הודעה על החמרה (מידע בטיחות)

תאריך: 26 ביוני 2012
שם תכשיר באנגלית: Sifrol Tablets 0.25 mg, 1 mg
מספר רישום: 126 16 30501, 126 17 30500
שם בעל הרישום: מעבדות רפא בע"מ

השינויים בעלון מסומנים בצבע - צהוב=הוספה, ~~ירוק~~=מחיקה, כחול=שינוי מקום.

בעלון לרופא

טקסט חדש	טקסט נוכחי	פרק בעלון
Sifrol is indicated in adults for treatment of the signs and symptoms of idiopathic Parkinson's disease, ~~it may be used as monotherapy or in combination with~~ alone (without levodopa) or in combination with levodopa~~.~~, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations). Sifrol is indicated in adults for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in doses up to 0.75 mg of salt (0.54 mg of base) (see section 4.2).	Sifrol is indicated for treatment of the signs and symptoms of idiopathic Parkinson's disease, it may be used as monotherapy or in combination with levodopa, i.e. over the course of the disease, through to late stages when the effect of levodopa wears off or becomes inconsistent and fluctuations of the therapeutic effect occur (end of dose or "on off" fluctuations). Sifrol is indicated for symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome.	**Therapeutic Indication**
Posology *Parkinson's disease:* ~~The tablets should be taken orally, swallowed with water, and can be taken either with or without food.~~ The daily dosage is administered in equally divided doses 3 times a day. Initial treatment Dosages should be increased gradually from a starting-dose of 0.375 mg salt (0.264 mg of base) per day and then increased every 5-7 days. Providing patients do not experience intolerable ~~side-~~ undesirable effects, the dosage should be titrated to achieve a maximal therapeutic effect. *Ascending – Dose Schedule of SIFROL table – no significant changes* If a further dose increase is necessary the daily dose should be increased by 0.75 mg of salt (0.54 mg base) at weekly intervals up to a maximum dose of 4.5 mg of salt (3.3 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) ~~/~~ per day (see section 4.8). Maintenance treatment The individual dose of pramipexole should be in the range of 0.375 mg salt (0.264 mg base) to a maximum of 4.5 mg salt (3.3 mg base) per day. During dose escalation in ~~three~~ pivotal studies, efficacy was observed starting at a	*Parkinson's disease:* The tablets should be taken orally, swallowed with water, and can be taken either with or without food.~~-~~The daily dosage is administered in equally divided doses 3 times a day. Initial treatment Dosages should be increased gradually from a starting-dose of 0.375 mg salt (0.264 mg base) per day and then increased every 5-7 days. Providing patients do not experience intolerable side- effects, the dosage should be titrated to achieve a maximal therapeutic effect. *Ascending – Dose Schedule of SIFROL table* If a further dose increase is necessary the daily dose should be increased by 0.75 mg salt (0.54 mg base) at weekly intervals up to a maximum dose of 4.5 mg salt (3.3 mg of base) per day. However, it should be noted that the incidence of somnolence is increased at doses higher than 1.5 mg salt a day (see section 4.8). Maintenance treatment The individual dose should be in the range of 0.375 mg salt (0.264 mg base) to a maximum of 4.5 mg salt (3.3 mg base) per day. During dose escalation in ~~t~~hree pivotal studies, efficacy was observed starting at a daily dose	**Posology and method of administration**

