Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Roni 0.25 mg Film Coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.25 mg ropinirole (as hydrochloride)
Excipient: each film-coated tablet contains 94.5 mg of lactose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet
White to off white, round, biconvex film-coated tablets, marked with “413” on one side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Roni is indicated for

- the treatment of Parkinson's disease under the following conditions:

  - Initial treatment as monotherapy, in order to delay the introduction of levodopa.

  - In combination with levodopa, over the course of the disease, when the effect of levodopa wears off or becomes inconsistent and fluctuations in the therapeutic effect occur ("end of dose" or "on-off" type fluctuations).

- the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome in dosages up to 4 mg daily (see section 5.1).

4.2 Posology and method of administration

Oral use.
Individual dose titration against efficacy and tolerability is recommended.

Parkinson’s Disease
Adults:
Daily dose:
Ropinirole should be taken three times a day, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation:
The initial dose should be 0.25 mg three times daily for 1 week. Thereafter, the dose can be increased in 0.25 mg three times daily increments, according to the following regimen:
Table 1: Dose titration (Parkinson's disease)

Week	1	2	3	4
Unit dose (mg)	0.25	0.5	0.75	1.0
Total daily dose (mg)	0.75	1.5	2.25	3.0

Therapeutic regimen:
After the initial titration, weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day) may be given. A therapeutic response may be seen between 3 and 9 mg/day. If sufficient symptomatic control is not achieved, or maintained, the dose of ropinirole may be increased up to 24 mg/day and this dose should not be exceeded. Doses above 24 mg/day have not been studied. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above. When ropinirole is administered as adjunct therapy to levodopa, the concurrent dose of levodopa may be reduced gradually by around 20%. In patients with advanced Parkinson's disease receiving ropinirole in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.8).
When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole. As with other dopamine agonists, it is necessary to discontinue ropinirole treatment gradually by reducing the number of daily doses over the period of one week.

For doses not realisable/practicable with this strength other strengths of this medicinal product are available.

Restless Legs Syndrome:
Daily dose:
Adults. Ropinirole should be taken just before bedtime, however the dose can be taken up to 3 hours before retiring. Ropinirole may be taken with food, to improve gastrointestinal tolerance.

Treatment initiation (week 1):
The recommended initial dose is 0.25 mg once daily (administered as above) for 2 days. If this dose is well tolerated the dose should be increased to 0.5 mg once daily for the remainder of week 1.

Therapeutic regimen (week 2 onwards):
Following treatment initiation, the daily dose should be increased until optimal therapeutic response is achieved. The average dose in clinical trials, in patients with moderate to severe Restless Legs Syndrome, was 2 mg once a day.
The dose may be increased to 1 mg once a day at week 2. The dose may then be increased by 0.5 mg per week over the next two weeks to a dose of 2 mg once a day. In some patients, to achieve optimal improvement, the dose may be increased gradually up to a maximum of 4 mg once a day. In clinical trials the dose was increased by 0.5 mg each week to 3 mg once a day and then by 1 mg up to the maximum recommended dose of 4 mg once a day as shown in table 2. Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 2: Dose titration (Idiopathic Restless Legs Syndrome)

Week	2	3	4	5*,	6*	7*
Dose (mg)/once daily:	1	1.5	2	2.5	3	4

* To achieve optimal improvement in some patients.

The patient's response to ropinirole should be evaluated after 3 months treatment (see section 5.1). At this time the dose prescribed and the need for continued treatment should be considered. If treatment is interrupted for more than a few days it should be reinitiated by dose titration carried out as above.

Children and adolescents
Ropinirole Sandoz is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Elderly
The clearance of ropinirole is decreased in patients over 65 years of age. The increase in dosage should be gradual and titrated against the symptomatic response.

Renal Impairment
In parkinsonian patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this

population.

Severe renal impairment is contraindicated (see section 4.3).

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- severe renal impairment (creatinine clearance <30ml/min)
- hepatic impairment.

4.4 Special warnings and precautions for use

Ropinirole 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. However, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. 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.

