequently and on a regular basis when using TEVA-PRAMIPEXOLE. Ideally, periodic skin examination should be performed by appropriately qualified individuals (e.g. dermatologists).

Sexual Function/Reproduction
No studies on the effect on human fertility have been conducted.

In rat fertility studies, pramipexole at a dose of 2.5 mg/kg/day, prolonged the estrus cycle and inhibited implantation. These effects were associated with a reduction in serum levels of prolactin, a hormone necessary for implantation and maintenance of early pregnancy in rats.

Pramipexole, at a dose of 2.5 mg/kg/day inhibited implantation. Pramipexole, at a dose of 1.5 mg/kg/day (4.3 times the AUC observed in humans at the maximal recommended clinical dose of 1.5 mg t i.d.) resulted in a high incidence of total resorption of embryos. This finding is thought to be due to the prolactin lowering effect of pramipexole. Prolactin is necessary for implantation and maintenance of early pregnancy in rats, but not in rabbits and humans. Because of pregnancy disruption and early embryonic loss, the teratogenic potential of pramipexole could not be assessed adequately. In pregnant rabbits which received doses up to 10 mg/kg/day during organogenesis (plasma AUC 71 times that seen in humans at the 1.5 mg t.i.d. dose), there was no evidence of adverse effects on embryo-fetal development. Postnatal growth was inhibited in the offspring of rats treated with a 0.5 mg/kg/day dose of pramipexole during the latter part of pregnancy and throughout lactation.

Use in Specific Populations

Pregnant Women: There are no studies of pramipexole dihydrochloride in pregnant women. Because animal reproduction studies are not always predictive of human response, TEVA-PRAMIPEXOLE should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Nursing Women: The excretion of pramipexole into breast milk has not been studied in women. Since pramipexole dihydrochloride suppresses lactation, it should not be administered to mothers who wish to breast-feed infants.

A single-dose, radio-labelled 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.

Geriatrics (> 65 years of age): Pramipexole dihydrochloride total oral clearance was approximately 25 to 30% lower in the elderly (aged 65 years and older) as a result 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 (See Pharmacokinetics).

In clinical studies, 40.8% (699 of 1715) of patients were between the ages of 65 and 75 years, and 6.5% (112 of 1715) of patients were >75 years old. 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 pramipexole dihydrochloride was increased in the elderly.

Pediatrics The safety and efficacy of pramipexole dihydrochloride in children under 18 years of age have not been established.

Monitoring and Laboratory Tests
There are no specific laboratory tests recommended for the management of patients receiving pramipexole dihydrochloride.

ADVERSE REACTIONS

PARKINSON'S DISEASE

Adverse Drug Reaction Overview

During the premarketing development of pramipexole dihydrochloride, patients enrolled in clinical trials had either early or advanced Parkinson's disease. Apart from the severity and duration of their disease, the two populations differed in their use of concomitant levodopa therapy. Namely, patients with early disease did not receive concomitant levodopa therapy during treatment with pramipexole dihydrochloride, while those with advanced Parkinson's disease did.

Because these two populations may have differential risk for various adverse events, adverse event data will be presented for both populations.

All controlled clinical trials performed during premarketing development (except one fixed dose study) used a titration design. Consequently, it was impossible to adequately evaluate the effects of a given dose on the incidence of adverse events.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Reactions Leading to Discontinuation of Treatment
Early Parkinson's Disease
Approximately 12% of 388 patients treated with pramipexole dihydrochloride and 11 % of 235 patients treated with placebo discontinued treatment due to adverse events. The events most commonly causing discontinuation of treatment were related to the nervous system, namely hallucinations (3.1% on pramipexole dihydrochloride vs 0.4% on placebo), dizziness (2.1% on pramipexole dihydrochloride vs 1.0% on placebo), somnolence (1.6% on pramipexole dihydrochloride vs 0% on placebo), headache and confusion (1.3% and 1.0%. respectively, on pramipexole dihydrochloride vs 0% on placebo), and to the gastrointestinal system (nausea 12.1% on pramipexole dihydrochloride vs 0.4% on placebo).

Advanced Parkinson's Disease.
Approximately 12% of 260 patients treated with pramipexole dihydrochloride and 16% of 264 patients treated with placebo discontinued treatment due to adverse events. The events most commonly causing discontinuation of treatment were related to the nervous system, namely hallucinations (2.7% on pramipexole dihydrochloride vs 0.4% on placebo), dyskinesia (1.9% on pramipexole dihydrochloride vs 0.8% on placebo), dizziness (1.2% on pramipexole dihydrochloride vs 1.5% on placebo), confusion (1.2% on pramipexole dihydrochloride vs 2.3% on placebo, and to the cardiovascular system (postural [orthostatic] hypotension (2.3% on pramipexole dihydrochloride vs 1.1% on placebo).

Most Frequent Adverse Events
Adverse events occurring with an incidence of greater than, or equal to, 10% and listed in decreasing order of frequency, were as follows:

Early Parkinson's Disease: nausea, dizziness, somnolence, insomnia, asthenia and constipation.

Advanced Parkinson's Disease: postural [orthostatic] hypotension, dyskinesia, insomnia, dizziness, hallucinations, accidental injury, dream abnormalities, constipation and confusion.

Incidence of Adverse Events in Placebo Controlled Trials
Table 1, lists treatment-emergent adverse events that were reported in the double-blind, placebo-controlled studies by ≥1% of patients treated with pramipexole dihydrochloride and were

numerically more frequent than in the placebo group. Adverse events were usually mild or moderate in intensity.

Table 1: Adverse Events from Placebo-controlled Early and Adjunct Therapy Studies (Incidence of Events ≥1% in Patients Treated with Pramipexole Dihydrochloride and Numerically More Frequent than in Patients Treated with Placebo)

	Early Therapy		Advanced Therapy	
Body System/Adverse Event	**Pramipexole Dihydrochloride N = 388 % occurrence**	**Placebo N = 235 % occurrence**	**Pramipexole Dihydrochloride† N = 260 % occurrence**	**Placebo † N = 264 % occurrence**
Body as a Whole				
Asthenia	14	12	10	8
General edema	5	3	4	3
Malaise	2	1	3	2
Reaction unevaluable	2	1	-	-
Fever	1	0	-	-
Chest pain	-	-	3	2
Accidental Injury	-	-	17	15
Cardiovascular System				
Postural hypotension	-	-	53	48
Digestive System				
Nausea	28	18	-	-
Constipation	14	6	10	9
Anorexia	4	2	-	-
Dysphagia	2	0	-	-
Dry Mouth	-	-	7	3
Metabolic & Nutritional System				
Peripheral edema	5	4	2	1
Decreased weight	2	0	-	-
Increased creatine PK	-	-	1	0
Musculoskeletal System				
Arthritis	-	-	3	1
Twitching	-	-	2	0
Bursitis	-	-	2	0
Myasthenia	-	-	1	0
Nervous System				
Dizziness	25	24	26	25
Somnolence	22	9	9	6
Insomnia	17	12	27	22
Hallucinations	9	3	17	4
Confusion	4	1	10	7
Amnesia	4	2	6	4
Hyperesthesia	3	1	-	-
Dystonia	2	1	8	7
Thinking abnormalities	2	0	3	2
Decreased libido	1	0	-	-
Myoclonus	1	0	-	-
Hypertonia	-	-	7	6
Paranoid reaction	-	-	2	0
Delusions	-	-	1	0
Sleep disorders	-	-	1	0

	Early Therapy		Advanced Therapy	
Body System/Adverse Event	**Pramipexole Dihydrochloride N = 388 % occurrence**	**Placebo N = 235 % occurrence**	**Pramipexole Dihydrochloride† N = 260 % occurrence**	**Placebo † N = 264 % occurrence**
Dyskinesia	-	-	47	31
Gait abnormalities	-	-	7	5
Dream abnormalities	-	-	11	10
Respiratory System				
Dyspnea	-	-	4	3
Rhinitis	-	-	3	1
Pneumonia	-	-	2	0
Skin & Appendages				
Skin disorders	-	-	2	1
Special Senses				
Vision Abnormalities	3	0	3	1
Accommodation abnormalities	-	-	4	2
Diplopia	-	-	1	0
Urogenital System				
Impotence	2	1	-	-
Urinary frequency	-	-	6	3
Urinary tract infection	-	-	4	3
Urinary incontinence	-	-	2	1

† Patients received concomitant Levodopa

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

Other Clinical Trial Adverse Drug Reactions (≥ 1%)

Other events reported by 1% or more of patients treated with pramipexole dihydrochloride but reported equally or more frequently in the placebo group were as follows:

Early Parkinson's Disease

Infection, accidental injury, headache, pain, tremor, back pain, syncope, postural hypotension, hypertonia, diarrhea, rash, ataxia, dry mouth, leg cramps, twitching, pharyngitis, sinusitis, sweating, rhinitis, urinary tract infection, vasodilation, flu syndrome, increased saliva, tooth disease, dyspnea, increased cough, gait abnormalities, urinary frequency, vomiting, allergic reaction, hypertension, pruritis, hypokinesia, increased creatine PK, nervousness, dream abnormalities, chest pain, neck pain, paresthesia, tachycardia, vertigo, voice alteration, conjunctivitis, paralysis, accommodation abnormalities, tinnitus, diplopia, and taste perversions.

Advanced Parkinson's Disease

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, hyperesthesia, neck pain, syncope, arthralgia, dysphagia, palpitations, pharyngitis, vertigo, leg cramps, conjunctivitis, and lacrimation.

Adverse Events: Relationship to Age, Gender, and Race

Among the treatment-emergent adverse events in patients treated with pramipexole dihydrochloride, hallucinations appeared to exhibit a positive relationship to age. No gender-related

differences were observed. Only a small percentage (4%) of patients enrolled were non-Caucasian, therefore, an evaluation of adverse events related to race is not possible.

Other Adverse Events Observed During all Phase 2 and 3 Clinical Trials
Pramipexole dihydrochloride has been administered to 1,715 subjects during the premarketing development program, 782 of who participated in double-blind, controlled studies. During these trials, all adverse events were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. These categories are used in the listing below.

The events listed below occurred in less than 1% of the 1,715 subjects exposed to pramipexole dihydrochloride. All reported events, except those already listed above, are included, without regard to determination of a causal relationship to pramipexole dihydrochloride.