daily dose of 1.5 mg salt (1.05 mg base). Further dose adjustments should be done based on the clinical response and the occurrence of ~~undesirable~~ ~~effects~~ adverse reactions. In clinical trials approximately 5% of patients were treated at doses below 1.5 mg salt (1.05 mg base). In advanced Parkinson's disease, pramipexole doses higher than 1.5 mg salt (1.05 mg base) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dos~~ag~~e 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). Treatment discontinuation Abrupt discontinuation of dopaminergic therapy can lead to the development of a neuroleptic malignant syndrome. ~~Therefore,~~ ~~p~~Pramipexole should be tapered off at a rate of 0.75 mg salt (0.54 mg base) per day until the daily dose has been reduced to 0.75 mg salt (0.54 mg base). Thereafter the dose should be reduced by 0.375 mg salt (0.264 mg base) per day (see section 4.4). Dosing in patients with renal impairment The elimination of pramipexole is dependent on renal function. The following dos~~ag~~e schedule is suggested for initiation of therapy: 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 20 and 50 ml/min, the initial daily dose of SIFROL should be administered in two divided doses, starting at 0.125 mg salt (0.088 mg base) twice a day (0.25 mg salt/0.176 mg base daily). A maximum daily dose of 2.25 mg salt (1.57 mg base) should not be exceeded. In patients with a creatinine clearance less than 20 ml/min, the daily dose of SIFROL should be administered in a single dose, starting at 0.125 mg salt (0.088 mg base) daily. A maximum daily dose of 1.5 mg salt (1.05 mg base) should not be exceeded. If renal function declines during maintenance therapy the ~~reduce~~ SIFROL daily dose should be reduced by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then ~~reduce~~ the SIFROL daily dose should be reduced by 30%. The daily dose can be administered in two divided doses if creatinine clearance is	of 1.5 mg salt (1.05 mg base). Further dose adjustments should be done based on the clinical response and the occurrence of undesirable effects . In clinical trials approximately 5% of patients were treated at doses below 1.5 mg salt (1.05 mg base). In advanced Parkinson's disease,doses higher than 1.5 mg salt (1.05 mg base) per day can be useful in patients where a reduction of the levodopa therapy is intended. It is recommended that the dosage of levodopa is reduced during both the dose escalation and the maintenance treatment with SIFROL, depending on reactions in individual patients. Treatment discontinuation Abrupt discontinuation of dopaminergic therapy can lead to the development of neuroleptic malignant syndrome. Therefore, pramipexole should be tapered off at a rate of 0.75 mg salt (0.54 mg base) per day until the daily dose has been reduced to 0.75 mg salt (0.54 mg base). Thereafter the dose should be reduced by 0.375 mg salt (0.264 mg base) per day (see section 4.4). Dosing in patients with renal impairment The elimination of pramipexole is dependent on renal function. The following dosage schedule is suggested for initiation of therapy: Patients with a creatinine clearance above 50 ml/min require no reduction in daily dose. In patients with a creatinine clearance between 20 and 50 ml/min, the initial daily dose of SIFROL should be administered in two divided doses, starting at 0.125 mg salt (0.088 mg base) twice a day (0.25 mg salt/0.176 mg base daily). In patients with a creatinine clearance less than 20 ml/min, the daily dose of SIFROL should be administered in a single dose, starting at 0.125 mg salt (0.088 mg base) daily. If renal function declines during maintenance therapy reduce SIFROL daily dose by the same percentage as the decline in creatinine clearance, i.e. if creatinine clearance declines by 30%, then reduce the SIFROL 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.	

between 20 and 50 ml/min and as a single daily dose if creatinine clearance is less than 20 ml/min. 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 in the paediatric population in Parkinson's Disease. *Restless Legs Syndrome:* ~~The tablets should be taken orally, swallowed with water, and can be taken either with or without food.~~ The recommended starting dose of SIFROL is 0.125 mg salt (0.088 mg base) taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days to a maximum of 0.75 mg salt (0.54 mg base) per day (as shown in the table below). *Dose Schedule of SIFROL table - no significant changes* ~~As long-term efficacy of SIFROL in the treatment of RLS has not been sufficiently tested,~~ pPatient´s response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above. Treatment discontinuation Since the daily dose for the treatment of Restless Legs Syndrome will not exceed 0.75 mg salt (0.54 mg base) SIFROL can be discontinued without tapering off. ~~Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded.~~ In a 26 week placebo controlled trial, rebound of RLS symptoms (worsening of symptom severity as compared to baseline) was observed in 10% of patients (14 out of 135) after abrupt discontinuation of treatment. This effect was found to be similar across all doses. Dosing in patients with renal impairment The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose. The use of SIFROL has not been studied in haemodialysis patients, or in patients with severe renal impairment. Dosing in patients with hepatic impairment Dose adjustment in patients with hepatic failure is not required, as approx. 90% of absorbed active substance is excreted through	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. *Restless Legs Syndrome:* The tablets should be taken orally, swallowed with water, and can be taken either with or without food. The recommended starting dose of SIFROL is 0.125 mg salt (0.088 mg base) taken once daily 2-3 hours before bedtime. For patients requiring additional symptomatic relief, the dose may be increased every 4-7 days to a maximum of 0.75 mg salt (0.54 mg base) per day (as shown in the table below). *Dose Schedule of SIFROL table* As long-term efficacy of SIFROL in the treatment of RLS has not been sufficiently tested, patient´s response should be evaluated after 3 months treatment and the need for treatment continuation should be reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above. Treatment discontinuation Since daily dose for the treatment of Restless Legs Syndrome will not exceed 0.75 mg salt (0.54 mg base) SIFROL can be discontinued without tapering off. Rebound (worsening of symptoms after abrupt discontinuation of treatment) cannot be excluded. Dosing in patients with renal impairment The elimination of pramipexole is dependent on renal function. Patients with a creatinine clearance above 20 ml/min require no reduction in daily dose. The use of SIFROL has not been studied in haemodialysis patients, or in patients with severe renal impairment. Dosing in patients with hepatic impairment Dose adjustment in patients with hepatic failure is not required, as approx. 90% of absorbed active substance is excreted through	