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

Pathological gambling, increased libido and hypersexuality have been reported in patients treated with dopamine agonists for Parkinson´s disease, including Roni.

Ropinirole should not be used to treat neuroleptic akathisia, tasikinesia (neuroleptic-induced compulsive tendency to walk), or secondary Restless Legs Syndrome (e.g. caused by renal failure, iron deficiency anaemia or pregnancy).

During treatment with ropinirole, paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed. If this occurs, treatment should be reviewed and dosage adjustment or discontinuation of treatment may be considered.

This medicinal product contains lactose.
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Precautions for Use

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the start of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

4.5 Interaction with other medicinal products and other forms of interaction

No pharmacokinetic interaction has been seen between ropinirole and levodopa or domperidone (a medicinal product used to treat nausea and vomiting) which would necessitate dosage adjustment of either medicinal product. Domperidone antagonises the dopaminergic actions of ropinirole peripherally and does not cross the blood brain barrier. Hence its value as an anti-emetic in patients treated with centrally acting dopamine agonists.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, it may be necessary to adjust the ropinirole dose, in accordance with clinical response, if HRT is stopped or introduced during treatment with ropinirole.

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP 1A2. A pharmacokinetic study (with a ropinirole dose of 2mg, three times a day) in Parkinson patients revealed that ciprofloxacine increased the Cmax and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events.

Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP 1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in Parkinson patients between ropinirole (at a dose of 2mg, three times a day) and theophylline, a substrate of CYP 1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Therefore, it is not expected that ropinirole will compete with the metabolism of other medicinal products which are metabolised by CYP1A2.

Based on *in-vitro* data, ropinirole has little potential to inhibit cytochrome P450 at therapeutic doses. Hence, ropinirole is unlikely to affect the pharmacokinetics of other medicinal products, via a cytochrome P450 mechanism.

Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with ropinirole, dose adjustment may be required.

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these drugs with ropinirole should be avoided.

Co-administration of ropinirole with antihypertensive and anti-arrhythmic agents has not been studied.

In study in patients with Parkinson’s disease receiving digoxine, no interaction was seen which would require dosage adjustment.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.

4.6 Fertility, pregnancy and lactation

There are no adequate data from the use of ropinirole in pregnant women.
Studies in animals have shown reproductive toxicity (see section 5.3). As the potential risk for humans is unknown, it is recommended that ropinirole is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

Ropinirole should not be used in nursing mothers as it may inhibit lactation.

4.7 Effects on ability to drive and use machines

Ropinirol may have influence on the ability to drive and use machines.
Patients should be warned about the possibility of dizziness (including vertigo).
Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse events are listed below by system organ class and frequency.
Frequencies are defined as: 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), not known (cannot be estimated from the available data).

- **Parkinson´s disease:**

Common and uncommon events were generally determined from pooled safety data from clinical trial populations and

are quoted as excess incidence over placebo. Rare and very rare events were generally determined from post-marketing data and refer to reporting rate rather than true frequency.

Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day:

Immune system disorders
Not known Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).

Psychiatric disorders
Common: hallucinations
Uncommon: psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.
Patients treated with dopamine agonists for treatment of Parkinson' s disease, including Roni, 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

Use in adjunct therapy studies:
Common: confusion.

Nervous system disorders
Very common: somnolence
Common: dizziness (including vertigo).
Uncommon: excessive daytime somnolence, sudden onset of sleep
Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

Use in monotherapy studies:
Very common: syncope.
Use in adjunct therapy studies:
Very common: dyskinesia. In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.2).

Vascular disorders
Uncommon: postural hypotension, hypotension.
Postural hypotension or hypotension is rarely severe.

Gastrointestinal disorders
Use in monotherapy studies:
Common: abdominal pain, vomiting, heartburn.

Use in adjunct therapy studies:
Very common: nausea.
Common: heartburn.

Hepatobiliary disorders
Not known: hepatic reactions, mainly increased liver enzymes.

General disorders and administrative site conditions
Use in monotherapy studies:
Common: leg oedema.