Events are listed within body-system categories in order of decreasing frequency.
Body as a whole: fever, enlarged abdomen, rigid neck, no drug effect.
Cardiovascular system: palpitations, angina pectoris, atrial arrhythmia, peripheral vascular disease.
Digestive system: tongue discoloration, GI hemorrhage, fecal incontinence
Endocrine system: diabetes mellitus
Hemic & lymphatic system: ecchymosis.
Metabolic & nutritional system: gout, blood triglyceride increased.
Musculoskeletal system: bursitis, myasthenia.
Nervous system: apathy, libido decrease, paranoid reaction, akinesia, coordination abnormalities, speech disorder, hyperkinesia, neuralgia.
Respiratory system: voice alteration, asthma, hemoptysis
Skin & appendages: skin disorder, herpes simplex.
Special senses: tinnitus, taste perversion otitis media, dry eye, ear disorder, hemianopia
Urogenital system: urinary incontinence, dysuria, prostate disorder, kidney calculus.

In individual patients, hypotension may occur at the beginning of treatment, especially if pramipexole dihydrochloride is titrated too rapidly.

Post-Market Adverse Drug Reactions

In addition to the adverse events reported during clinical trials, the following adverse reactions have been identified (essentially in Parkinson's disease patients) during post-approval use of pramipexole dihydrochloride. 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.

<u>Sudden Onset on Sleep</u>
Patients treated with pramipexole dihydrochloride have rarely reported suddenly falling asleep while engaged in activities of daily living; including operation of motor vehicles which has sometimes resulted in accidents (see WARNINGS AND PRECAUTIONS).

Behavioural Changes
Abnormal behaviour (reflecting symptoms of impulse control disorders and compulsive behaviours), such as pathological (compulsive) gambling, hypersexuality, compulsive spending or buying, compulsive or binge eating, libido disorders, paranoia, and restlessness.have been reported. These behavioral changes were generally reversible upon dose reduction or treatment discontinuation.

A cluster of symptoms, such as anxiety, panic attacks, depression, agitation, irritability, and drug craving, have been reported during dose reduction/ tapered discontinuation. (see WARNINGS AND PRECAUTIONS, Behavioural Changes)

Other post-marketing reports
As a result of pooled clinical trial data analysis and review of post-marketing experience hiccups and visual impairment (including diplopia) have been reported.

Based on post-marketing experience inappropriate antidiuretic hormone secretion has been reported. One of the diagnostic criteria of inappropriate antidiuretic hormone secretion is hyponatremia. Signs and symptoms of hyponatremia include headache, nausea, malaise, lethargy, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

In clinical studies and post-marketing experience cardiac failure has been reported in patients with pramipexole. In a pharmacoepidemiological study pramipexole use was associated with an increased risk of cardiac failure compared with non-use of pramipexole. A causal relationship between pramipexole and cardiac failure has not been demonstrated.

DRUG INTERACTIONS

Drug-Drug Interactions
The drugs listed in table 2 are based on information collected in clinical studies, interaction case reports, or pharmacological properties of the drug that may be used. See ACTION AND CLINICAL PHARMACOLGY, Drug-drug Interactions for more information.

Pramipexole dihydrochloride is bound to plasma proteins to a very low extent (<20%) and little biotransformation is seen in humans. Therefore, interactions with other medication affecting plasma protein binding or elimination by biotransformation are unlikely. Medication that inhibit the active renal tubular secretion of basic (cationic) drugs or are themselves eliminated by active renal tubular secretion may interact with pramipexole dihydrochloride resulting in reduced clearance of either or both medications.

Table 2: Established or Potential Pharmacokinetic Interactions

Pramipexole Dihydrochloride	Effect	Clinical comment
Antiparkinsonian Drugs		
Levodopa/carbidopa	Pramipexole increases levodopa C_{max}	The combined use of pramipexole

Pramipexole Dihydrochloride	Effect	Clinical comment
	by about 40% and reduces T_{max} from 2.5 to 0.5 hours. No change in total exposure (AUC) was observed. Levodopa/carbidopa has no effect on the pharmacokinetics of pramipexole in healthy volunteers.	and levodopa increases the frequency of hallucination. Dosage adjustment, even discontinuation, may be necessary. While increasing the dose of pramipexole dihydrochloride in Parkinson's disease patients it is recommended that the dosage of levodopa is reduced and the dosage of other anti-parkinsonian medication is kept constant.
Selegiline	Selegiline has no effect on the pharmacokinetics of pramipexole in volunteers	
Amantadine	Amantadine inhibits the renal cationic transport system. Amantadine might alter the clearance of pramipexole.	Dosage adjustment may be necessary See below.
Anticholinergics		
Anticholinergics	As anticholinergics are mainly eliminated by hepatic metabolism, pharmacokinetic drug-drug interactions with pramipexole are rather unlikely.	
Other drugs eliminated via renal secretion		
Drugs eliminate via the renal cationic transport system Amantadine Cimetidine Ranitidine Diltiazem Triamterene Verapamil Quinidine Quinine	These drugs inhibit the renal tubular secretion of organic bases via the cationic transport system. They reduce the renal clearance of pramipexole to various degrees.	Dosage adjustment should be considered if concomitant treatment is necessary. Dosage reduction is necessary if adverse reactions, such as dyskinesia, agitation, or hallucination, are observed.
Drugs eliminate via the renal anionic transport system. Probenecid Cephalosporins Penicillins Indomethacin Hydrochlorothiazide Chloropramide	These drugs inhibit the renal tubular secretion of organic bases via the anionic transport system. They are unlikely to reduce the renal clearance of pramipexole.	Dosage adjustment is not necessary.
Interactions mediated by CYP isoenzymes		
Drugs metabolized by CYP isoenzymes	Inhibitors of CYP isoenzymes are not expected to affect the elimination of pramipexole. Pramipexole has no inhibitory action on CYP1A2, CYP2C9, CYP2C19,	

Pramipexole Dihydrochloride	Effect	Clinical comment
	CYP2E1, and CYP3A4. Inhibition of CYP2D6 is observed with an apparent Ki of 30 μM, suggesting that pramipexole dihydrochloride will not inhibit CYP enzymes at plasma concentrations following the highest recommended clinical dose (1.5 mg tid).	
Dopamine antagonists		
Neuroleptics, e.g. phenothiazines. butyrophenones. thioxathines Metoclopramide	Pramipexole is a dopamine agonist. Dopamine antagonists reduce its therapeutic effects	Concurrent use is not recommended. Pramipexole can exacerbate psychotic symptoms
Miscellaneous		
Sedating medication or alcohol	Possible additive effects	Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with pramipexole dihydrochloride.

Drug-Food Interactions
Interactions with food have not been established.

Drug-Herb Interactions
Interactions with herbal products have not been established.

Drug-Laboratory Interactions
There are no known interactions between pramipexole dihydrochloride and laboratory tests.

DOSAGE AND ADMINISTRATION

Parkinson's Disease
TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) should be taken orally three times daily. The tablets can be taken with or without food.

Missed Dose
Patients should be advised that if a dose is missed, they should not take a double dose, but continue with the regular treatment schedule.

Dosing Considerations
Adults
In all clinical studies, dosage was initiated at a subtherapeutic level to avoid orthostatic hypotension and severe adverse effects. TEVA-PRAMIPEXOLE should be titrated gradually in all patients. The

dosage should be increased to achieve maximal therapeutic effect, balanced against the principal adverse reactions of dyskinesia, nausea, dizziness and hallucinations.

Initial treatment
Dosages should be increased gradually from a starting dose of 0.375 mg/day given in three divided doses and should not be increased more frequently than every 5 to 7 days. A suggested ascending dosage schedule that was used in clinical studies is shown in the following table.

Table 3: Ascending-Dose Schedule of TEVA-PRAMIPEXOLE

Week	Dosage (mg)	Total Daily Dose (mg)
1	0.125 tid	0.375
2	0.25 tid	0.75
3	0.50 tid	1.5
4	0.75 tid	2.25
5	1.00 tid	3.0
6	1.25 tid	3.75
7	1.50 tid	4.5

Maintenance treatment
Pramipexole dihydrochloride was 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, as monotherapy or in combination with levodopa (approximately 800 mg/day). In a fixed-dose study in patients with early Parkinson's disease, pramipexole dihydrochloride at doses of 3, 4.5 and 6 mg/day was not shown to provide any significant benefit beyond that achieved at a daily dose of 1.5 mg/day. For individual patients who have not achieved efficacy at 1.5 mg/day, higher doses can result in additional therapeutic benefit.

When TEVA-PRAMIPEXOLE is used in combination with levodopa, a reduction of the levodopa dosage should be considered. In the controlled study in advanced Parkinson's disease, the dosage of levodopa was reduced by an average of 27% from baseline.

Discontinuation of Treatment
TEVA-PRAMIPEXOLE tablets should be tapered off at a rate of 0.75 mg per day until the daily dose has been reduced to 0.75 mg. Thereafter the dose should be reduced by 0.375 mg per day. (See WARNINGS AND PRECAUTIONS)

Recommended Dose and Dosage Adjustment
The maximal recommended dose of TEVA-PRAMIPEXOLE is 4.5 mg per day. TEVA-PRAMIPEXOLE is not recommended at the 6 mg per day dose since the incidence of some adverse reactions is higher.

Dosing in patients with concomitant levodopa therapy
In patients with concomitant levodopa therapy it is recommended that the dosage of levodopa is reduced during both dose escalation and maintenance treatment with TEVA-PRAMIPEXOLE. This may be necessary in order to avoid excessive dopaminergic stimulation.

Patients with Renal Impairment

Since the clearance of pramipexole dihydrochloride is reduced in patients with renal impairment (see Pharmacokinetics), the following dosage recommendation should be considered.

Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose or dosing frequency.

In patients with a creatinine clearance between 30 and 50 ml/min, the initial daily dose of TEVA-PRAMIPEXOLE should be administered in two divided doses, starting at 0.125 mg twice a day (0.25 mg daily). A maximum daily dose of 2.25 mg pramipexole should not be exceeded.
In patients with a creatinine clearance between 15 and 30 ml/min, the daily dose of TEVA-PRAMIPEXOLE should be administered in a single dose, starting at 0.125 mg daily. A maximum daily dose of 1.5 mg pramipexole should not be exceeded.

Pramipexole has not been adequately studied in patients with very severe renal impairment (creatinine Cl< 15 mL/min and haemodialysis patients) and its administration to patients with end stage renal disease is not recommended.

If renal function declines during maintenance therapy reduce TEVA-PRAMIPEXOLE daily dose by same percentage as decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce TEVA-PRAMIPEXOLE daily dose by 30%. The daily dose can be administered in two divided doses if creatinine clearance is between 20 and 50 ml/min and as a single daily dose if creatinine clearance is less than 20 ml/min.

Patients with hepatic impairment
Dose reduction is not considered necessary in patients with hepatic impairment, as approx. 90% of absorbed drug is excreted through the kidneys.