the kidneys. ~~Dosing in children and adolescents~~ Paediatric population SIFROL is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy. *Tourette Disorder* Paediatric population SIFROL is not recommended for use in children and adolescents below 18 years since the efficacy and safety has not been established in this population. SIFROL should not be used in children or adolescents with Tourette Disorder because of a negative benefit-risk balance for this disorder (see section 5.1). **Method of administration** The tablets should be taken orally, swallowed with water, and can be taken either with or without food.	the kidneys. Dosing in children and adolescents SIFROL is not recommended for use in children and adolescents below 18 years due to a lack of data on safety and efficacy.	
When prescribing SIFROL ~~tablets~~ in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2. Hallucinations Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. Dyskinesia In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesia~~s~~ can occur during the initial titration of SIFROL. If they occur, the dose of levodopa should be decreased. Sudden onset of sleep and somnolence ~~SIFROL~~ Pramipexole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with SIFROL. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of the dosa~~g~~e or termination of therapy may be considered. 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 4.5, 4.7 and section 4.8). Impulse control disorders and compulsive behaviours	When prescribing SIFROL tablets in a patient with Parkinson's disease with renal impairment a reduced dose is suggested in line with section 4.2. Hallucinations are known as a side effect of treatment with dopamine agonists and levodopa. Patients should be informed that (mostly visual) hallucinations can occur. In advanced Parkinson's disease, in combination treatment with levodopa, dyskinesias can occur during the initial titration of SIFROL. If they occur, the dose of levodopa should be decreased. SIFROL has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson's disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported uncommonly. Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with SIFROL. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore a reduction of dosage or termination of therapy may be considered. 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 4.7 and section 4.8). Pathological gambling, increased libido and	**Special Warning and Precautions for Use**

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including SIFROL. Furthermore, patients and caregivers should be aware of the fact that other behavioural ~~changes~~ symptoms of impulse control disorders and compulsions such as binge eating and compulsive shopping can occur. Dose reduction/tapered discontinuation should be considered. Patients with psychotic disorders Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5). Ophthalmologic monitoring Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. Severe cardiovascular disease In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. Neuroleptic malignant syndrome Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2). Augmentation Reports in the literature indicate that treatment of Restless Legs Syndrome with dopaminergic medicinal~~ations~~ products can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. ~~The controlled trials of SIFROL in patients with Restless Legs Syndrome were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of SIFROL and the appropriate management of these events have not been evaluated in controlled clinical trials.~~ Augmentation was specifically investigated in a controlled clinical trial over 26 weeks. Augmentation was observed in 11.8% of patients in the pramipexole group (N = 152) and 9.4% of patients in the placebo group (N = 149). Kaplan-Meier analysis of time to augmentation showed no significant difference between pramipexole and placebo groups.	hypersexuality have been reported in patients treated with dopamine agonists for Parkinson's disease, including SIFROL. Furthermore, patients and caregivers should be aware of the fact that behavioural changes can occur. Dose reduction/taper discontinuation should be considered. Patients with psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks. Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.5). Ophthalmologic monitoring is recommended at regular intervals or if vision abnormalities occur. In case of severe cardiovascular disease, care should be taken. It is recommended to monitor blood pressure, especially at the beginning of treatment, due to the general risk of postural hypotension associated with dopaminergic therapy. Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy (see section 4.2). Reports in the literature indicate treatment of Restless Legs Syndrome with dopaminergic mediations can result in augmentation. Augmentation refers to the earlier onset of symptoms in the evening (or even the afternoon), increase in symptoms, and spread of symptoms to involve other extremities. The controlled trials of SIFROL in patients with Restless Legs Syndrome were generally not of sufficient duration to adequately capture augmentation phenomena. The frequency of augmentation after longer use of SIFROL and the appropriate management of these events have not been evaluated in controlled clinical trials.	
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	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	**Interaction with other medicinal products and other forms of interaction**

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, ~~and~~ amantadine, 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. Combination with levodopa When SIFROL is given in combination with levodopa, it is recommended that the dos~~ag~~e of levodopa is reduced and the dos~~ag~~e of other anti-parkinsonian medic~~ation~~inal 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 section 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.	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. 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, and amantadine may interact with pramipexole resulting in reduced clearance of either or both medicinal products. Reduction of the pramipexole dose should be considered when these medicinal products are administered concomitantly with SIFROL. When SIFROL is given in combination with levodopa, it is recommended that the dosage of levodopa is reduced and the dosage of other anti-parkinsonian medication 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. Co-administration of antipsychotic medicinal products with pramipexole should be avoided (see section 4.4), e.g. if antagonistic effects can be expected.	
Pregnancy The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3). SIFROL should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus. **Breast-feeding** As ~~SIFROL~~ pramipexole treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of ~~SIFROL~~ pramipexole into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma. In the absence of human data, SIFROL should	The effect on pregnancy and lactation has not been investigated in humans. Pramipexole was not teratogenic in rats and rabbits, but was embryotoxic in the rat at maternotoxic doses (see section 5.3). SIFROL should not be used during pregnancy unless clearly necessary, i.e. if the potential benefit justifies the potential risk to the foetus. As SIFROL treatment inhibits secretion of prolactin in humans, inhibition of lactation is expected. The excretion of SIFROL into breast milk has not been studied in women. In rats, the concentration of active substance-related radioactivity was higher in breast milk than in plasma. In the absence of human data, SIFROL should not be used during breast-feeding. However, if	**Fertility, ~~P~~pregnancy and lactation**

