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תאריך: **9 בנובמבר 2011**  
שם תכשיר באנגלית: **SIFROL ER Tablets 0.375mg, 0.75mg, 1.5mg, 4.5mg**  
מספרי רישום: **144-95-33088, 144-96-33089, 144-97-33090, NEW 33439, 33441**  
שם בעל הרישום: **מעבדות רפא בע"מ**

**השינויים בעלון מסומנים ברקע צהוב**

עלון לרופא

פרטים על השינויים המבוקשים	
טקסט חדש	פרק בעלון
(no change)	Special Warn-ings and PrecauTions
(no change)	Contra-indications
<p><u>Expected adverse reactions</u></p> <p>The following adverse reactions are expected under the use of SIFROL: abnormal dreams, amnesia, behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality and pathological gambling; <b>cardiac failure</b>, confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, <b>hiccups</b>, hyperkinesia, hyperphagia, hypotension, insomnia, libido disorders, nausea, paranoia, peripheral oedema, pneumonia, pruritus, rash and other hypersensitivity; restlessness, somnolence, sudden onset of sleep, syncope, visual <b>disturbance</b> <b>impairment</b> including <b>diplopia</b>, vision blurred and visual acuity reduced, vomiting, weight decrease <b>including decreased appetite</b>, weight increase.</p> <p>Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,778 Parkinson's disease patients on pramipexole and 1,297 patients on placebo, adverse drug reactions were frequently reported for both groups. 67% of patients on pramipexole and 54% of patients on placebo reported at least one adverse drug reaction.</p> <p>The adverse drug reactions reported in the table below are those events that occurred in 0.1% or more of patients treated with pramipexole and were reported significantly more often in patients taking pramipexole than placebo, or where the event was considered clinically relevant. The majority of adverse drug reactions were mild to moderate, they usually start early in therapy and most tended to disappear even as therapy was continued.</p>	Adverse Events

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories: very common ( $\geq 1/10$ ); common ( $\geq 1/100$  to  $< 1/10$ ); uncommon ( $\geq 1/1,000$  to  $< 1/100$ ); rare ( $\geq 1/10,000$  to  $< 1/1,000$ ); very rare ( $< 1/10,000$ ); not known (cannot be estimated from the available data).

The most commonly ( $\geq 5\%$ ) reported adverse drug reactions in patients with Parkinson's disease more frequent with pramipexole treatment than with placebo were nausea, dyskinesia, hypotension, dizziness, somnolence, insomnia, constipation, hallucination, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg pramipexole salt per day (see section 4.2). A more frequent adverse drug reaction in combination with levodopa was dyskinesia. Hypotension may occur at the beginning of treatment, especially if pramipexole is titrated too fast.

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia
Psychiatric disorders	
Common	abnormal dreams, behavioural symptoms of impulse control disorders and compulsions; confusion, hallucinations, insomnia,
Uncommon	binge eating <sup>1</sup> , compulsive shopping, delusion, hyperphagia <sup>1</sup> , hypersexuality, libido disorder, paranoia, pathological gambling, restlessness
Nervous system disorders	
Very common	dizziness, dyskinesia, somnolence
Common	headache
Uncommon	amnesia, hyperkinesia, sudden onset of sleep, syncope
Eye disorders	
Common	visual impairment including diplopia, vision blurred and visual acuity reduced
Cardiac disorders	
Uncommon	cardiac failure <sup>1</sup>
Vascular disorders	
Common	hypotension
Respiratory, thoracic, and mediastinal disorders	
Uncommon	dyspnoea, hiccups
Gastrointestinal disorders	
Very common	nausea
Common	constipation, vomiting
Skin and subcutaneous tissue disorders	
Uncommon	hypersensitivity, pruritus, rash
General disorders and administration site conditions	
Common	fatigue, peripheral oedema
Investigations	
Common	weight decrease including decreased appetite
Uncommon	weight increase

<sup>1</sup> This side effect has been observed in post-marketing experience. With

95 % certainty, the frequency category is not greater than uncommon, but might be lower. A precise frequency estimation is not possible as the side effect did not occur in a clinical trial database of 2,762 patients with Parkinson's Disease treated with pramipexole.