Dosing in children and adolescents
Safety and efficacy of TEVA-PRAMIPEXOLE have not been established in children and adolescents up to 18 years of age.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Signs and Symptoms

There is no clinical experience with massive overdosage. The expected adverse events are those related to the pharmacodynamic profile of a dopamine agonist including nausea, vomiting, hyperkinesia, hallucinations, agitation and hypotension.

One patient with a 10-year history of schizophrenia (who participated in a schizophrenia study) took 11 mg/day of pramipexole dihydrochloride for two days, this was two to three times the daily

dose recommended in the protocol. No adverse events were reported related to the increased dose. The blood pressure remained stable although pulse rates 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.

Recommended Management
There is no known antidote for overdosage of a dopamine agonist. If signs of central nervous system stimulation are present, a phenothiazine or other butyrophenone neuroleptic agent may be indicated; the efficacy of such drugs in reversing the effects of overdosage has not been assessed. Management of the overdose may require general supportive measures along with gastric lavage, intravenous fluids, and electrocardiogram monitoring. Haemodialysis has not been shown to be helpful.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action
Pramipexole dihydrochloride is a non ergot dopamine agonist with high in vitro specificity at the D_2 subfamily of dopamine receptors. Pramipexole is a full agonist and exhibits higher affinity to the D_3 receptor subtypes (which are in prominent distribution within the mesolimbic area) than to D_2 or D_4 receptor subtypes. While pramipexole dihydrochloride exhibits high affinity for the dopamine D_2 receptor subfamily, it has low affinity for α_2 adrenergic receptors and negligible or undetectable affinity for other dopaminergic, adrenergic, histaminergic, adenosine and benzodiazepine receptors.

The ability of pramipexole to alleviate the signs and symptoms of Parkinson's disease is believed to be related to its ability to stimulate dopamine receptors in the striatum. This assumption is supported by a dose-dependent antagonism of Parkinsonian symptoms in rhesus monkeys pre-treated with the neurotoxin N-methyl-4-phenyl-1.2.3.6-tetrahydropyridine (MPTP) which destroys dopamine cell bodies in the substantia nigra.

In human volunteers a dose-dependent decrease in prolactin was observed.

Pharmacokinetics
Absorption: Following oral administration pramipexole is rapidly absorbed reaching peak concentrations between 1 and 3 hours. The absolute bioavailability of pramipexole is greater than 90%. Pramipexole can be administered with or without food. A high-fat meal did not affect the extent of pramipexole absorption (AUC and C_{max}) in healthy volunteers, although the time to maximal plasma concentration (T_{max}) was increased by about 1 hour.

Pramipexole displays linear pharmacokinetics over the range of doses that are recommended for patients with Parkinson's disease.

Distribution: Pramipexole is extensively distributed, having a volume of distribution of about 500 L. Protein binding is less than 20% in plasma; with albumin accounting for most of the protein binding in human serum. Pramipexole distributes into red blood cells as indicated by an erythrocyte to plasma ratio of approximately 2.0 and a blood to plasma ratio of approximately 1.5. Consistent

with the large volume of distribution in humans, whole body autoradiography and brain tissue levels in rats indicated that pramipexole was widely distributed throughout the body, including the brain.

Metabolism and Excretion: Urinary excretion is the major route of pramipexole elimination. Approximately 88% of a 14C-labelled dose was recovered in the urine and less than 2% in the faeces following single intravenous and oral doses in healthy volunteers. The terminal elimination half-life was about 8.5 hours in young volunteers (mean age 30 years) and about 12 hours in elderly volunteers (mean age 70 years). Approximately 90% of the recovered 14C-labelled dose was unchanged drug; with no specific metabolites having been identified in the remaining 10% of the recovered radio-labelled dose. Pramipexole is the levorotational (-) enantiomer, and no measurable chiral inversion or racemization occurs in vivo.

The renal clearance of pramipexole is approximately 400 mL/min, approximately three times higher than the glomerular filtration rate. Thus, pramipexole is secreted by the renal tubules, probably by the organic cation transport system.

Special Populations and Conditions
Because therapy with pramipexole is initiated at a subtherapeutic dose and gradually titrated according to clinical tolerability to obtain optimal therapeutic effect, adjustment of the initial dose based on gender, weight, or age is not necessary. However, renal insufficiency, which can cause a large decrease in the ability to eliminate pramipexole, may necessitate dosage adjustment.

Early vs. advanced Parkinson's disease patients: The Pharmacokinetics of pramipexole was comparable between early and advanced Parkinson's disease patients.

Healthy Volunteers: In a clinical trial with healthy volunteers, where pramipexole extended release tablets were titrated faster than recommended (every 3 days) up to 4.5 mg per day, an increase in blood pressure and heart rate was observed. Such effect was not observed in patient studies.

Pediatrics: The pharmacokinetics of pramipexole in the pediatric population has not been evaluated.

Geriatrics: Renal function declines with age. Since pramipexole clearance is correlated with renal function, the drug's total oral clearance was approximately 25% to 30% lower in elderly (aged 65 years or older) compared with young healthy volunteers (aged less than 40 years).The decline in clearance resulted in an increase in elimination half-life from approximately 8.5 hours in young volunteers (mean age 30 years) to 12 hours in elderly volunteers (mean age 70 years).

Gender: Pramipexole renal clearance is about 30% lower in women than in men, most of this difference can be accounted for by differences in body weight. The reduced clearance resulted in a 16 to 42% increase in AUC and a 2 to 10% increase in C_{max}. The differences remained constant over the age range of 20 to 80 years. The difference in pramipexole half-life between males and females was less than 10%.

Race: A retrospective population pharmacokinetic analysis on data from patients with Parkinson's disease receiving immediate-release pramipexole suggests that oral clearance of pramipexole is 17% higher in black male patients compared to white male patients.

Hepatic Insufficiency: The potential influence of hepatic insufficiency on pramipexole pharmacokinetics has not been evaluated; however, it is considered to be small. Since approximately 90% of the recovered 14C-labelled dose was excreted in the urine as unchanged drug, hepatic impairment would not be expected to have a significant effect on pramipexole elimination.

Renal Insufficiency: The clearance of pramipexole was about 75% lower in patients with severe renal impairment (creatinine clearance approximately 20 mL/min) and about 60% lower in patients with moderate impairment (creatinine clearance approximately 40 mL/min) compared with healthy volunteers. A lower starting and maintenance dose is recommended in patients with renal impairment (see DOSAGE AND ADMINISTRATION). In patients with varying degrees of renal impairment, pramipexole clearance correlates well with creatinine clearance. Therefore, creatinine clearance can be used as a predictor of the extent of decrease in pramipexole clearance. As pramipexole clearance is reduced even more in dialysis patients (N=7), than in patients with severe renal impairment, the administration of pramipexole to patients with end stage renal disease is not recommended.

Drug-drug interactions

Anticholinergics
As anticholinergics are mainly eliminated by hepatic metabolism, pharmacokinetic drug-drug interactions with pramipexole are rather unlikely.

Antiparkinsonian drugs
In volunteers (N = 11), selegiline did not influence the pharmacokinetics of pramipexole. Population pharmacokinetic analysis suggests that amantadine may alter the oral clearance of pramipexole (N = 54). Levodopa/carbidopa did not influence the pharmacokinetics of pramipexole in volunteers (N = 10) Pramipexole did not alter the extent of absorption (AUC) or elimination of levodopa/carbidopa, although it increased levodopa C_{max} by about 40%, and decreased T_{max} from 2.5 to 0.5 hours.

While increasing the dose of TEVA-PRAMIPEXOLE in Parkinson's disease patients it is recommended that the dosage of levodopa is reduced and the dosage of other antiparkinsonian medication is kept constant.

Cimetidine
Cimetidine, a known inhibitor of renal tubular secretion of organic bases via the cationic transport system, increased pramipexole dihydrochloride AUC by 50% and increased its half-life by 40% in volunteers (N = 12).

Probenecid

Probenecid, a known inhibitor of renal tubular secretion of organic acids via the anionic transport system, did not influence the pharmacokinetics of pramipexole dihydrochloride in volunteers (N = 12).

Other drugs eliminated via renal secretion
Concomitant therapy with drugs secreted by the renal cationic transport system (e g, amantadine, cimetidine, ranitidine, diltiazem, triamterene, verapamil, quinidine, and quinine), may decrease the oral clearance of pramipexole dihydrochloride and thus, may necessitate an adjustment in the dosage of TEVA-PRAMIPEXOLE. In case of concomitant treatment with these kinds of drugs (incl. amantadine) attention should be paid to signs of dopamine overstimulation, such as dyskinesias, agitation or hallucinations. In such cases a dose reduction is necessary. Concomitant therapy with drugs secreted by the renal anionic transport system (e g, cephalosporins, penicillins, indomethacin, hydrochlorothiazide and chlorpropamide) are not likely to have any effect on the oral clearance of TEVA-PRAMIPEXOLE.

CYP interactions
Inhibitors of cytochrome P450 enzymes would not be expected to affect TEVA-PRAMIPEXOLE elimination because pramipexole dihydrochloride is not appreciably metabolized by these enzymes in vivo or in vitro. Pramipexole dihydrochloride does not inhibit CYPlA2, CYP2C9, CYP2C19, CYP2E1, and CYP3A4. Inhibition of CYP2D6 was observed with an apparent Ki of 30 μM, suggesting that pramipexole dihydrochloride will not inhibit CYP enzymes at plasma concentrations observed following the highest recommended clinical dose (1.5 mg tid).

Dopamine antagonists
Since pramipexole dihydrochloride is a dopamine agonist, dopamine antagonists such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide may diminish the effectiveness of TEVA-PRAMIPEXOLE and should ordinarily not be administered concurrently.

Miscellaneous
Because of possible additive effects, caution should be advised when patients are taking other sedating medication or alcohol in combination with TEVA-PRAMIPEXOLE and when taking concomitant medication that increase plasma levels of pramipexole (e.g. cimetidine).

STORAGE AND STABILITY

Store at controlled room temperature of 15°C to 25°C, protected from light and moisture.

SPECIAL HANDLING INSTRUCTIONS

The product should be dispensed in the original container. The product should be protected from light and moisture.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The tablet formulations contain the following non-medicinal ingredients Colloidal Silicon Dioxide, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate.

TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) Tablets are available in bottles of 90 tablets.

0.25 mg: White to off-white, round, flat face bevel edge tablets, debossed with "P1" over, and "P1" under the horizontal scoreline on the scored side, and "TV" on the other side.

0.5 mg: White to off-white, oval, biconvex tablets, debossed with "P" vertical scoreline "P" on the scored side, and "TV" on the other side.