not be used during breast-feeding. However, if its use is unavoidable, breast-feeding should be discontinued. **Fertility** No studies on the effect on human fertility have been conducted. In animal studies, pramipexole affected oestrous cycles and reduced female fertility as expected for a dopamine agonist. However, these studies did not indicate direct or indirect harmful effects with respect to male fertility	its use is unavoidable, breast-feeding should be discontinued.	
~~Patients treated with pramipexole tablets have reported falling asleep during activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole tablets at doses above 1.5 mg/day, and which, according to the current knowledge of sleep physiology, always proceeds falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy.~~ Expected adverse reactions 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; cardiac failure, confusion, constipation, delusion, dizziness, dyskinesia, dyspnoea, fatigue, hallucinations, headache, hiccups, hyperkinesia, hyperphagia, hypotension, ~~increased eating (binge eating, hyperphagia),~~ insomnia, libido disorders, nausea, paranoia, peripheral oedema, ~~paranoia,~~ pneumonia, pruritus rash and other hypersensitivity; ~~pathological gambling, hypersexuality and other abnormal behaviour,~~ restlessness, somnolence, sudden onset of sleep, syncope, visual impairment including diplopia, vision blurred and visual acuity reduced, vomiting, weight decrease including decreased appetite, weight increase~~, sudden onset of sleep, pruritis and rash and other hypersensitivity~~. Based on the analysis of pooled placebo-controlled trials, comprising a total of 1,923 patients on ~~SIFROL~~ pramipexole and 1,354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on ~~SIFROL~~ pramipexole and 52% of patients on placebo reported at least one adverse drug reaction.	Patients treated with pramipexole tablets have reported falling asleep during activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Some of them did not report a warning sign such as somnolence, which is a common occurrence in patients receiving pramipexole tablets at doses above 1.5 mg/day, and which, according to the current knowledge of sleep physiology, always proceeds falling asleep. There was no clear relation to the duration of treatment. Some patients were taking other medication with potentially sedative properties. In most cases where information was available, there were no further episodes following reduction of dosage or termination of therapy. The following adverse reactions are expected under the use of SIFROL: abnormal dreams, confusion, constipation, delusion, dizziness, dyskinesia, fatigue, hallucinations, headache, hyperkinesia, hypotension, increased eating (binge eating, hyperphagia), insomnia, libido disorders, nausea, peripheral oedema, paranoia, pathological gambling, hypersexuality and other abnormal behaviour, somnolence, weight increase, sudden onset of sleep, pruritis rash and other hypersensitivity. Based on the analysis of pooled placebo-controlled trials, comprising a total of 1923 patients on SIFROL and 1354 patients on placebo, adverse drug reactions were frequently reported for both groups. 63% of patients on SIFROL and 52% of patients on placebo reported at least one adverse drug reaction. The most commonly (≥ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with SIFROL treatment than with Placebo were nausea, dyskinesia, orthostatic hypotension, dizziness, somnolence, insomnia, constipation, hallucination visual, headache and fatigue. The incidence of somnolence is increased at doses higher than 1.5 mg/ day (see section 4.2.). A More frequent adverse drug reactions in	**Undesirable effects**