Post marketing reports
In Parkinson's disease, ropinirole is associated with somnolence and has been associated uncommonly (>1/1,000, <1/100) with excessive daytime somnolence and sudden sleep onset episodes, however, in Restless Legs Syndrome, this phenomenon is very rare (<1/10,000). Following ropinirole therapy, postural hypotension or hypotension has been reported uncommonly (>1/1,000, <1/100), rarely severe.

- **Restless Legs Syndrome:**

In Restless Legs Syndrome clinical trials the most common adverse drug reaction was nausea (approximately 30% of patients). Undesirable effects were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to undesirable effects.

Below the adverse drug reactions reported for ropinirole in the 12 week clinical trials at 1.0% above the placebo rate or those reported uncommonly but known to be associated with ropinirole are listed:

Adverse drug reactions reported in 12 week Restless Legs Syndrome clinical trials (ropinirole n=309, placebo n=307):

Psychiatric disorders
Common: Nervousness
Uncommon: Confusion

Nervous system disorders
Common: Syncope, somnolence, dizziness
(including vertigo)

Vascular disorders
Uncommon: Postural hypotension, hypotension

Gastrointestinal disorders
Very common: Vomiting, nausea
Common: Abdominal pain

General disorders and administration site conditions
Common: Fatigue

Hallucinations were reported uncommonly in the open label long term studies.

Paradoxical worsening of Restless Legs Syndrome symptoms occurring with earlier onset (augmentation), and reoccurrence of symptoms in the early morning hours (early morning rebound), may be observed during treatment with ropinirole.

Management of undesirable effects
Dose reduction should be considered if patients experience significant undesirable effects.

If the undesirable effect abates, gradual up-titration can be re instituted. Anti nausea medicinal products that are not centrally active dopamine antagonists, such as domperidone, may be used, if required.

4.9 Overdose

There have been no incidences of intentional overdose with ropinirole in clinical trials.
It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacodynamic properties
Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists, ATC code: N04BC04.

Ropinirole is a non-ergoline dopamine agonist.

- **Parkinson's disease:**

Ropinirole alleviates the dopamine deficiency which characterises Parkinson's disease by stimulating striatal dopamine receptors.
Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

- **Restless Legs Syndrome:**

Clinical efficacy
Ropinirole should only be prescribed to patients with moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe idiopathic Restless Legs Syndrome is typically represented by patients who suffer with insomnia or severe discomfort in the limbs. In the four 12 week efficacy studies, patients with Restless Legs Syndrome were randomised to ropinirole or placebo, and the effects on the IRLS scale scores at week 12 were compared to baseline. The mean dose of ropinirole for the moderate to severe patients was 2.0 mg/day. In a combined analysis of moderate to severe Restless Legs Syndrome patients from the four 12 week studies, the adjusted treatment difference for the change from baseline in IRLS scale total score at week 12 Last Observation Carried Forward (LOCF) Intention To Treat population was -4.0 points (95% CI -5.6, -2.4, p<0.0001; baseline and week 12 LOCF mean IRLS points: ropinirole 28.4 and 13.5; placebo 28.2 and 17.4).

A 12 week placebo controlled polysomnography study in Restless Legs Syndrome patients examined the effect of treatment with ropinirole on periodic leg movements of sleep. A statistically significant difference in the periodic leg movements of sleep was seen between ropinirole and placebo from baseline to week 12.

Although sufficient data are not available to adequately demonstrate the long term efficacy of ropinirole in Restless Legs Syndrome (see section 4.2), in a 36 week study, patients who continued on ropinirole demonstrated a significantly lower relapse rate compared with patients randomised to placebo (33% versus 58%, p=0.0156).

A combined analysis of data from moderate to severe Restless Legs Syndrome patients, in the four 12 week placebo controlled studies, indicated that ropinirole -treated patients reported significant improvements over placebo on the parameters of the Medical Outcome Study Sleep Scale (scores on 0 100 range except sleep quantity). The adjusted treatment differences between ropinirole and placebo were: sleep disturbance (-15.2, 95% CI -19.37, -10.94; p<0.0001), sleep quantity (0.7 hours, 95% CI 0.49, 0.94); p<0.0001), sleep adequacy (18.6, 95% CI 13.77, 23.45; p<0.0001) and daytime somnolence (-7.5, 95% CI -10.86, -4.23; p<0.0001).