1 mg: White to off-white, round, flat face bevel edge tablets, debossed with "P3" over, and "P3" under the horizontal scoreline on the scored side, and "TV" on the other side.

1.5 mg: White to off-white, round, flat face bevel edge tablets, debossed with "P4" over, and "P4" under the horizontal scoreline on the scored side, and "TV" on the other side.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance: Pramipexole dihydrochloride monohydrate

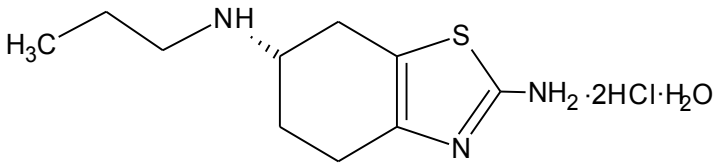
Proper name: Pramipexole dihydrochloride monohydrate (INN/USAN)

Chemical name (IUPAC): (S)-2-Amino-4,5,6,7-tetrahydro-6-propylamino-benzothiazole dihydrochloride monohydrate

Molecular formula: $C_{10}H_{21}Cl_2N_3OS$

Molecular Weight: 302.25 g/mol

Structural formula:



Physicochemical properties: Pramipexole dihydrochloride is a white to off-white crystalline powder, soluble in methanol. The specific optical rotation is between -64.00° and -70.00°.

CLINICAL TRIALS

Comparative Bioavailability Studies

A Blinded, Single-Dose, Two-Way, Crossover Comparative Bioavailability Study was performed on Two Formulations of Pramipexole Dihydrochloride Monohydrate products, Teva-Pramipexole 0.25mg (Teva Canada Limited) and Sifrol® 0.25 mg (Boehringer Ingelheim International, Germany. Equivalent to the Canadian Reference Product, Mirapex, marketed by Boehringer Ingelheim Canada limited) tablets in 24 Healthy Subjects, Under Fasting Conditions.

The pharmacokinetic data calculated for the TEVA-PRAMIPEXOLE and SIFROL® tablet formulations, is tabulated as below:

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Pramipexole (1 x 0.25mg) From measured data **uncorrected for potency** Geometric Mean Arithmetic Mean (CV %)				
Parameter	Test*	Reference†	% Ratio of Geometric Means	Confidence Interval, 90%
AUC_T (ng*h/mL)	9.7463 9.8452 (14)	9.3579 9.4683 (16)	104.15	99.51 - 109.01
AUC_I (ng*h/mL)	10.4613 10.5598 (14)	10.0698 10.1930 (16)	103.89	99.20 - 108.80
C_{max} (ng/mL)	0.8607 0.9138 (38)	0.8139 0.8492 (33)	105.74	97.68 - 114.47
T_{max}§ (h)	2.43 (35)	2.53 (34)		
$T_{½}$§ (h)	9.09 (18)	9.13 (19)		

* Pramipexole Dihydrochloride 0.25 mg Tablets (Teva Canada Limited, Canada)
† Sifrol® 0.18 mg Tablets (0.25 mg pramipexole dihydrochloride monohydrate containing 0.18 mg pramipexole) (Boehringer Ingelheim International GmbH, Germany)
§ Expressed as the arithmetic mean (CV%) only

Parkinson's Disease

Study demographics and trial design

Up to February 29, 1996, 1715 patients have been exposed to pramipexole dihydrochloride, with 669 patients being exposed for over one year and 222 patients being exposed for over two years.

The effectiveness of pramipexole dihydrochloride in the treatment of Parkinson's disease was evaluated in a multinational drug development program consisting of seven randomized controlled trials. Three were conducted in patients with early Parkinson's disease who were not receiving concomitant levodopa, and four were conducted in patients with advanced Parkinson's disease who were receiving concomitant levodopa. Among these seven studies, three Phase 3 studies provide the most persuasive evidence of pramipexole dihydrochloride's effectiveness in the management of patients with Parkinson's disease who were or were not receiving concomitant levodopa. Two of the trials enrolled patients with early Parkinson's disease (not receiving levodopa), and one enrolled patients with advanced Parkinson's disease who were receiving maximally tolerated doses of levodopa.

Study results
In all studies, the Unified Parkinson's Disease Rating Scale (UPDRS), or one or more of its subscales, served as the primary outcome assessment measure.

Studies in patients with early Parkinson's disease
Patients in the two studies with early Parkinson's disease had mean disease duration of 2 years, limited or no prior exposure to levodopa, and were not experiencing the "on-off" phenomenon and dyskinesia characteristics of later stages of the disease.

One of the trials was a double-blind, placebo-controlled, parallel study in which patients were randomized to pramipexole dihydrochloride (N = 164) or placebo (N = 171). The trial consisted of a 7-week dose escalation period and a 6- month maintenance period. Patients could be on selegiline and/or anticholinergics but not on levodopa products. Patients treated with pramipexole dihydrochloride had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose, but no higher than 4.5 mg/day, administered in three divided doses. At the end of the 6-month maintenance period: the mean improvement from baseline on the UPDRS Part II (activities of daily living [ADL] subscale) score was 1.9 in the pramipexole dihydrochloride group and -0.4 in the placebo group. The mean improvement from baseline on the UPDRS part III (motor subscale) was 5.0 in the pramipexole dihydrochloride group and -0.8 in the placebo group. Both differences were statistically significant. The mean daily dose of pramipexole dihydrochloride during the maintenance period was 3.8 mg/day.

The difference in mean daily dose between males and females was less than 10%. Patients >75 years (N = 26) received the same mean daily dose as younger patients.

The second early Parkinson's disease study was a double-blind, placebo-controlled parallel trial which evaluated dose-response relationships. It consisted of a 6-week dose escalation period and a 4-week maintenance period. A total of 264 patients were enrolled. Patients could be on selegiline, anticholinergics, amantadine, or any combination of these, but not on levodopa products. Patients were randomized to 1 of 4 fixed doses of pramipexole dihydrochloride (1.5 mg, 3.0 mg, 4.5 mg, or 6.0 mg per day) or placebo. No dose-response relationship was demonstrated. The between treatment differences on both parts of the UPDRS were statistically significant in favour of pramipexole dihydrochloride at all doses.

In both studies in early Parkinson's disease patients, no differences in effectiveness were detected based upon age or gender. Patients receiving selegiline or anticholinergics had responses similar to patients not receiving these drugs.

To date, results comparing pramipexole dihydrochloride to levodopa are not available.

Studies in patients with advanced Parkinson's disease

In the advanced Parkinson's disease study, the primary assessments were the UPDRS and daily diaries that quantified amounts of "on" and "off" times.

Patients (N = 181 on pramipexole dihydrochloride, N = 179 on placebo) had a mean disease duration of 9 years, had been exposed to levodopa for a mean of 8 years, received concomitant levodopa during the trial and had "on-off" periods. Patients could additionally be on selegiline, anticholinergics, amantadine or any combination of these. The study consisted of a 7-week dose-escalation period and a 6-month maintenance period. Patients treated with pramipexole dihydrochloride had a starting dose of 0.375 mg/day and were titrated to a maximally tolerated dose but no higher than 4.5 mg/day, administered in three divided doses. At the end of the 6-months maintenance period, the mean improvement from baseline on the UPDRS part II (ADL) score was 2.7 in the pramipexole dihydrochloride group and 0.5 in the placebo group. The mean improvement from baseline on the UPDRS part III (motor) score was 5.6 in the pramipexole dihydrochloride group and 2.8 in the placebo group. Both differences were statistically significant. The mean daily dose of pramipexole dihydrochloride during the maintenance period was 3.5 mg/day. The dose of levodopa could be reduced if dyskinesia or hallucinations developed. Levodopa dose reduction occurred in 76% and 54% of pramipexole dihydrochloride and placebo-treated patients, respectively. On average, the percent decrease was 27% in the pramipexole dihydrochloride group and 5% in the placebo group.

In females the mean daily dose was approximately 10% lower than in male patients. Patients aged over 75 years (N = 24) had approximately a 10% lower dose than younger patients.

The mean number of "off" hours per day during baseline was approximately 6 hours for both groups. Throughout the trial, patients treated with pramipexole dihydrochloride had a mean "off" period of approximately 4 hours, while the duration of "off" periods remained essentially unchanged in the placebo-treated subjects.

No differences in effectiveness were detected based upon age or gender.

DETAILED PHARMACOLOGY

Receptor binding studies

Preclinical studies, which compared the relative pharmacological activities and receptor binding affinities (displacement of [3H] spiroperidol) of the pramipexole racemate and its optical isomers, showed the levorotational (-) enantiomer to be more potent.

Studies with cloned human receptors, expressed in cultured Chinese hamster ovary (CHO) cells, indicate that, within the recently discovered D2 receptor subfamily, pramipexole binds with highest affinity to the D3 subtype (Ki=0.5 nM). Pramipexole has approximately a 5- to 10-fold preferential affinity for the D3 receptor when compared to its affinities for the high affinity forms of the D2S, D2L and D4 subtypes (Ki values 3.3, 3.9 and 5.1 nM, respectively). As is true for other dopamine agonists, exposure of the receptor to a non-hydrolyzable analog of GTP decreases the affinity of pramipexole for the cloned D3 receptor much less than it does for the cloned D2 or D4 subtypes. The small GTP-shift for agonists of the D3 receptor site is an indication of the weak coupling of this receptor to the G-protein second messenger system in CHO cells.

Besides binding to the dopamine-D2 receptor subfamily, pramipexole has a low affinity for α2 adrenoreceptors and a very low affinity for histamine H2 and serotonin 5-HT1A receptors. Its affinity for other dopaminergic, adrenergic, histaminergic, serotonergic, cholinergic, glutamatergic, adenosine and benzodiazepine receptors is negligible or undetectable.

Receptor binding autoradiography with [3H] pramipexole (5 nM, 62 Ci/mmole) was used to evaluate the distribution of pramipexole binding sites within the rat brain. The highest concentrations of [3H] pramipexole binding sites were found in the Islets of Calleja, previously reported to contain D3, but not D2 or D4 mRNA. [3H]Pramipexole binding was also high in other mesolimbic areas, such as the nucleus accumbens, olfactory tubercle, and amygdala. [3H] Pramipexole binding was also high in caudate, although slightly less than in mesolimbic areas. Striatal areas have higher D2: D3 mRNA ratios than do mesolimbic regions. Fewer [3H] pramipexole binding sites were found in VTA and substantia nigra, areas rich in cell bodies for dopamine neurons. Although it is likely that much of this [3H] pramipexole binding reflects D2 receptors, the relatively high mesolimbic binding could reflect the preferential affinity pramipexole has for the D3 receptor subtype.