Tables 1 and 2 ~~below~~ display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 0.1% or more of patients treated with ~~SIFROL~~ pramipexole and were reported significantly more often in patients taking ~~SIFROL~~ pramipexole than placebo, or where the event was considered clinically relevant. ~~However,~~ 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. 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 (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Parkinson's disease, most common adverse reactions The most commonly (≥ 5%) reported adverse drug reactions in patients with Parkinson's disease more frequent with ~~SIFROL~~ pramipexole treatment than with Placebo were nausea, dyskinesia, ~~orthostatic~~ hypotension, dizziness, somnolence, insomnia, constipation, hallucination ~~visual~~, 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 ~~M~~more frequent adverse drug reaction~~s~~ in combination with levodopa ~~were~~ was dyskinesia~~s~~. Hypotension may occur at the beginning of treatment, especially if ~~SIFROL~~ pramipexole is titrated too fast. Table 1: Parkinson's disease (ON FORM, SEE AT END OF DOCTORS' LEAFLET) [1] 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. Restless Legs Syndrome, most common adverse reactions The most commonly (≥ 5%) reported adverse drug reactions in patients with Restless Legs Syndrome treated with ~~SIFROL~~ Pramipexole were nausea, headache, dizziness and fatigue. Nausea and fatigue were more often reported in female patients treated with SIFROL (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively). Table 2: Restless Legs Syndrome (ON FORM, SEE AT END OF DOCTORS' LEAFLET) [1] This side effect has been observed in post-	combination with levodopa were dyskinesias. Hypotension may occur at the beginning of treatment, especially if SIFROL is titrated too fast. (on form, see Table 1 at end of doctors' leaflet) The most commonly (≥ 5%) reported adverse drug reactions in patients with Restless Legs Syndrome treated with SIFROL were nausea, headache, and fatigue. Nausea and fatigue were more often reported in female patients treated with SIFROL (20.8% and 10.5%, respectively) compared to males (6.7% and 7.3%, respectively). (on form, see table 2 at end of doctors' leaflet) Tables 1 and 2 below display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug-reactions reported in these tables are those events that occurred in 1% or more of patients treated with SIFROL and were reported significantly more often in patients taking SIFROL than placebo, or where the event was considered clinically relevant. However, the majority of common drug adverse reactions were mild to moderate; they usually start early in therapy, and most tended to disappear even as therapy was continued. Table 1: Very common Adverse Drug Reactions (≥1/10) (on form, see at end of doctors' leaflet) Table 2: Common Adverse Drug Reactions (≥ 1/100 to <1/10) (on form, see at end of doctors' leaflet) SIFROL is associated with somnolence (8.6%) and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes (0.1%). See also section 4.4. SIFROL may be associated with libido disorders [(increased (0.1%) or decreased (0.4%)]. 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	

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 1,395 patients with Restless Legs Syndrome treated with pramipexole.

~~Tables 1 and 2 below display the frequency of adverse drug reactions from placebo-controlled clinical trials in Parkinson's disease and Restless Legs Syndrome. The adverse drug reactions reported in these tables are those events that occurred in 1% or more of patients treated with SIFROL and were reported significantly more often in patients taking SIFROL than placebo, or where the event was considered clinically relevant. However, the majority of common drug adverse reactions were mild to moderate; they usually start early in therapy, and most tended to disappear even as therapy was continued.~~

~~Table 1: Very common Adverse Drug Reactions (≥1/10)~~ (ON FORM, SEE AT END OF DOCTORS' LEAFLET)

~~Table 2: Common Adverse Drug Reactions (≥ 1/100 to <1/10)~~ (ON FORM, SEE AT END OF DOCTORS' LEAFLET)

Somnolence

~~SIFROL~~ Pramipexole is commonly associated with somnolence ~~(8.6%)~~ and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes ~~(0.1%). S~~(see also section 4.4).

Libido disorders

~~SIFROL~~ Pramipexole may ~~be~~ uncommonly be associated with libido disorders ~~[~~(increased ~~(0.1%)~~ or decreased ~~(0.4%)~~~~]~~.

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 (≤ 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).		

טקסט חדש

Table 1: Parkinson's disease

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[1], compulsive shopping, delusion, hyperphagia[1], 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[1]
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

Table 2: Restless Legs Syndrome

System Organ Class	Adverse Drug Reaction
Infections and infestations	
Uncommon	pneumonia[1]
Psychiatric disorders	
Common	abnormal dreams, insomnia
Uncommon	behavioural symptoms of impulse control disorders and compulsions such as binge eating, compulsive shopping, hypersexuality, and pathological gambling[1]; confusion, delusion[1], hallucinations, hyperphagia[1], libido disorder, paranoia[1], restlessness
Nervous system disorders	
Common	dizziness, headache, somnolence
Uncommon	amnesia[1], dyskinesia, hyperkinesia[1], sudden onset of sleep, syncope
Eye disorders	
Uncommon	visual impairment including diplopia,vision blurred and visual acuity reduced
Cardiac disorders	
Uncommon	cardiac failure[1]
Vascular disorders	
Uncommon	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
Uncommon	peripheral oedema
Investigations	
Uncommon	weight decrease including decreased appetite, weight increase

טקסט נוכחי

Table 1: Very common Adverse Drug Reactions (≥1/10)

System organ class	Adverse reaction	Pramipexole N = 1923 (%)
Nervous system disorders	Dizziness	15.5
	Dyskinesia	12.9
Gastrointestinal disorders	Nausea	17.2
Vascular disorders	Hypotension	12.6

Table 2: Common Adverse Drug Reactions (≥1/100 to <1/10)

System organ class	Adverse reaction	Pramipexole N = 1923 (%)
Psychiatric disorders	Abnormal dreams	3.5
	Confusional state	3.0
	Hallucinations	6.6
	Insomnia	8.2
Nervous system disorders	Somnolence	8.6
	Headache	6.5
Gastrointestinal Disorders	Constipation	5.5
General disorders and administration site conditions	Fatigue	6.1
	Peripheral oedema	1.9

