Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Ropinirole 2 mg Film-Coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One Ropinirole 2 mg film-coated tablet contains 2 mg of ropinirole (as hydrochloride).

Excipient with known effect:
54.250 mg lactose/film-coated tablet

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Light pink, capsule shaped biconvex, film-coated tablets with break-line on both sides.
The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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) for the symptomatic treatment of moderate to severe idiopathic Restless Legs Syndrome (see section 5.1)

4.2 Posology and method of administration

Oral use.

Individual dose titration is recommended, based on efficacy and tolerability.

Parkinson's disease
Ropinirole should be taken three times daily, preferably with meals to improve gastrointestinal tolerance.

Treatment initiation
The initial dose should be 0.25 mg Ropinirole three times daily for 1 week. Thereafter, the dose can be increased upwards in 0.25 mg three times daily increments three times daily according to the following regimen:

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

Therapeutic regimen
Following initial dose titration, the Ropinirole dose may be increased by weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day)
A therapeutic response may be seen between 3 and 9 mg/day of ropinirole. If sufficient symptomatic control is not achieved, or maintained after the initial titration as described above, the dose of ropinirole may be increased up to 24 mg/day.

Doses above 24 mg/day have not been studied.

If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above).

When ropinirole is administered as adjunct therapy to L-dopa, the concurrent dose of L-dopa may be reduced gradually according to the symptomatic response. In clinical trials, the levodopa dose was reduced gradually by around 20% in patients treated with ropinirole as adjunct therapy.
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 Ldopa dose may ameliorate dyskinesia (see also section 4.8).

When switching treatment from another dopamine agonist to Ropinirole, the manufacturer's guidelines on discontinuation should be followed prior to initiating Ropinirole therapy.

As with other dopamine agonists, Ropinirole should be tapered off gradually, by reducing the number of daily doses over a 1-week period.

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

Restless Legs Syndrome
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 0.25mg 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 1.

Doses above 4 mg once daily have not been investigated in Restless Legs Syndrome patients.

Table 1 Dose titration

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 efficacy of ropinirole treatment has not been shown beyond 12 weeks (see Section 5.1). Patient response should be evaluated after 12 weeks treatment and the need for treatment continuation reconsidered. If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

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

Elderly patients
The clearance of ropinirole is decreased by approximately 15% in patients aged 65 years or above. Although a dose adjustment is not required, ropinirole dose should be individually titrated, with careful monitoring of tolerability, to the optimal clinical response.

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

Parkinson's disease
A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the initial dose of Ropinirole should be 0.25 mg three times a day. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 18 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

Restless Legs Syndrome
A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: the recommended initial dose of Ropinirole is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose of Ropinirole is 3 mg/day in patients receiving regular haemodialysis. Supplemental doses after haemodialysis are not required (see section 5.2).

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 ml/min) without regular haemodialysis has not been studied.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Severe renal impairment (creatinine clearance < 30 ml/min) without regular haemodialysis.
- 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. There have been (uncommon) reports of sudden sleep onset during daily activities. In some cases, such episodes occurred without any warning signs or awareness by the patient. 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 dose reduction or discontinuation of therapy should be considered.

Patients with major psychiatric or psychotic disorders, or a history of these disorders should only be treated with dopamine agonists only if the potential benefits outweigh the risks.

Impulse control disorders

Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Ropinirole. Dose reduction/tapered discontinuation should be considered if such symptoms develop.

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

Co-administration of Ropinirole with anti-hypertensive and anti-arrhythmic agents has not been studied. As with other dopaminergic drugs, caution should be exercised when these compounds are given concomitantly with Ropinirole because of the unknown potential for the occurrence of hypotension, bradycardias or other arrhythmias.

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.

Ropinirole should be administered with caution to patients with moderate hepatic impairment. Undesirable effects should be closely monitored.

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.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone that 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.

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

Elevated ropinirole plasma levels have been observed in patients receiving high-dose oestrogen. In patients already receiving hormone replacement therapy (HRT), Ropinirole treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during Ropinirole therapy, adjustment of the Ropinirole dose may be required, depending on the response to treatment.

Ropinirole is mainly metabolised by the cytochrome P450 isoenzyme CYP1A2. One pharmacokinetic study on parkinsonian patients (who were given a 2 mg ropinirole dose three times a day.) revealed that, following concomitant administration of ciprofloxacin, C_{max} and AUC values for ropinirole increased by 60% and 84% respectively. There is hence a potential risk of adverse effects. Therefore, in patients already receiving Ropinirole, the Ropinirole dose may have to be reduced, if active substances that inhibit CYP1A2 (such as ciprofloxacin, enoxacin or fluvoxamine) are concomitantly administered. This also applies when such medicinal products are being withdrawn.
A pharmacokinetic study on Parkinson patients – which set out to investigate interactions between ropinirole (at a dose of 2 mg three times a day.) and theophylline (a CYP1A2 substrate) – revealed no changes in the pharmacokinetics of either ropinirole or theophylline.

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 the patients stop or start smoking during treatment with Ropinirole, dose adjustment may be required.

4.6 Fertility, pregnancy and lactation

Pregnancy
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.

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

4.7 Effects on ability to drive and use machines

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 of sudden sleep onset and somnolence have resolved (see also section 4.4).