Animal Studies

Antagonism of Reserpine-Induced Akinesia

Reserpine treatment leads to depletion of monoamines, including dopamine. Animals so treated are essentially akinetic, but can be activated by dopamine agonists.
Pramipexole (30 μmole/kg = 9 mg/kg IP) stimulated locomotor activity in reserpinized mice. These data are consistent with a pramipexole-induced stimulation of postsynaptic dopamine receptors in the basal ganglia.

Antagonism of Haloperidol-Induced Catalepsy
The dopamine receptor antagonist haloperidol induces hypomotility, rigidity, and catalepsy in the rat. The cataleptic behaviour is regard to be highly predictive of neuroleptic-induced Parkinson like extrapyramidal side effects.

In one study, rats were injected with haloperidol, 1 mg/kg. Rats were considered cataleptic if they maintained a position with their forepaws elevated on a 6 to 8 cm high rod for at least 30 seconds two hours after haloperidol. Pramipexole dose-dependently suppressed catalepsy, with an ED50 of 4.4 mg/kg SC.

In a second study, catalepsy, produced by 5 µmole/kg SC (= 2 mg/kg) of haloperidol, was scored by measuring the time rats remained with their forepaws on a squared wooden cube. Pramipexole (50 µmole/kg = 15.1 mg/kg) readily blocked the catalepsy.

Rotational Behavior in 6-Hydroxydopamine (6-OHDA) Lesioned Rats

When 6-OHDA is injected unilaterally into the medial forebrain bundle of rats, a selective degeneration of presynaptic dopaminergic neurons occurs, rendering the animals essentially hemi-Parkinsonian. The postsynaptic neurons at the site of the lesion become hypersensitive to dopamine agonists. When dopamine agonists are administered to lesioned rats, a contralateral rotational behaviour can be observed. The number of rotations is evaluated in a rotameter.

In an initial study, pramipexole and, for comparison, apomorphine was tested in doses of 0.01 to 0.1 mg/kg. The D1 - and D2-selective dopamine antagonists, SCH 23390 and haloperidol, respectively, were used to determine the subfamily of receptors involved. All compounds were administered SC.

Both pramipexole (ED50 0.026 mg/kg, maximum effect 80 to 140 minutes after administration) and apomorphine (ED50 0.030 mg/kg, maximum effect 5 to 65 minutes after administration) induced contralateral turning behaviour in 6-OHDA-lesioned rats. Whereas the effect of apomorphine ceased after 80 minutes, pramipexole was effective throughout the recording period of 2 hours.

Pretreatment with 0.05 mg/kg of haloperidol markedly attenuated the effect of pramipexole (0.05 mg/kg). The very high dose of 2 mg/kg of SCH 23390 also inhibited the effect, albeit to a smaller extent.

A second study confirmed the potent and long-lasting effects of pramipexole in this animal model of Parkinson's disease: maximal effects occurred with a dose of 0.3 µmoles/kg (= 0.09 mg/kg) SC. Higher doses produced less effect.

MPTP-Induced Parkinsonian Symptoms in Rhesus Monkeys

MPTP (n-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine) is a highly selective neurotoxin which destroys the dopamine cell bodies in the zona compacta of the substantia nigra. The chronic dopamine depletion in the substantia nigra, results in a syndrome which resembles severe Parkinsonism, observed in patients. The effect of MPTP is irreversible. Due to chronic denervation, the postsynaptic dopamine D2 receptors become hypersensitive. A presynaptic action of a compound in the substantia nigra is excluded in this model because the presynaptic neurons have been destroyed.

Pramipexole (0.03 to 0.1 mg/kg IM) dose-dependently reversed the Parkinson-like symptoms in MPTP-treated rhesus monkeys. The dose which antagonized the symptoms in 50% of the animals (ED50) was 0.045 mg/kg IM. A dose of 0.06 mg/kg was effective in all animals. The animals' locomotor activity, recorded with an electronic device mounted on their arm, returned to normal and did not exceed that of monkeys not pretreated with MPTP. Stereotyped movements, abnormal

excitation, salivation, or sedation were not observed in the dose range tested. A dose of 0.1 mg/kg IM was effective for more than 5h.

In another study, oral doses of 0.05 to 0.1 mg/kg of pramipexole were evaluated in MPTP treated rhesus monkeys. At a dose of 0.075 mg/kg, the compound completely reversed the Parkinsonian symptoms. The duration of action varied between 5 and 24 hours.

TOXICOLOGY

Acute toxicity

The acute toxicity of pramipexole was studied in mice, rats, and dogs following oral and intravenous single doses. Administration of the pramipexole dose was followed by a 14 day observation period. Comparative lethality data are presented in the table below.

Table 4: Species Comparison of LD50

Strain	Initial Group	Route	Doses (mg/kg)	Approximate LD50 (95% Confidence Limits) mg/kg
Studies in the Mouse				
Chbi:NMRI	5M, 5F	Oral	1400, 2000	M, F: 1700
Chbi:NMRI	5M, 5F	Intravenous	100, 125, 160, 200	M: 155 F:1883 (151.9—194.9) M,F:168.8 (150.8 – 195.2)
Chbi:NMRI	5M, 5F	Intravenous	0, 70, 100 (in 20% PEG) 100 (in 0.9% saline)	In 20% PEG: M: 94.4 F: 87.9 M, F: 90.6 In 0.9% saline: There were no deaths, therefore no determination could be made
Studies in the Rat				
Chbb:THOM	5M, 5F	Oral	100, 200, 200, 400, 560, 800	M: >800 F: >548.0 M, F: >809.4
Chbb:THOM	5M, 5F	Intravenous	100, 140, 140, 180, 225	M, F: 210
Studies in the Dog				
Chbi: Beagle	1M, 1F	Oral	0.001, 0.01, 0.1, 1.0	Not determined
Chbi: Beagle	1M, 1F	Intravenous	0.001, 0.003, 0.005, 0.01	Not determined

Clinical symptoms following acute dosing in rats and mice included ataxia, convulsions, dyspnoea, tachypnea, reduced motility, increased nervousness or hyperactivity. In dogs, oral and intravenous dosing resulted in frequent and prolonged vomiting.

Long-term toxicity

The effects of long-term administration of pramipexole were evaluated in the rat, minipig, and monkey. Definitive studies have been summarized in Table 5.

Table 5: Summary Of Long-Term Toxicity Studies

Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
Rat Crl:(WI) BR	20M, 20F in control, 25 mg/kg groups 10M, 10F in other groups	Oral, gavage (in saline)	0, 0.5, 4, 25	13 weeks with 8 week post-treatment follow-up for controls, 25 mg/kg group	Unscheduled deaths occurred in 3 F controls, IM, 1F: at 4 mg/kg. 1M. 1F at 25 mg/kg. and in one moribund female at 0.5 mg/kg. The incidence and distribution of the unscheduled deaths was not dose or treatment related. Clinical signs included slight sedation in 0.5 mg/kg males and increased spontaneous activity in all other treated groups. Reduced body weight gain and increased water consumption was noted in males at 4 mg/kg, while the females of this group had increased food consumption, reduced blood cholesterol levels, increased ovarian weight, reduced spleen weight, histologically diagnosed increases in the size of corpora lutea and lipid depletion in the adrenal cortex. At 25 mg/kg all changes noted in the 4 mg/kg group occurred. In addition, water consumption was increased in males, with a corresponding increase in urine production. Also noted were a slight, reversible, relative rise in granulocytes with a corresponding decrease in lymphocytes in females (week 13): a decrease in serum cholesterol, triglycerides and phospholipids in both sexes, reduced serum fatty acid levels in males. Females also had reduced thymic weight, and retained uterine fluid was noted. There were no oculotoxic changes and no urinalysis changes attributable to treatment. All drug-induced findings were reversed by the end of the 8 week recovery period. The NOEL of pramipexole in rats as defined in this study was 0.5 mg/kg/day.
Rat Chbb:THOM	20M, 20F	Oral, diet	0, 0.5, 3, 15	52 weeks	There were 6 intercurrent deaths (2 F; controls, 2M at 0.5 mg/kg: 2 M, 1 F at 15 mg/kg) and 2 moribund sacrifices (1 M control. 1 M at 15 mg/kg).The three high dose animals died during or after blood sampling. At 0.5 mg/kg, no toxic changes were noted. Pharmacological effects included increased diurnal and nocturnal activity, particularly in females. In females, increased feed intake with reduced body weight gain, slightly reduced serum cholesterol and triglycerides, slightly increased ovarian weight and a relative granulocytosis (neither of which was accompanied by relevant histopathological changes) were recorded. At 3 mg/kg, the same changes were noted, but to a greater degree. Food consumption reduced body weight gain, slightly reduced triglycerides were also observed in males. In females, slight thrombocytopenia and slight elevated serum GPT, GOT, AP and urea values were recorded. Ovarian weight was significantly increased, reflecting a mild to marked luteal enlargement seen histologically in 18 of 20 animals. In females only, absolute

Table 5: Summary Of Long-Term Toxicity Studies					
Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
					thymic weight was significantly reduced and adrenal weight nonsignificantly increased, without histological changes. Concurrent with a proliferation of the glandular epithelium in females of the mid and high dose groups, a change of the female-like tubuloalveolar morphology of the mammary gland to the typical male-like lobuloalveolar or mixed male/female lobuloalveolar/tubuloalveolar glandular pattern, occurred. Secretory activity in the changed glandular pattern was inconspicuous and consistent with the prolactin-inhibiting effects of the compound. These changes are regarded as reflective of a physiological aspect of mammary development attributable to a hormonal imbalance induced by the prolactin-inhibitory effect of pramipexole combined with the prolonged duration of treatment. Mammary glands of the male rats were unaffected. At 15 mg/kg, all changes noted in the 3 mg/kg group were noted, to a more pronounced degree. The exception was increased food consumption in males, which remained comparable to controls in the high dose group. Additional observations in the high dose group included haemorrhagic vaginal discharge, significantly increased adrenal weight in females: significantly decreased liver weight (with no accompanying histological changes) and esophageal dilatation/impaction in 2 of 20 males. Histologically, pyometra was recorded at a higher frequency in the 15 mg/kg/day group. Depletion of adrenocortical lipids and/or birefringent substances was diagnosed in a small number of females at 15 mg/kg. Chronic pharmacological examination established an increase in spontaneous activity in all treated animals (particularly marked in the 3 and 15 mg/kg groups) as well as an increase in nocturnal activity at 15 mg/kg. Mean plasma concentrations of pramipexole varied within two orders of magnitude. The dose-dependent increase in plasma concentrations was steeper in males than in females. Plasma levels at weeks 26 and 52 were higher in males than in females at 15 mg/kg/day in spite of the fact that drug-related signs were more marked in females. The majority of findings were dose-related from 0.5 to 15 mg/kg/day and were consistent with the pharmacological properties of dopamine agonists. Under the conditions of the study, the toxic NOEL was 0.5 mg/kg/day.
Rat Chbb:THOM	10M, 10F	Intravenous	0, 0.2, 1, 10	5	There were 7 intercurrent deaths - 3M, 1F at 0.2 mg/kg; 1M, 2F at 10 mg/kg. These deaths were not attributed to treatment with pramipexole. There were no treatment related differences in the incidence of clinical findings, ophthalmology, blood parameters or urinalysis. Measurement of spontaneous activity at week 3 showed an increase lasting from 4 to 6