פרק בעלון	טקסט נוכחי	טקסט חדש
מתי אין להשתמש בתכשיר	אל תשתמשי בתכשיר כאשר הינך מניקה. אין להשתמש בתכשיר אם ידועה רגישות לאחד ממרכיביו. אין להשתמש בתכשיר זה אם הינך נוטל/ת במקביל תרופה אנטי פסיכוטית. [הועבר לסעיף "תגובות בין תרופתיות" ע"פ דרישת משרד הבריאות באישור של עלון סיפרול ER מנובמבר 2011]	אין להשתמש בתכשיר אם ידועה רגישות לאחד ממרכיביו. אל אין להתשתמש בתכשיר כאשר אם הינך מניקה. ~~אין להשתמש בתכשיר אם ידועה רגישות לאחד ממרכיביו.~~ ~~אין להשתמש בתכשיר זה אם הינך נוטל/ת במקביל תרופה אנטי פסיכוטית.~~ [הועבר לסעיף "תגובות בין תרופתיות" ע"פ דרישת משרד הבריאות באישור של עלון סיפרול ER מנובמבר 2011]
אין להשתמש בתכשיר מבלי להיוועץ ברופא לפני התחלת הטיפול	אם הינך בהריון; אם הינך סובל/ת או סבלת בעבר מליקוי בתפקוד: הלב ו/או כלי הדם, העיניים, הכליה/מערכת השתן, מערכת העצבים; אם הינך סובל/ת מבעיות פסיכוטיות, הזיות, שינויים התנהגותיים ו/או אם הינך סובל מעייפות יתרה או הירדמויות פתאומיות.	אם הינך בהריון; או מתכננת הריון. אם הינך סובל/ת או סבלת בעבר מליקוי בתפקוד: הלב ו/או כלי הדם, העיניים, הכליה/מערכת השתן, מערכת העצבים,; או אם הינך סובל/ת מבעיות פסיכוטיות, הזיות, שינויים התנהגותיים (הימורים פתולוגיים, עריכת קניות באופן כפייתי, התנהגות מינית חריגה, התקפי אכילה מופרזת); ~~ו/או אם הינך סובל מעייפות יתרה~~ ליקוי בתנועה (דיסקינזיה), ישנוניות או הירדמויות פתאומיות. אם הנך נוטל לבודופה בנוסף לסיפרול- היוועץ ברופא בנוגע להורדת מינון הלבודופה לפני תחילת השימוש בסיפרול (ראה גם בסעיף "תגובות בין תרופתיות").
איך תשפיע התרופה על חיי היום יום שלך?	השימוש בתרופה זו עלול לפגום בערנות ועל כן מחייב זהירות בנהיגה ברכב, בהפעלת מכונות מסוכנות בכל פעילות המחייבת ערנות. באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת הכביש וכדומה. אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם התרופה.	השימוש בתרופה זו עלול לפגום בערנות ולגרום לישנוניות או לגרום להופעת הזיות. אם התכשיר השפיע עליך באופן זה, אין לנהוג או להפעיל ~~ועל כן מחייב זהירות בנהיגה ברכב, בהפעלת~~ מכונות מסוכנות או לעסוק בכל פעילות המחייבת ערנות. ~~באשר לילדים יש להזהירם מרכיבה על אופניים או ממשחקים בקרבת הכביש וכדומה.~~ אין לשתות יינות או משקאות חריפים בתקופת הטיפול עם ~~ה~~התרופה זו.
אזהרות	השימוש בתרופה זו עלול לגרום לטשטוש הראייה. יש לנטר את לחץ הדם, בעיקר בתחילת הטיפול בתרופה. במהלך הטיפול בתכשיר יש לבצע בדיקות עיניים במרווחים קבועים. בטיפול ב"רגליים חסרות מנוחה" יש להיבדק אצל הרופא לאחר 3 חודשים, על מנת להעריך את יעילות הטיפול. אם הינך רגיש/ה למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפי נטילת התרופה.	אם הינך רגיש למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפי נטילת התרופה. השימוש בתרופה זו עלול לגרום לטשטוש הראייה. במהלך הטיפול בתכשיר, ובמיוחד בתחילת הטיפול, יש לנטר באופן קבוע את לחץ הדם, בעיקר ~~בתחילת הטיפול~~ בתרופה. במהלך הטיפול בתכשיר יש לבצע בדיקות עיניים במרווחים קבועים. בטיפול ב"רגליים חסרות מנוחה" יש להיבדק אצל הרופא לאחר 3 חודשים, על מנת להעריך את יעילות הטיפול. ~~אם הינך רגיש/ה למזון כלשהו או לתרופה כלשהי, עליך להודיע על כך לרופא לפי נטילת התרופה.~~ אין להפסיק ליטול תרופה זו בצורה פתאומית מבלי להיוועץ ברופא, היות ויתכן כי קיים צורך להפסיק את המינון בצורה הדרגתית,על מנת להימנע מתופעות לוואי.
תגובות בין תרופתיות	אם הינך נוטל/ת תרופה נוספת, או אם גמרת זה עתה טיפול בתרופה אחרת, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין תרופתיות. במיוחד, לגבי תרופות מהקבוצות הבאות: המשפיעות על מערכת העצבים המרכזית(כגון: תרופות להרגעה, לשינה	אם הינך נוטל/ת תרופה נוספת, או אם גמרת זה עתה טיפול בתרופה אחרת, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין תרופתיות. במיוחד, לגבי תרופות מהקבוצות הבאות: תרופות הנמכרות ללא מרשם ותוספי תזונה או אם סיימת ~~גמרת~~ זה עתה טיפול בתרופה אחרת, עליך לדווח לרופא המטפל כדי למנוע סיכונים או אי-יעילות הנובעים מתגובות בין תרופתיות. במיוחד, לגבי תרופות מהקבוצות הבאות: תרופות הפועלות להרגעת ~~המשפיעות על~~ מערכת העצבים