A rebound phenomenon following discontinuation of ropinirole treatment (end of treatment rebound) cannot be excluded. In clinical trials, although the average IRLS total scores 7 - 10 days after withdrawal of therapy were higher in ropinirole treated patients than in placebo treated patients, the severity of symptoms following withdrawal of therapy generally did not exceed the baseline assessment in ropinirole treated patients. In clinical studies most patients were of Caucasian origin.

Study of the effect of ropinirole on cardiac repolarisation
A thorough QT study conducted in male and female healthy volunteers who received doses of 0.5, 1, 2 and 4 mg of ropinirole film-coated (immediate release) tablets once daily showed a maximum increase of the QT interval duration at the 1 mg dose of 3.46 milliseconds (point estimate) as compared to placebo. The upper bound of the one sided 95% confidence interval for the largest mean effect was less than 7.5 milliseconds. The effect of ropinirole at higher doses has not been systematically evaluated. The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. A risk of QT prolongation cannot be excluded as a thorough QT study at doses up to 24 mg/day has not been conducted.

5.2 Pharmacokinetic properties

Absorption
Bioavailability of ropinirole is approximately 50% (36% to 57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations of ropinirole achieved at a median time of 1.5 hours post-dose . A high fat meal decreases the rate of absorption of ropinirole, as shown by a delay in median T_{max} by 2.6 hours and an average 25% decrease in C_{max}.

Distribution
Plasma protein binding of ropinirole is low (10 – 40%).
Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx 7 l/kg).

Metabolism
Ropinirole is primarily cleared by the cytochrome P450 enzyme, CYP1A2 and its metabolites are mainly excreted in the urine The major metabolite is at least 100 times less potent than ropinirole in animal models of dopaminergic function.

Elimination
Ropinirole is cleared from the systemic circulation with an average elimination half-life of approximately 6 hours. The increase in systemic exposure (C_{max} and AUC) to ropinirole is approximately proportional over the therapeutic dose range. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed.

Linearity
The pharmacokinetics of ropinirole are linear overall (Cmax and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
In patients over 65 years of age, a reduction in the systemic clearance of ropinirole by about 30% is possible. In patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min), no change in the pharmacokinetics of ropinirole is observed. No data are available in patients with severe renal impairment.

5.3 Preclinical safety data

Toxicology: The toxicology profile is principally determined by the pharmacological activity of the drug: behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation. In the albino rat only, retinal degeneration was observed in a long term study at the highest dose (50mg/kg), probably associated with an increased exposure to light.

Genotoxicity: Genotoxicity was not observed in the usual battery of *in vitro* and *in vivo* tests.

Carcinogenicity: From two-year studies conducted in the mouse and rat at dosages up to 50 mg/kg there was no evidence of any carcinogenic effect in the mouse. In the rat, the only drug-related lesions were Leydig cell hyperplasia and testicular adenoma resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

Reproductive Toxicity: Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately twice the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 4 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

Safety Pharmacology: *In vitro* studies have shown that ropinirole inhibits hERG-mediated currents. The IC50 is 5 fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day), see section 5.1.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose anhydrous
Cellulose Microcrystalline,
Croscarmellose sodium,
Magnesium stearate.

Coating:
Hypromellose,
Titanium dioxide (E171),
Macrogol 400,
Polysorbate 80

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

Al/Al blister:
18 months

HDPE Containers:
18 months

After first opening: use within 6 months

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

Al/Al blister: 14, 20, 21, 42, 49, 50, 84, 90, 98, 100, 112, 120, 150, 168, 196, 200 and 210 film-coated tablets
HDPE tablet container with child-resistant PP closure and silica gel packet: 21 and 84 film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork

8 MARKETING AUTHORISATION NUMBER

PA0711/116/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st February 2008

10 DATE OF REVISION OF THE TEXT

October 2010