Table 5: Summary Of Long-Term Toxicity Studies					
Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
					hours in low and mid dose animals, and from 12 to 15 hours in high dose rats. Food consumption was reduced in rats at 10 mg/kg during the first week of the study. Treated animals showed a tendency to consume more feed. Water consumption was increased at 10 mg/kg. Spleen weight was decreased in males, reaching statistical significance for absolute and relative values only in the 1 mg/kg group. Ovarian weight and size were increased and thymus weight was decreased in females at 10 mg/kg. No treatment related histopathological changes were observed. In females at 10 mg/kg a slight fall in cholesterol levels was noted, in the 10 mg/kg males, reduced triglyceride and potassium values and a slight rise in chloride levels were recorded. Based on the results of this study the toxic NOEL was approximately 1 mg/kg/day.
Minipig Troll	3M, 3F 6M, 6F in 5 mg/kg group	Oral, diet	0, 0.3, 1, 5	13 8 week follow-up observation	There were no unscheduled deaths during the study. Mild ataxia, tremors, hyperactivity, and piloerection were observed in all treated groups. Behavioural changes noted 1 hour after administration of 0.3 mg/kg or higher doses were considered to be a pharmacodynamic effect, occurring regularly only in the first few weeks of the study and lessening after 2 to 4 weeks. These signs were not dose dependent. A stagnation in body weight gain was noted in treated animals up to the 9th week of the study. Although the same amount of food was consumed by the treated minipigs and the controls, body weight gain was clearly reduced. It is doubtful that the substance-induced hyperactivity and increased motility of the animals is a sufficient explanation because the recovery group females did not show a clear increase in body weight gain with the cessation of dosing. The serous atrophy of the fatty tissue of the atrioventricular groove and of the fats cells in the bone marrow detected at autopsy and histopathologically in sows and one male pig is characteristic of animals in a poor nutritional state. Apart from a slight increase in the reticulocyte count in the animals at 5 mg/kg, in week 2, no other treatment-related or histopathological changes were seen. ECGs (weeks 2, 6, 12) revealed a decrease in heart rate at 1 and 3 hours after ingestion of pramipexole. The rates decreased from pretreatment values by 16% to 35% (0.3 mg/kg). 17% to 32% (l mg/kg) and 12% to 33% (5 mg/kg). These changes were considered to be a pharmacodynamic effect of the compound. Increased locomotion caused by pramipexole lasting for several hours was observed in all treated groups in weeks 4, 8, 10 and 11. Chronic pharmacology examinations (blood pressure and heart rate) of the 0.3 mg/kg supplemental groups (weeks 1, 5, 11) showed a decrease in systolic and

Table 5: Summary Of Long-Term Toxicity Studies					
Strain	Initial Group	Route	Doses (mg/kg/day)	Duration (weeks)	Results
					diastolic blood pressure. Under the conditions of this study, a NOEL was not established.

A delay in sexual development (i.e., preputial separation and vaginal opening) was observed in rats. The relevance for humans is unknown.

CARCINOGENICITY STUDIES

Mouse

Pramipexole was administered to Chbb:NMRI mice, 50/sex/group for two years at drug in-diet-doses of 0.3, 2, or 10 mg/kg/day. Two control groups received only powdered feed.

Plasma concentrations of pramipexole rose with increasing doses in an almost linear, or more steeply than linear, manner. On average, females had higher plasma levels than males.

No distinct, drug-related clinical effects were noted at 0.3 mg/kg/day, although this group had a tendency to consume less feed than the control groups. In the 2 and 10 mg/kg groups, lower body weights and a tendency for increased food and water consumption were noted. Increased spontaneous activity was noted in females at 2 mg/kg, and in both sexes at 10 mg/kg.

The following non-neoplastic changes were noted: increased incidence of fibro-osseous proliferative lesions in the femurs of treated females, decreased incidence of tubular atrophy in the testes of treated males. Increased haemopoietic activity was noted in the femoral bone marrow of females at 2 and 10 mg/kg.

With the exception of a nonsignificant decrease in hepatocellular adenomas in males in all treated groups, and statistically significant decreases in adrenal cortical adenomas in males at 10 mg/kg and malignant lymphomas in females at 2 and 10 mg/kg, the incidence of neoplastic changes was similar in treated and control animals.

Therefore, under the conditions of the study, no carcinogenic effect of the test compound could be established.

Rat

Pramipexole was administered to Chbb:THOM rats, 50/sex/group, for two years by drug-in-diet, at doses of 0.3, 2 or 8 mg/kg/day. Two control groups received only vehicle (powdered feed).

Plasma concentrations of pramipexole increased almost proportionally with increasing dose.

The incidence of mortality (unscheduled deaths and sacrifices) was similar in the treated and two control groups.

Increased spontaneous activity was observed in females at 8 mg/kg. A dose-related, slight to marked decrease in body weight gain was observed in all treated groups, particularly in females. Food consumption was slightly decreased in males from all treated groups, but was moderately increased in females at 2 and 8 mg/kg.

An increased incidence of the following non-neoplastic changes was noted, Leydig cell hyperplasia in males at 2 and 8 mg/kg; large, prominent corpora lutea in females at 8 mg/kg, chronic suppurative inflammatory lesions and haemorrhages in the uteri of females at 2 and 8 mg/kg; change in normal glandular pattern in the mammary gland parenchyma in females at 2 and 8 mg/kg, retinal degeneration in males and females at 2 and 8 mg/kg, minimal to slight diffuse hepatocellular fatty change in females at 2 and 8 mg/kg. A treatment-related decrease in the incidence of focal/multifocal medullary hyperplasia of the adrenal gland and cystic changes of the mammary gland were observed in females at 2 and 8 mg/kg.

A statistically significant increase in the incidence of Leydig cell adenomas was noted in males at 2 and 8 mg/kg. The following neoplasms were significantly decreased in rats at 2 and 8 mg/kg: mammary gland neoplasia in females, pituitary adenomas in both sexes, total number of primary neoplasms in females. Additionally, a decrease in the incidence of benign adrenal medullary neoplasms was observed in female rats at 0.3, 2 and 8 mg/kg/day.

Although retinal degeneration was observed in albino rats given 2 or 8 mg/kg/day, no retinal degeneration was noted at the low dose of 0.3 mg/kg/day. No retinal degeneration was seen in the two year carcinogenicity study in mice at doses of 0.3, 2 or 10 mg/kg/day, in the one year drug-in-diet rat study at doses of 0.5, 3, or 15 mg/kg/day, or in any other study in any species. In investigative studies, the treatment of albino rats with pramipexole clearly reduced the rate of disk shedding from photoreceptor cells, suggesting a perturbation of the steady-state necessary for maintenance of membrane integrity. This change was associated with increased sensitivity of the retina of albino rats to the damaging effects of light. In contrast, pigmented rats exposed to the same levels of pramipexole and even higher intensities of light had absolutely no degeneration of any portion of the retina.

In conclusion, under the conditions of this study, apart from slight decreases in body weight gain, no drug-related adverse effects, including hyperplastic/neoplastic lesions, were recorded at the lowest dose of 0.3 mg/kg/day. Therefore, the NOAEL was 0.3 mg/kg/day.

Mutagenicity studies

In a standard battery of in vitro and in vivo studies, pramipexole was found to be non-mutagenic and non-clastogenic.

REPRODUCTION AND TERATOLOGY

Reproduction and general fertility

Groups of 24 male and 24 female Chbb:THOM rats were administered pramipexole in distilled water at doses of 0 (vehicle), 0.1, 0.5, or 2.5 mg/kg/day. Males were treated for 10 weeks prior to

mating and throughout copulation; females were treated 2 weeks prior to mating during the mating period, and during the gestation and lactation periods.

No treatment-related effects were observed in adults in the 0.1 mg/kg/day group. Additionally, no treatment-related effects were observed in the offspring in this group.

Rats in the 0.5 mg/kg/day group (particularly females) showed clinical signs of CNS excitation (agitation and constant running lasting 6 to 7 hours). Food consumption, body weight, mating, and pregnancy parameters were not affected. A dose of 2.5 mg/kg/day caused moderate to severe agitation in adults, associated with temporary retardation of body weight and food consumption. Treatment-related irregularities in the estrous cycle and/or the severe agitation observed over the treatment period in the 2.5 mg/kg/day group may have been connected to the longer mating performance and the high percentage (61%) of females which failed to become pregnant in this group. The high percentage of non-pregnant females may also have been due to an inhibition of prolactin secretion by pramipexole since the maintenance of functional corpora lutea and successful implantation are dependent upon prolactin.

In the 0.5 mg/kg group, litter parameters of the Caesarean-section group were unchanged, but in the spontaneous delivery group pup body weight development was delayed. While it was not possible to evaluate litter parameters for the Caesarean-section group at 2.5 mg/kg (only one dam produced living progeny), the few pups from the 2.5 mg/kg spontaneous delivery group weighed less at birth and had an even smaller weight increase during the rearing than the 0.5 mg/kg group. In both groups, a slight delay in opening of the eyes was observed. Effects observed in pups in the 0.5 and 2.5 mg/kg/day groups were believed to result from maternal toxicity.

Under the conditions of this study, pramipexole produced maternal toxicity at doses of 0.5 mg/kg/day and greater. There was no indication of impaired male fertility. No teratogenic effects were seen. Apart from retarded weight gain and a retardation in the maturation parameter ‘opening of the eyes’ in the mid- and high-dose pups, the fertility test on the F1 generation showed no impairments. The maximum no-effect dose was 0.1 mg/kg/day.

Due to the lower conception rate in rats administered 2.5 mg/kg/day in the above study; a second Segment I study was conducted. Pramipexole in distilled water was administered to rats at oral doses of 0 (vehicle) or 2.5 mg/kg/day to groups of 24 males at least 9 weeks before mating and during the mating period, and to groups of 24 females at least 2 weeks before mating and during the mating and gestation period as follows: Group 0 (vehicle control): males and females treated with distilled water; Group 1 (positive control): males and females treated with 2.5 mg/kg/day pramipexole; Group 2: males treated with 2.5 mg/kg/day pramipexole, females with distilled water; and Group 3: males treated with distilled water, females with 2.5 mg/kg/day of pramipexole.