	פרקינסון, אפילפסיה, תרופות אנטי פסיכוטיות, סכיזופרניה), תרופות המשפיעות על התפקוד/הפינוי הכליתי (כגון סימטידין ו אמאנטאדין)	המרכזית, (כגון: תרופות להרגעה, או לשינה (זהירות יתרה נדרשת בנהיגה או בהפעלת מכונות מסוכנות, ראה גם סעיף "איך תשפיע התרופה על חיי היום יום שלך?"), ~~פרקינסון, אפילפסיה, תרופות אנטי פסיכוטיות, סכיזופרניה), תרופות המשפיעות על התפקוד/הפינוי הכליתי (כגון~~ סימטידין (לטיפול בצרבת וכיב קיבה או), אמאנטאדין) (לטיפול במחלת הפרקינסון), פרוקאינאמיד (לטיפול בקצב לב לא סדיר), זידובודין (לטיפול באיידס/ HIV), ציספלטין (לטיפול בסרטן), קווינין. אם הנך מטופל בלבודופה- היועץ ברופא בנוגע להורדת מינון הלבודופה עם תחילת הטיפול בסיפרול. (ראה גם בסעיף:"אין להשתמש בתכשיר מבלי להיוועץ ברופא לפני התחלת הטיפול"). יש להימנע משימוש בתכשיר זה, אם הינך נוטל תרופות אנטי פסיכוטיות.
תופעות לוואי	בנוסף לפעילות הרצויה של התרופה, בזמן השימוש בה עלולות להופיע השפעות לוואי, כגון: עצירות, טשטוש הראיה, בחילה, הקאה, בצקות, כאב ראש, בלבול,הזיות (בעיקר חזותיות), ליקוי תנועה, תת לחץ דם, הפרעות שינה, ישנוניות, עייפות, סחרחורת, חלומות מוזרים, ירידה במשקל תופעות אלו חולפות בדרך כלל תוך זמן קצר לאחר תקופת ההסתגלות לתכשיר. אם התופעות הנ"ל מתמשכות ו/או מטרידות יש לפנות לרופא. השימוש בתרופה עלול לגרום לשינוי בהתנהגות (נטייה להימורים, הפרעות בחשק המיני, אכילה מופרזת). במקרה כזה יש לפנות לרופא המטפל.	בנוסף לפעילות הרצויה של התרופה, בזמן השימוש בה עלולות להופיע ~~השפעות~~ תופעות לוואי, כגון: דחף ~~ל~~להתנהגות בלתי רגילה, עצירות, ~~ט~~טשטוש הפרעות ~~ה~~בראיה, בחילה, הקאה, בצקות (בעיקר ברגליים), כאב ראש, אי שקט, בלבול, הפרעות בזיכרון, ~~הזיות (בעיקר חזותיות)~~, ליקוי תנועה, ~~תת~~ ירידה בלחץ דם, הפרעות שינה, ישנוניות, עייפות, סחרחורת, חלומות מוזרים, ירידה במשקל כולל ירידה בתאבון. תופעות אלו חולפות בדרך כלל תוך זמן קצר לאחר תקופת ההסתגלות לתכשיר. אם ~~ה~~תופעות הלוואי אינן חולפות או שהן ~~הנ"ל מתמשכות ו/או~~ מטרידות, יש להתייעץ עם ~~לפנות ל~~הרופא. ~~השימוש בתרופה עלול לגרום לשינוי בהתנהגות (נטייה להימורים, הפרעות בחשק המיני, אכילה מופרזת). במקרה כזה יש לפנות לרופא המטפל.~~
תופעות לוואי הדורשות התייחסות מיוחדת	הירדמויות פתאומיות עם או בלי תחושת עייפות, קשיי נשימה או דלקת ריאות (לא שכיח), המשך טיפול ופנה לרופא מיד! לעיתים טיפול התחלתי בתסמונת "הרגליים חסרות המנוח" עלול לגרום להגברה/שינוי של התסמינים הראשוניים (נדיר): המשך בטיפול ופנה לרופא מיד! בכל מקרה שבו הינך מרגיש/ה תופעות לוואי שלא צוינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד	אי ספיקה לבבית (יכולה לגרום לבצקות ברגליים או קוצר נשימה); הירדמויות פתאומיות עם או בלי תחושת עייפות, ~~קשי נשימה~~ או דלקת ריאות (לא שכיח), הזיות, פרנויה, עילפון; ~~–~~ ~~המשך טיפול~~ ~~ו~~פנה לרופא מיד! בהופיעה תגובה אלרגית המתבטאת בפריחה, גירוי, רגישות יתר בעור, או קשיי נשימה - פנה לרופא מיד! לעיתים טיפול התחלתי בתסמונת "הרגליים חסרות המנוח" עלול לגרום להגברה/שינוי של התסמינים הראשוניים (נדיר): המשך בטיפול ופנה לרופא מיד! השימוש בתרופה עלול לגרום להתנהגות חריגה (לא שכיח), כגון: אכילה מופרזת, קניה כפייתית, שינויים בהתנהגות מינית ונטייה להימורים, אשר דווחו בחולים הנוטלים תרופות מקבוצה זו. במקרה כזה יש לפנות לרופא המטפל. בכל מקרה שבו הינך מרגיש~~ה~~ תופעות לוואי שלא צוינו בעלון זה, או אם חל שינוי בהרגשתך הכללית עליך להתייעץ עם הרופא מיד
מינון	מינון לפי הוראות הרופא בלבד. אין לעבור על המנה המומלצת. תרופה זו אינה מיועדת לילדים תחת גיל 18. יש להשתמש בתרופה זו בזמנים קצובים כפי שנקבע על-ידי הרופא המטפל. אם שכחת ליטול תרופה זו בזמן קצוב, יש ליטול מנה מיד כשנזכרת, אך בשום אופן אין ליטול שתי מנות ביחד!	תרופה זו אינה מיועדת לילדים ומתבגרים מתחת לגיל 18. מינון לפי הוראות הרופא בלבד. אין לעבור על המנה המומלצת. ~~תרופה זו אינה מיועדת לילדים תחת גיל 18.~~ יש להשתמש בתרופה זו בזמנים קצובים כפי שנקבע על-ידי הרופא המטפל. אם שכחת ליטול תרופה זו בזמן קצוב, יש לדלג