#### Somnolence

Pramipexole is commonly associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (see also section 4.4).

#### Libido disorders

Pramipexole may uncommonly be associated with libido disorders (increased or decreased).

#### Impulse control disorders and compulsive behaviours

Patients treated with dopamine agonists for Parkinson's disease, including SIFROL, especially at high doses, have been reported as exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation. See also section 4.4.

In a cross-sectional, retrospective screening and case-control study including 3,090 Parkinson's disease patients, 13.6% of all patients receiving dopaminergic or non-dopaminergic treatment had symptoms of an impulse control disorder during the past six months. Manifestations observed include pathological gambling, compulsive shopping, binge eating, and compulsive sexual behaviour (hypersexuality). Possible independent risk factors for impulse control disorders included dopaminergic treatments and higher doses of dopaminergic treatment, younger age ( $\leq 65$  years), not being married and self-reported family history of gambling behaviours.

#### Cardiac failure

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 (observed risk ratio 1.86; 95% CI, 1.21-2.85).

#### Plasma protein binding

Pramipexole is bound to plasma proteins to a very low ( $< 20\%$ ) extent, and little biotransformation is seen in man. Therefore, interactions with other medicinal products affecting plasma protein binding or elimination by biotransformation are unlikely. As anticholinergics are mainly eliminated by biotransformation, the potential for an interaction is limited, although an interaction with anticholinergics has not been investigated. There is no pharmacokinetic interaction with selegiline and levodopa.

#### Inhibitors/competitors of active renal elimination pathway

Cimetidine reduced the renal clearance of pramipexole by approximately 34%, presumably by inhibition of the cationic secretory transport system of the renal tubules. Therefore, medicinal products that are inhibitors of this active renal elimination pathway or are eliminated by this pathway, such as cimetidine, amantadine, and mexiletine, zidovudine, cisplatin, quinine, and procainamide, may interact with pramipexole resulting in reduced clearance of pramipexole either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with SIFROL.

### **Drug Inter-actions**

### Combination with levodopa

When SIFROL is given in combination with levodopa, it is recommended that the dose of levodopa is reduced and the dose of other anti-parkinsonian medicinal products is kept constant while increasing the dose of SIFROL.

Because of possible additive effects, caution should be advised when patients are taking other sedating medicinal products or alcohol in combination with pramipexole (see sections 4.4, 4.7 and 4.8).

### Antipsychotic medicinal products

Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.

## **Posology**

SIFROL prolonged-release tablets are a once-a-day oral formulation of pramipexole.

### Initial treatment

Doses should be increased gradually from a starting dose of 0.375 mg of salt (0.26 mg of base) per day and then increased every 5 - 7 days. Providing patients do not experience intolerable undesirable effects, the dose should be titrated to achieve a maximal therapeutic effect.

Ascending dose schedule of SIFROL prolonged-release tablets		
Week	Daily dose (mg of salt)	Daily dose (mg of base)
1	0.375	0.26
2	0.75	0.52
3	1.5	1.05

If a further dose increase is necessary the daily dose should be increased by 0.75 mg of salt (0.52 mg of base) at weekly intervals up to a maximum dose of 4.5 mg of salt (3.15 mg of base) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg of salt (1.05 mg of base) per day (see section 4.8).

Patients already taking SIFROL tablets may be switched to SIFROL prolonged-release tablets overnight, at the same daily dose. After switching to SIFROL prolonged-release tablets, the dose may be adjusted depending on the patient's therapeutic response (see section 5.1).

### Maintenance treatment

The individual dose of pramipexole should be in the range of 0.375 mg of salt (0.26 mg of base) to a maximum of 4.5 mg of salt (3.15 mg of base) per day. During dose escalation in pivotal studies, efficacy was observed starting at a daily dose of 1.5 mg of salt (1.05 mg of base). Further dose adjustments should be done based on the clinical response and the occurrence of adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.5 mg of salt (1.05 mg of base). In advanced Parkinson's disease, pramipexole doses higher than 1.5 mg of salt (1.05 mg of base) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dose of levodopa is reduced during both the dose escalation and the maintenance treatment with SIFROL, depending on reactions in individual patients (see section 4.5).