Slight toxic effects were noted in treated animals (temporary reduction in body weight gain in males, body weight loss in females at study initiation accompanied by decreased feed intake followed by overcompensation). Both sexes reacted with moderate to severe agitation, which lasted 8 hours or more after administration.

Although treated and untreated couples mated as expected, the number and percentage of pregnant dams were significantly reduced in treated females regardless of whether or not the male partners had been treated. The estrous cycle of about 50% of treated females was prolonged. Light microscopical examination of ovaries from treatment groups 1 and 3 showed an increase in the number of corpora lutea by 75% and 62.5%, respectively. A slight decrease in number of ovarian follicles (showing all stages of folliculogenesis) was noted. A significant ($p < 0.001$) decrease in prolactin levels in all treated males and in eight out of 10 treated females after the administration of 2.5 mg/kg per day was found. The prolonged estrous cycle, the inhibition of nidation, and the increased number of corpora lutea were regarded as a consequence of the marked reduction in prolactin levels. No evidence of embryo- /fetotoxicity or teratogenicity was noted.

Plasma levels taken two hours after the last administration showed concentrations of pramipexole in the range of 93 to 236 ng/mL (females) and 134 ng/mL (males).

In conclusion, under the conditions of this study, the effect of lowered fertility in females was clearly shown to be a consequence of female rather than male treatment with pramipexole.

Teratogenicity
Groups of 36 female Chbb:THOM rats were administered pramipexole in distilled water at oral doses of 0 (vehicle), 0.1, 0.5 or 1.5 mg/kg/day from days 7 to 16 of gestation.

Treatment-related CNS stimulation and a dose-dependent decrease in food intake was observed at 0.5 and 1.5 mg/kg/day. In the majority of high-dose (1.5 mg/kg/day) dams (approximately 78%), there were early resorptions of the entire litter. All surviving pups developed normally. The embryotoxicity (resorptions) seen in the high-dose group were associated with predominantly pharmacodynamically-induced CNS effects (agitation and increased spontaneous activity) in the dams. Although a dose of 0.5 mg/kg/day also produced CNS symptoms in the dams, it did not cause embryo toxic or fetotoxic effects in the offspring. No teratogenicity was observed up to and including the high dose of 1.5 mg/kg/day.

Under the conditions of this study, the NOAEL for maternal toxicity, was 0.1 mg/kg/day, the NOAEL for embryo-fetal toxicity was 0.5 mg/kg/day, and the teratogenic NOAEL was 1.5 mg/kg/day.

Groups of 18 mated female Chbb:HM rabbits were administered pramipexole in distilled water at oral doses of 0 (vehicle). 0.1, 1, or 10 mg/kg/day from day 6 to 18 of gestation. Fetuses were delivered by C-section on day 29.

Reversible excitation and restlessness after 3 to 4 days of treatment were observed at 10 mg/kg/day. Maternal toxicity was observed at 10 mg/kg per day (temporary dose-dependent weight loss or retarded weight gains, one intercurrent death after the third dose of 10 mg/kg probably due to shock-like cardiovascular collapse). Embryo-/fetotoxicity or teratogenicity was not observed.

Under the conditions of this study the NOAEL, for maternal toxicity was 1 mg/kg/day and the embryo/fetotoxic and teratogenic NOAEL was 10 mg/kg/day.

Peri-postnatal toxicity
Groups of 24 pregnant Chbb:THOM rats were administered pramipexole in distilled water at oral doses of 0 (vehicle), 0.1, 0.5, or 1.5 mg/kg/day from day 16 of gestation through day 21 of parturition.

The low dose of 0.1 mg/kg/day was well tolerated. Doses of 0.5 and 1.5 mg/kg/day caused considerable agitation and hyperactivity particularly in lactating rats. Slight maternal toxicity (decreased food consumption) was observed in the 1.5 mg/kg/day dose group. No effects on the duration of pregnancy were observed at any dose.

In the 3-week rearing phase, during which dams in the 0.5 and 1.5 mg/kg/day groups showed signs of great agitation, the body weight increase of pups in those groups was less than that of the controls, perhaps due to insufficient opportunity to suckle. There was no increase in pup mortality, and no fetotoxicity was observed.

The physiological behaviour of the pups during the rearing period and the marginal differences between a few behavioural and developmental parameters in the 0.5 and 1.5 mg/kg/day dose groups, show that despite the great state of excitement in the dams, the vast majority of pups developed normally. Only body weight, which was less (to a dose-dependent degree) than that of control animals, had not recuperated by the time the offspring reached sexual maturity). While the F1 females were lighter, there was no biologically relevant effect on mating and gestational parameters.

Under the conditions of this study, the NOEL for maternal toxicity and fetal development was 0.1 mg/kg/day.

Local tolerance
Pramipexole at a single dose of 100 mg or repeated doses of 0.05% to 0.5% for three days was not irritating to rabbit eyes. Doses of 0.00625% to 0.5% administered to rabbits for four weeks caused mild to moderated increased conjunctival secretion and isolated mild reddening. There was no concentration-effect relationship and findings were fully reversible. No treatment-related histopathological changes of dose-related systemic reactions were observed.

Pramipexole at a single dose of 0.5 g applied occlusively and semi-occlusively to the intact skin of male rabbits was not irritating. Repeated doses of 0.1 g applied to the skin of male rabbits under occlusion for 24-hour periods for five consecutive days was not irritating to intact skin but caused mild, reversible irritation to abraded skin.

A 0.1% injectable solution of pramipexole injected paravenously into the jugular vein was conditionally tolerated by rats. Single intravenous injections of pramipexole 0.1% solution into the marginal vein of the ear were tolerated by rabbits. Single intraarterial injections of pramipexole into the central artery of the ear were tolerated by rabbits.

A skin sensitization (Maximization Test) study in guinea pigs with pramipexole base resulted in a mild sensitizing potential based on sensitization rates of 25% (first challenge) and 20%

(rechallenge) A skin sensitization (Modification of Beuhler Test) study in guinea pigs with pramipexole base as a CPA-patch formulation did not reveal any sensitizing potential.

A 0.1% pramipexole solution for injection added to freshly drawn citrated human blood had no haemolytic effect.

RETINOPATHY IN ALBINO RATS

(See Part I: WARNINGS AND PRECAUTIONS)

REFERENCES

1. Bouthenet ML, Souil E, Martres MP, Sokoloff P, Giros B, Schwartz JC. Localization of a dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: Comparison with dopamine D2 receptor mRNA. Brain Res 1991, 564:203-219.

2. Carter AJ, Müller RE. Pramipexole, a dopamine D2 autoreceptor agonist, decreases the extracellular concentration of dopamine in vivo. Eur J Pharmacol 1991;200:65-72

3. Ensinger HA, Mierau J, Schneider FJ, Hammer R. Effect of a GTP analogue on the binding of pramipexole to the cloned human dopamine receptor subtypes D2, D3, D4. Neuroscience Abstracts 1994;20:526.

4. Mierau J, Schingnitz G. Biochemical and pharmacological studies on pramipexole, a potent and selective dopamine D2 receptor agonist. Eur J Pharmacol 1992; 215:161-170.

5. Mierau J, Schneider FJ, Ensinger HA, Chio CL, Lajiness ME, Huff RM. Pramipexole binding and activation of cloned and expressed dopamine D2, D3 and D4 receptors. Eur J Pharmacol 1995; 290:29-36.

6. Piercey MF, Hoffmann WE, Smith MW, Hyslop DK. Inhibition of dopamine neuron firing by pramipexole, a D3 receptor preferring agonist. Comparison to other dopamine receptor agonists. Eur J Pharmacol 1996; 312:35-44

7. Sokoloff P, Giros B, Martres MP, Bouthenet ML, Schwartz JC. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 1990; 347:146-151

8. Stock B, Spiteller G. Metabolism of antiparkinson drugs. An example of competitive hydroxylation. Arzneimittelforschung 1979; 29(4):610-615. (R96-0702)

Clinical:

9. Dalvi A, Ford B. Antiparkinson Agents: Clinically significant drug interactions and adverse effects, and their management. CNS Drugs 1998; 9(4):291-310.

10. El-Ad B, Korczyn AD. Disorders of excessive daytime sleepiness - an update. J Neurol Sci 1998; 153:192-202.

11. Factor SA, et al. Sleep disorders and sleep effect in Parkinson's disease. Movement Disorders 1990; 5:280-285

12. Frucht S, et a1. Falling asleep at the wheel: Motor vehicle mishaps in persons taking pramipexole and ropinirole. Neurology 1999; 52:1908-1910.

13. Frucht S, et a1. Sleep Episodes in Parkinson's Disease: A Wake-Up Call. Movement Disorders 2000; 15:601-603.

14. Guttman M (International Pramipexole-Bromocriptine Study Group). Double blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. Neurology 1997; 49:1060-1065.

15. Hauser R, et al. Pramipexole-Induced Somnolence and Episodes of Daytime Sleep. Movement Disorders 2000; 15:658-663.

16. Health Canada. Antiparkinsonian drugs and “sleep attacks”. Canadian Adverse Drug Reaction Newsletter Vol 11, No 2. CMAJ 2001; 164(7):1038-1041.

17. Hubble JP, Koller WC, Cutler NR, et al. Pramipexole in patients with early Parkinson's disease. Clin Neuropharmacol 1995; 18:338-347.

18. Kieburtz K, Shoulson I, McDermott M. (Parkinson Study Group). Safety and efficacy of pramipexole in early Parkinson's disease. A randomized dose-ranging study. JAMA, 1997; 278:125-130

19. Lieberman A, Ranhosky A, Korts D. Clinical evaluation of pramipexole in advanced Parkinson's disease. Results of a double-blind, placebo-controlled, parallel-group study. Neurology 1997; 49:162-168.

20. Novak M, Shapiro CM. Drug-induced sleep disturbances. Drug safety 1997; 16:133-149.

21. Reactions 26 Feb 2000; 790:2.

22. Schilling JC, Adamus WS, Palluk R. Neuroendocrine and side effect profile of pramipexole, a new dopamine receptor agonist in humans. Clin Pharmacol and Ther 1992; 51:541-548.

23. Shannon KM, Bennett JP, Jr, Friedman JH. Efficacy of pramipexole, a novel dopamine agonist, as monotherapy in mild to moderate Parkinson's disease. Neurology 1997; 49:724-728.

