This leaflet format has been determined by the Ministry of Health and the content thereof has been checked and approved on October 2016

1. Name of the medicinal product

ROPINIROLE TEVA® 0.25 mg
ROPINIROLE TEVA® 2 mg

2. Qualitative and quantitative composition

Each film coated tablet of ROPINIROLE TEVA® 0.25 mg contains 0.285 mg ropinirole hydrochloride equivalent to 0.25 mg ropinirole.
Each film coated tablet of ROPINIROLE TEVA® 2 mg contains 2.28 mg ropinirole hydrochloride equivalent to 2 mg ropinirole.

Excipient(s) with known effect:
ROPINIROLE TEVA® 0.25 mg: lactose monohydrate (110.615 mg)
ROPINIROLE TEVA® 2 mg : lactose monohydrate -108.62 mg, Lecitin (soya) E322 (0.1575 mg)

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film coated tablets

ROPINIROLE TEVA 0.25 mg: White, round slightly arched tablet, debossed "R 0.25" on one side and plain on the other.
ROPINIROLE TEVA 2 mg : Pink, round slightly arched tablet. Debossed "R 2"on one side and plain on the other.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of idiopathic Parkinson's disease :
Ropinirole may be used alone in the treatment of idiopathic Parkinson's disease.
Addition of ropinirole to levodopa may be used to control " on - off " fluctuations and permit a reduction in the total daily dose of levodopa.

4.2 Posology and method of administration

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole.
Patients should be down-titrated if they experience disabling somnolence at any dose level. For other adverse events, down-titration followed by more gradual up-titration has been shown to be beneficial.

Populations:

Adults

Individual dose titration against efficacy and tolerability is recommended.
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 of ropinirole can be increased in 0.25 mg three times daily increments, 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:

After the initial titration, weekly increments of 0.5 to 1 mg three times daily (1.5 to 3 mg/day) of ropinirole may be given. 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 of ropinirole 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 L-dopa dose may ameliorate dyskinesia (see also section 4.8).

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 (see section 4.4).

Elderly
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. In patients aged 75 years and above, slower titration during treatment initiation may be considered.

Children and Adolescents
The safety and efficacy of ropinirole have not been established in patients under 18 years of age; therefore ropinirole is not recommended for use in patients within this age group.

Renal impairment

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

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

Hepatic impairment
The use of ropinirole in patients with hepatic impairment has not been studied. Administration of ropinirole to such patients is not recommended.

4.3 Contraindications

Hypersensitivity to ropinirole or to any of the excipients listed in section 6.1.

Severe renal impairment (creatinine clearance <30ml/min) without regular haemodialysis.

Hepatic impairment.

4.4 Special warnings and 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).

Psychotic-like Behavior
Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with ropinirole or after starting or increasing the dose of ropinirole. Other drugs prescribed to improve the symptoms of Parkinson‟s disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.

Patients with a major psychotic disorder should ordinarily not be treated with ROPINIROLE TEVA® because of the risk of exacerbating the psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson‟s disease and may decrease the effectiveness of ROPINIROLE TEVA® (see section 4.5).

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 TEVA®. Dose reduction/tapered discontinuation should be considered if such symptoms develop.
Impulse control disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).
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 (see section 4.8). 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.

<u>Neuroleptic malignant syndrome</u>
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

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

Elevation of blood pressure and changes in heart rate
In the placebo-controlled trial in advanced Parkinson‟s disease, there were no clear effects of ROPINIROLE TEVA® on average changes in blood pressure or heart rate compared with placebo. Elevation of blood pressure and/or changes in heart rate in patients taking ROPINIROLE TEVA® should be considered when treating patients with cardiovascular disease.
Withdrawal-emergent Hyperpyrexia and Confusion
A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in dopaminergic therapy. Therefore, it is recommended that the dose be tapered at the end of treatment with ROPINIROLE TEVA® as a prophylactic measure.
Melanoma
Epidemiological studies have shown that patients with Parkinson‟s disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson‟s disease or other factors, such as drugs used to treat Parkinson‟s disease, is unclear. In the clinical development program (N = 613), one patient treated with Ropinirole and also levodopa/carbidopa developed melanoma.
For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using ROPINIROLE TEVA®. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).
Fibrotic Complications
Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis, and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur.
Although these adverse reactions are believed to be related to the ergoline structure of these compounds, whether other, non-ergot-derived dopamine agonists, such as ropinirole, can cause them is unknown.
Cases of possible fibrotic complications, including pleural effusion, pleural fibrosis, interstitial lung disease, and cardiac valvulopathy have been reported in the development program and postmarketing experience for ropinirole. In the clinical development program (N = 613), 2 patients treated with Ropinirole had pleural effusion. While the evidence is not sufficient to establish a causal relationship between ropinirole and these fibrotic complications, a contribution of ropinirole cannot be excluded.

4.5 Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of these drugs. 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.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study (with a ropinirole film-coated (immediate-release) tablet dose of 2 mg, three times a day) in Parkinson‟s disease patients, revealed that ciprofloxacin increased the C_{max} 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 know to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin, cimetidine or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson‟s disease between ropinirole (with a ropinirole film-coated (immediate-release) tablet dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

In a study in patients with Parkinson's disease receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

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, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

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.