## **Dosage and Administration**

### Missed dose

When the intake of a dose is missed, SIFROL prolonged-release tablets should be taken within 12 hours after the regularly scheduled time. After 12 hours, the missed dose should be left out and the next dose should be taken on the following day at the next regularly scheduled time.

### Treatment discontinuation

Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.75 mg of salt (0.52 mg of base) per day until the daily dose has been reduced to 0.75 mg of salt (0.52 mg of base). Thereafter the dose should be reduced by 0.375 mg of salt (0.26 mg of base) per day (see section 4.4).

### Dosing in patients with renal impairment

The elimination of pramipexole is dependent on renal function. The following dose schedule is suggested:

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, treatment should be started with 0.375 mg SIFROL prolonged-release tablets every other day. Caution should be exercised and careful assessment of therapeutic response and tolerability should be made before increasing to daily dosing after one week. If a further dose increase is necessary, doses should be increased by 0.375 mg pramipexole salt at weekly intervals up to a maximum dose of 2.25 mg of salt (1.57 mg pramipexole base) per day.

The treatment of patients with a creatinine clearance below 30 ml/min with SIFROL prolonged-release tablets is not recommended as no data are available for this patient population. The use of SIFROL tablets should be considered. If renal function declines during maintenance therapy, the recommendations given above should be followed.

### Dosing in patients with hepatic impairment

Dose adjustment in patients with hepatic failure is probably not necessary, as approx. 90% of absorbed active substance is excreted through the kidneys. However, the potential influence of hepatic insufficiency on SIFROL pharmacokinetics has not been investigated.

### Paediatric population

The safety and efficacy of SIFROL in children below 18 years has not been established. There is no relevant use of SIFROL prolonged-release tablets in the paediatric population in Parkinson's Disease.<sup>1</sup>

### **Method of administration**

The tablets should be swallowed whole with water, and must not be chewed, divided or crushed. The tablets may be taken either with or without food and should be taken each day at about the same time.

### Prolonged-release tablets.

The tablets are white to off-white, (0.375, 0.75 mg of round shape and 1.5 mg of oval shape), with bevelled edges, and have a code embossed (one side with the code P1, P2 or P3 respectively, and one side with the Boehringer Ingelheim company symbol).

Strength (mg salt)	Appearance
Sifrol ER 0.375	round, with bevelled edges, code embossed (one side with code P1 and one side with the Boehringer Ingelheim company symbol).
Sifrol ER 0.75	round, with bevelled edges, code embossed (one side with code P2 and one side with the Boehringer Ingelheim company symbol).
Sifrol ER 1.5	oval, code embossed (one side with code P3 and one side with the Boehringer Ingelheim company symbol).
Sifrol ER 4.5	oval, code embossed (one side with code P5 and one side with the Boehringer Ingelheim company symbol).

### Pharma- Ceutical Form

Repeated dose toxicity studies showed that pramipexole exerted functional effects, mainly involving the CNS and female reproductive system, and probably resulting from an exaggerated pharmacodynamic effect of pramipexole.

Decreases in diastolic and systolic pressure and heart rate were noted in the minipig, and a tendency to a hypotensive effect was discerned in the monkey.

The potential effects of pramipexole on reproductive function have been investigated in rats and rabbits. Pramipexole was not teratogenic in rats and rabbits but was embryotoxic in the rat at maternally toxic doses. Due to the selection of animal species and the limited parameters investigated, the adverse effects of pramipexole on pregnancy and male fertility have not been fully elucidated.

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

Pramipexole was not genotoxic. In a carcinogenicity study, male rats developed Leydig cell hyperplasia and adenomas, explained by the prolactin-inhibiting effect of pramipexole. This finding is not clinically relevant to man. The same study also showed that, at doses of 2 mg/kg (of salt) and higher, pramipexole was associated with retinal degeneration in albino rats. The latter finding was not observed in pigmented rats, nor in a 2-year albino mouse carcinogenicity study or in any other species investigated.

### Pre-clinical safety data