	אם לא חל שיפור במצבך, יש לפנות לרופא. כאשר מפסיקים את הטיפול בתרופה יש לעשות זאת באופן הדרגתי במשך מספר ימים.	על המנה ששכחת ולקחת את המנה הבאה במועדה. ליטול מנה מיד כשנזכרת, אך בכל מקרה בשום אופן אין ליטול שתי מנות ביחד! אם לא חל שיפור במצבך, יש לפנות לרופא. כאשר מפסיקים את הטיפול בתרופה יש לעשות זאת באופן הדרגתי במשך מספר ימים.
אופן השימוש	אין ללעוס! יש לבלוע את התרופה עם כוס מים. ניתן ליטול את התרופה ללא קשר לזמני הארוחות.	אין לכתוש או ללעוס את הטבליה! יש לבלוע את התרופה עם כוס מים. ניתן ליטול את התרופה ללא קשר לזמני הארוחות. אין להחזיק את התרופה בפה מעבר לזמן הדרוש לבליעתה. ניתן לחצות את הטבליה על פי קו החציה המסומן.
כיצד תוכל לסייע להצלחת הטיפול?	עליך להשלים את הטיפול שהומלץ על-ידי הרופא. גם אם חל שיפור במצב בריאותך אין להפסיק הטיפול בתרופה ללא התייעצות עם הרופא, וגם אז רק באופן הדרגתי.	עליך להשלים את הטיפול שהומלץ על-ידי הרופא. גם אם חל שיפור במצב בריאותך אין להפסיק הטיפול בתרופה ללא התייעצות עם הרופא, וגם אז רק באופן הדרגתי. הפסקה פתאומית של השימוש בתרופה עלולה להוביל למצב רפואי חמור, הקרוי סינדרום סרוטונין, הכולל: אקינזיה (אובדן כושר התנועה בשרירים), נוקשות של השרירים, חום, לחץ דם לא יציב, קצב לב מואץ, בלבול, ירידה במצב ההכרה.