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

Breast-feeding
Ropinirole should not be used in nursing mothers as it may inhibit lactation.
No human fertility data are available.

4.7 Effects on ability to drive and use machines

Ropinirole may have a major effect on the 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 and somnolence have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000) very rare (<1/10,000), not known (cannot be estimated from the available data).

	In monotherapy	In adjunct therapy
Immune system disorders		
Not known	*Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).*	
Psychiatric disorders		
Common	hallucinations	Confusion
Uncommon	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.	Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.
Not known	Aggression*	
	Dopamine dysregulation syndrome	
Not known	Impulse control disorders including pathological gambling, compulsive shopping, binge eating and hypersexuality and increased libido, have been reported in post marketing reports (see section 4.4)	

Nervous system disorders		
Very common	Syncope , Somnolence	Somnolence, 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)	dizziness (including vertigo).
Uncommon	Sudden onset of sleep, excessive daytime somnolence	Sudden onset of sleep, excessive daytime somnolence
	Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.	
Vascular disorders		
Uncommon	Postural hypotension or hypotension is rarely severe	
Gastrointestinal disorders		
Very common		Nausea
Common	Vomiting, abdominal pain	Heartburn
Hepatobiliary disorders		
Not known	Hepatic reactions, mainly increased liver enzymes	
General disorders and administrative site condiions		
Common	oedema peripheral (including leg oedema).	

* Aggression has been associated with psychotic reactions as well as compulsive symptoms

Additional adverse events observed during clinical trial with Ropinirole film-coated (immediate-release) tablets in patients in early stage Parkinson‟s disease: dyskinesia, dizziness, hallucinations, headache and increased sweating.
Additional adverse events observed during clinical trial with Ropinirole film-coated (immediate-release) tablets in patients in advanced stage Parkinson‟s disease: dizziness, asthenic condition and viral infection.
Other adverse events were reported but their frequency is not known (see section 4.4. „Special warnings and precautions for use‟):
□□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 TEVA® *(see section 4.4.)*.
□□Elevation of Blood Pressure and Changes in Heart Rate.
□□Withdrawal-emergent Hyperpyrexia and Confusion.
□□Melanoma.
□□Fibrotic Complications.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

4.9 Overdose

The symptoms of ropinirole overdose are generally 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

Pharmacotherapeutic group

Dopamine agonist.

ATC code: N04BC04

Mechanism of action

Parkinson's disease is characterised by a marked dopamine deficiency in the nigral striatal system. Ropinirole is a non-ergoline D2/D3 dopamine agonist that alleviates this deficiency by stimulating striatal dopamine receptors.
Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

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% (36-57%). Oral absorption of ropinirole film-coated (immediate-release) tablets is rapid with peak concentrations 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 Tmax by 2.6 hours and an average 25% decrease in Cmax.

Distribution

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

Biotransformation

Ropinirole is primarily cleared by CYP1A2 metabolism 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 about six hours. The increase in systemic exposure (Cmax 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.

Special Patient Populations
Renal impairment: There was no change observed in the pharmacokinetics of ropinirole in Parkinson‟s disease patients with mild to moderate renal impairment.
In patients with end stage renal disease receiving regular dialysis, 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 18 mg/day in these patients with Parkinson‟s disease.

5.3. Preclinical safety data

Reproductive toxicity

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

General 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 (50 mg/kg/day), and was probably associated with an increased exposure to light.

Genotoxicity

Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

Carcinogenicity

Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis 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.

Safety pharmacology

In vitro studies have shown that ropinirole inhibits hERG-mediated currents. The IC_{50} 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

ROPINIROLE TEVA 0.25 mg

Tablet core:
Lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate.
Tablet coating
polyvinyl alcohol, titanium dioxide (E171), macrogol (PEG 3350), talc

ROPINIROLE TEVA 2 mg

Tablet core:
Lactose monohydrate, microcrystalline cellulose, hydroxypropylcellulose, croscarmellose sodium, magnesium stearate.

Tablet coating

polyvinyl alcohol, titanium dioxide (E171), macrogol (PEG 3350), talc, lecitin (soya), carmine E120 , iron oxide yellow E172, iron oxide black E172

6.2. Incompatibilities

Not applicable.

6.3. Shelf life

18 months

6.4. Special precautions for storage

Store below 25°C, in a dark and dry place.

6.5. Nature and contents of container

OPA/ALU/PVC blisters.

ROPINIROLE TEVA 0.25 mg
Quantity per package: 12, 21 84 or 210 tablets

ROPINIROLE TEVA 2 mg
Quantity per package: 21 or 84 tablets

Not all package sizes may be marketed

6.6. Special precautions for disposal

No special requirements.

7. MANUFACTURER

Teva Pharmaceutical Works Private Ltd. Company, Debrecen H-4042 Hungary

8. LICENSE HOLDER AND IMPORTER

Teva Pharmaceutical Industries Ltd, Israel, P.O Box 3190 Petach Tikva.

9. LICENSE NUMBERS

ROPINIROLE TEVA 0.25 mg - 32982
ROPINIROLE TEVA 2 mg- 32984