24. Wright CE, et a1. Steady-state pharmacokinetic properties of pramipexole in healthy volunteers. J Clin Pharmacol 1997; 37:520-525.

25. Guttman M, Kish S, Furukawa Y. Current concepts in the diagnosis and management of Parkinson's Disease. CMAJ 2003; 168(3):293-301.

26. McDonald WM, Richard IH, DeLong M. Prevalence, Etiology and Treatment of Depression in Parkinson’s Disease. Biol Bsychiatry 2003; 54:363-375.

27. Young R. Update on Parkinson’s Disease. AAFP 1999; 59:2155-2169.

28. A Blinded, Single-Dose, Two-Way, Crossover Comparative Bioavailability Study of Two Formulations of Pramipexole Dihydrochloride Monohydrate 0.5mg Tablets in Healthy

Subjects, Under Fasting Conditions. Completed October 20, 2003. Data on file at Teva Canada Limited.

29. Product monograph for Mirapex® manufactured by Boehringer Ingelheim (Canada) Ltd., Date of Revision: July 25, 2017.

PART III: CONSUMER INFORMATION
PrTEVA-PRAMIPEXOLE
(pramipexole dihydrochloride monohydrate tablets)

This leaflet is part III of a three-part "Product Monograph" published when TEVA-PRAMIPEXOLE was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-PRAMIPEXOLE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-PRAMIPEXOLE is used to treat early and late stage Parkinson's disease. TEVA-PRAMIPEXOLE provides relief of signs and symptoms of Parkinson's Disease. Sign and symptoms of the disease include: shaking (tremor), slowness in performing activities of daily living (bradykinesia), muscle stiffness (rigidity) and mood changes (depression). In late stage Parkinson's disease, TEVA-PRAMIPEXOLE will be used in combination with levodopa.

What it does:
TEVA-PRAMIPEXOLE belongs to a group of medicines known as "dopamine agonists". TEVA-PRAMIPEXOLE improves some of the chemical imbalance in the part of the brain affected by Parkinson's Disease.

When it should not be used:
If you are allergic to TEVA-PRAMIPEXOLE, or any of the nonmedicinal ingredients of the product (see list below). TEVA-PRAMIPEXOLE is not recommended for children under 18 years of age.

What the medicinal ingredient is:
pramipexole dihydrochloride monohydrate

What the nonmedicinal ingredients are:
Colloidal Silicon Dioxide, Magnesium Stearate, Mannitol, Microcrystalline Cellulose, Povidone, Sodium Starch Glycolate, Sodium Stearyl Fumarate

What dosage forms it comes in:
TEVA-PRAMIPEXOLE (pramipexole dihydrochloride monohydrate) tablets are available in bottles of 90 tablets; tablets are 0.25 mg, 0.5 mg, 1mg, and 1.5 mg.

WARNING AND PRECAUTIONS

You are warned of a sudden onset of sleep condition and the strong desire to sleep which may occur without warning, while taking TEVA-PRAMIPEXOLE. You should not drive, operate machinery or engage in activities that require alertness, as you may put yourself and others at risk of serious injury or death. This sudden onset of sleep condition has also been reported in patients taking other anti-Parkinson drugs of the same class.

Studies of people with Parkinson's disease show that they may be at an increased risk of developing melanoma (a form of skin cancer) when compared to people without Parkinson's disease. It is not known if this problem is associated with Parkinson's disease or the drugs used to treat Parkinson's disease. TEVA-PRAMIPEXOLE is one of the drugs used to treat Parkinson's disease; therefore, patients treated with TEVA-PRAMIPEXOLE should have periodic skin examinations.

Patients and caregivers should be made aware of the fact that:
- abnormal behaviour such as pathological gambling, increased sexual desire, excessive sexual activity, compulsive shopping or binge eating have been reported. Those changes have also been reported in patients taking other anti-Parkinson drugs of the same class.
- there is a risk in patients with Parkinson's Disease of thoughts or feelings related to suicide (thinking about or feeling like killing yourself) and suicide action (suicide attempt, completed suicide). This risk may still be there even if patients see an improvement in their condition.

BEFORE you use TEVA-PRAMIPEXOLE talk to your doctor or pharmacist if you:
- have any health problems, especially kidney problems or blood pressure problems;
- have any unusual conditions related to your eyes or eyesight;
- have previously taken TEVA-PRAMIPEXOLE and became unwell;
- have any allergies or reactions to foods or drugs;
- are pregnant or intend to become pregnant;
- are breast feeding;
- are taking any other medications, including any drugs you can buy without a prescription;
- have any psychotic disorders;
- drive a vehicle or perform hazardous tasks during your work.

INTERACTIONS WITH THIS MEDICATION

Other medications may be affected by TEVA-PRAMIPEXOLE or may affect how TEVA-PRAMIPEXOLE works. Do not take any other medication, including over-the-counter medications or herbal products unless your doctor tells you to. Tell any other doctor, dentist or pharmacist that you talk to that you are taking TEVA-PRAMIPEXOLE.

Drugs that may interact with TEVA-PRAMIPEXOLE include:

- Levodopa/carbidopa (used to treat Parkinson's disease). TEVA-PRAMIPEXOLE may increase the frequency of hallucinations;
- Amantadine (used to treat Parkinson's disease and used to treat viral infections);
- Drugs used to treat ulcers (such as cimetidine and ranitidine);
- Drugs used to treat high blood pressure and chest pain (such as diltiazem and verapamil);
- Triameterene (used to treat fluid retention in people with heart failure);
- Quinidine (used to treat heart rhythm conditions)
- Quinine (used to treat malaria);
- Antipsychotic medications (dopamine antagonists such as phenothiazines, butyrophenones, thioxathines and metoclopramide). TEVA-PRAMIPEXOLE can make your psychotic symptoms worse;
- Avoid alcohol or other sedatives while taking TEVA-PRAMIPEXOLE.

PROPER USE OF THIS MEDICATION

Usual Adult dose:

Parkinson's disease

Take TEVA-PRAMIPEXOLE in equal doses, three times daily as prescribed by your doctor. Dosages should be increased gradually from a starting dose of 0.125 mg three times daily and should not be increased more frequently than every 5 to 7 days. It is important that your doctor increases your dosage of TEVA-PRAMIPEXOLE gradually to avoid side effects and to achieve the best therapeutic effect. Your dose will probably change each week until your doctor and you decide what the best dose is for you. Make sure that you only use the tablet strength that your doctor has prescribed. The maximal recommended dose of TEVA-PRAMIPEXOLE is 4.5 mg per day. Lower doses are recommended for patients with kidney disease.

Your doctor may decide to lower your dose of levodopa to prevent excessive side effects and to make sure that you are getting the best results from both drugs. Pay close attention to your doctor's instructions and never change the dose of either drug yourself.

You should not change the dose or discontinue treatment with TEVA-PRAMIPEXOLE without the recommendation of your doctor.

You may take TEVA-PRAMIPEXOLE without food or with food if you find that you feel sick to your stomach while taking the tablets.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison ControlCentre immediately, even if there are no symptoms.

If you accidentally take too many tablets, you should get medical help immediately; either by calling your doctor, the regional Poison Control Centre or by going to the nearest hospital (do not drive yourself). Always take the labelled medicine container with you whether or not there are any TEVA-PRAMIPEXOLE tablets left.

Missed Dose:

If you forget to take a dose, take it as soon as you remember, then carry on as before. However, if it is almost time for your next dose, skip the dose you missed and take the next dose when you are supposed to. Do not take more than one dose at a time.

TEVA-PRAMIPEXOLE has been prescribed for you. Do not give these tablets to anyone else, even if you think they have the same condition as you.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

You should be aware that prescription medicines carry some risks and that all possible risks may not be known at this stage. Discuss with your doctor the risks of taking TEVA-PRAMIPEXOLE against the expected benefits.

If you do experience any unusual or unwanted effects while you are taking TEVA-PRAMIPEXOLE, be sure to tell your doctor. It is important that he/she knows of any unwanted effects to determine the best dose of TEVA-PRAMIPEXOLE for you.

- TEVA-PRAMIPEXOLE may cause unwanted effects such as nausea, constipation, sleepiness, dizziness, dream abnormalities, amnesia (memory loss), fatigue, muscle weakness, restlessness, weight decrease, including decreased appetite, weight increased, hiccups, accidental injury, confusion, increase in cholesterol, aggressive behavior, pneumonia, abnormal behaviour (reflecting symptoms of impulse control disorders and compulsions), overeating, headache, hyperkinesia (unusually overactive), fainting, visual impairment, including double vision, vision blurred and visual acuity reduced, shortness of breath, vomiting, heart failure, and peripheral oedema (swelling of hands, ankles or feet).
- TEVA-PRAMIPEXOLE does not usually affect people's normal activities. However, some people may feel dizzy or sleepy while taking TEVA-PRAMIPEXOLE, especially during the first few weeks of treatment.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom /effect		**Talk with your doctor or pharmacist**		**Stop taking drug and call your doctor or pharmacist**
		Only if severe	In all cases	
Common	Dyskinesia **(**Difficulty performing voluntary movements)		√	
	Hallucinations (see, hear, smell, taste or feel something that is not there)		√	
	Insomnia (Difficulty falling asleep)		√	
	Low blood pressure with dizziness when rising to a sitting or standing position. You may feel sick, light-headed, faint or you may sweat		√	
Uncom-mon	Behavioral changes such as compulsive gambling, compulsive shopping, changes in sexual desire or sexual activity, increased eating			
	Delusion (a false belief, despite incontrovertible evidence, that something is false)		√	
	Paranoia (unrealistic and excessive anxiety and worry)		√	
	Sudden onset of sleep and the strong desire to sleep		√	
	Hypersensitivity (allergic reaction) with symptoms such as: red, itchy swellings on the skin, swelling of the face, lips, mouth, tongue or throat, difficulty swallowing or breathing, rash or intense itching.			√

Do not be alarmed by this list of possible side effects. You may not experience any of them. This is not a complete list of side effects. For any unexpected effects while taking TEVA-PRAMIPEXOLE, contact your doctor or pharmacist immediately, so that these effects may be properly addressed.

HOW TO STORE IT

- Keep this drug away from light and moisture. TEVA-PRAMIPEXOLE may change colour when exposed to light.
- TEVA-PRAMIPEXOLE should be stored at room temperature (15 – 25°C) in the original container.
- The expiry date of this medicine is printed on the label. Do not use the medicine after this date.
- Keep this drug out of the reach of children.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com ; or
Fax: 1-416-335-4472

This leaflet was prepared by:
Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

www.tevacanada.com

Last revised: September 20, 2017