4.8 Undesirable effects

Undesirable effects 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: frequency cannot be estimated from the available data.

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

Use of ropinirole in 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.

Table 2 lists 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.

Table 2 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

Table 3 Adverse drug reactions reported in other Restless Legs Syndrome clinical trials

Psychiatric disorders	
Uncommon	Hallucinations
Nervous system disorders	
Common	Augmentation, Early morning rebound (see section 4.4)

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.

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.

Ropinirole is also indicated for the treatment of Parkinson's disease. The adverse drug reactions reported in patients with Parkinson's disease on ropinirole monotherapy and adjunct therapy at doses up to 24 mg/day at an excess incidence over placebo are described below.

		In monotherapy studies	In adjunct therapy studies
Immune system disorders			
Not known	Hypersensitivity reactions including urticarial, angioedema, rash, pruritus		
Psychiatric disorders			
Common	Hallucinations		Confusion
Uncommon	Psychotic reactions (other hallucinations) including delirium, delusion, paranoia. Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in postmarketing reports (see section 4.4).		
Nervous system disorders			
Very common	Somnolence	Syncope	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)
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.		
Vascular disorders			
Uncommon	Hypotension, postural hypotension Hypotension or postural hypotension is rarely severe		
Gastrointestinal disorders			
Very common	Nausea		
Common	Heartburn	Vomiting, abdominal pain	
Hepatobiliary disorders			
Not known	Hepatic reactions, mainly increased liver enzymes		
General disorders and administration site coniditions			
Common		Leg oedema	

Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus)

Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia have been reported.

Impulse control disorders

Pathological gambling, increased libido, hypersexuality compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Ropinirole. (see section 4.4 ‘Special warnings and precautions for use’).

Ropinirole is associated with somnolence and has been associated very rarely with excessive daytime somnolence and sudden sleep onset episodes.

Very rarely, hepatic reactions, mainly increased liver enzymes, have been reported.

4.9 Overdose

It is anticipated that the symptoms of ropinirole overdose will be related to the dopaminergic activity.
These symptoms can be alleviated by appropriate treatment with dopamine antagonists, such as a neuroleptic or metoclopramide.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Dopaminergic agents, dopamine agonists.

ATC code: N04BC04.

Mechanism of action

Ropinirole is a non-ergoline D_2/D_3 dopamine agonist which stimulates striatial dopamine receptors.

Ropinirole alleviates the symptoms of dopamine deficiency, which characterises Parkinson's disease, by stimulating dopamine receptors in the striatum.

Due to its action in the hypothalamus and pituitary, ropinirole inhibits prolactin secretion.

Clinical efficacy

Restless Legs Syndrome

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.

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; $p<0.0001$).

Long term efficacy was evaluated in a randomised, double-blind, placebo-controlled clinical trial of 26 weeks. Overall results were difficult to interpret due to significant centre treatment interaction and the high proportion of missing data. No maintenance of efficacy at 26 weeks compared to placebo could be shown.

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 4mg/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
Oral absorption of ropinirole is rapid. Bioavailability of ropinirole is approximately 50 % (36 to 57 %) and average peak concentrations of ropinirole are achieved at a median time of 1.5 hours post-dose. A high fat meal decreases the rate of absorption or ropinirole, as shown by a delay in median T_{max} by 2.6 hours and an average 25% decrease in C_{max}.

Distribution
The binding of ropinirole to plasma proteins 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 (C_{max} and AUC) in the therapeutic range between 0.25 mg and 4 mg, after a single dose and after repeated dosing.

Population-related characteristics
Oral clearance of ropinirole is reduced by approximately 15% in elderly patients (65 years or above) compared to younger patients. Dosage adjustment is not necessary in the elderly.

Renal Impairment
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.

In patients with end stage renal disease receiving regular haemodialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively**.** Therefore, the recommended maximum dose is limited to 3 mg/day in patients with RLS and 18 mg/day in patients with Parkinson's disease (see section 4.2).

Paediatric population
Limited pharmacokinetic data obtained in adolescents (12-17 years, n=9) showed that the systemic exposure following single doses of 0.125 mg and 0.25 mg was similar to that observed in adults (see also section 4.2; subparagraph "Children and adolescents).

5.3 Preclinical safety data

Toxicology
The toxicology profile is principally determined by the pharmacological activity of ropinirole: 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 a high dose (50 mg/kg/day), and was 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/day there was no evidence of any carcinogenic effect in the mouse. In the rat, the only ropinirole−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/day (approximately equivalent to the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 2 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 2.5 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 IC_{50} is at least 30-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (4 mg/day) (see section 5.1).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:
Cellulose, Microcrystalline
Lactose Monohydrate
Croscarmellose Sodium
Hypromellose
Magnesium stearate

Film Coat:
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Ferric Oxide Red (E172)
Ferric Oxide Yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 Years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

HDPE mulitdose container with child resistant closure (PP)

Silica gel canister

21, 28, 84 & 126 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

McDermott Laboratories
t/a Gerard Laboratories
Baldoyle Industrial Estate
Grange Road
Dublin 13

8 MARKETING AUTHORISATION NUMBER

PA 577/94/3

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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