

ANNEX I

**LIST OF THE NAMES, PHARMACEUTICAL FORM, STRENGTHS OF THE MEDICINAL
PRODUCTS, ROUTE OF ADMINISTRATION, APPLICANT, MARKETING
AUTHORISATION HOLDER IN THE MEMBER STATES**

<u>Member state</u>	<u>Marketing authorisation Holder</u>	<u>Applicant</u>	<u>Invented name</u>	<u>Strengths</u>	<u>Pharmaceutical form</u>	<u>Route of administra tion</u>
Austria		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Austria		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Austria		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Austria		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Belgium		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Belgium		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Belgium		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use

<u>Member state</u>	<u>Marketing authorisation Holder</u>	<u>Applicant</u>	<u>Invented name</u>	<u>Strengths</u>	<u>Pharmaceutical form</u>	<u>Route of administra tion</u>
Belgium		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Cyprus		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Cyprus		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Cyprus		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Cyprus		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Czech Republic		GlaxoSmithKline s.r.o., Na Pankráci 17/1685, 140 21 Praha 4, Czech Republic	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Czech Republic		GlaxoSmithKline s.r.o., Na Pankráci 17/1685, 140 21 Praha 4, Czech Republic	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Czech Republic		GlaxoSmithKline s.r.o., Na Pankráci 17/1685, 140 21 Praha 4, Czech Republic	ADARTREL	1.0 mg	Film-coated tablet	Oral use

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Czech Republic		GlaxoSmithKline s.r.o., Na Pankráci 17/1685, 140 21 Praha 4, Czech Republic	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Denmark		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Denmark		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Denmark		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Denmark		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Estonia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Estonia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Estonia		Laboratoire GlaxoSmithKline, 100	ADARTREL	1.0 mg	Film-coated tablet	Oral use

<u>Member state</u>	<u>Marketing authorisation Holder</u>	<u>Applicant</u>	<u>Invented name</u>	<u>Strengths</u>	<u>Pharmaceutical form</u>	<u>Route of administra tion</u>
Estonia		Route de Versailles, 78163 Marly-le-Roi Cedex, France Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Finland		GlaxoSmithKline Oy, ADARTREL Piispansilta 9 A, 02230 Espoo, Suomi		0.25 mg	Film-coated tablet	Oral use
Finland		GlaxoSmithKline Oy, ADARTREL Piispansilta 9 A, 02230 Espoo, Suomi		0.5 mg	Film-coated tablet	Oral use
Finland		GlaxoSmithKline Oy, ADARTREL Piispansilta 9 A, 02230 Espoo, Suomi		1.0 mg	Film-coated tablet	Oral use
Finland		GlaxoSmithKline Oy, ADARTREL Piispansilta 9 A, 02230 Espoo, Suomi		2.0 mg	Film-coated tablet	Oral use
France	Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France		ADARTREL	0.25 mg	Film-coated tablet	Oral use
France	Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex,		ADARTREL	0.5 mg	Film-coated tablet	Oral use

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	France					
France	Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France		ADARTREL	1.0 mg	Film-coated tablet	Oral use
France	Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France		ADARTREL	2.0 mg	Film-coated tablet	Oral use
Germany		GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Germany		GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Germany		GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Germany		GlaxoSmithKline GmbH & Co. KG, Theresienhöhe 11, 80339 München, Germany	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Greece		GlaxoSmithKline α.ε.β.ε, Κηφισίας 266, 152 32 Χαλάνδρι, Αθήνα, Ελλάδα	ADARTREL	0.25 mg	Film-coated tablet	Oral use

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Greece		GlaxoSmithKline α.ε.β.ε, Κηφισίας 266, 152 32 Χαλάνδρι, Αθήνα, Ελλάδα	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Greece		GlaxoSmithKline α.ε.β.ε, Κηφισίας 266, 152 32 Χαλάνδρι, Αθήνα, Ελλάδα	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Greece		GlaxoSmithKline α.ε.β.ε, Κηφισίας 266, 152 32 Χαλάνδρι, Αθήνα, Ελλάδα	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Hungary		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Hungary		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Hungary		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Hungary		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Iceland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use

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Iceland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Iceland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Iceland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Ireland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Ireland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Ireland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Ireland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use

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Italy		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Italy		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Italy		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Italy		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Latvia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Latvia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Latvia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use

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Latvia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Lithuania		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Lithuania		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Lithuania		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Lithuania		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Luxembourg		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Luxembourg		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use

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Luxembourg		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Luxembourg		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Malta		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Malta		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Malta		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Malta		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Netherlands		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use

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Netherlands		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Netherlands		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Netherlands		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Norway		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Norway		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Norway		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Norway		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use

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Poland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Poland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Poland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Poland		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Portugal		Beecham Portuguesa, Produtos Farmacêuticos e Químicos, Lda., Rua Dr. António Loureiro Borges, n.º 3, Arquiparque - Miraflores, 1495-131 Algés	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Portugal		Beecham Portuguesa, Produtos Farmacêuticos e Químicos, Lda., Rua Dr. António Loureiro Borges, n.º 3, Arquiparque - Miraflores, 1495-131 Algés	ADARTREL	0.5 mg	Film-coated tablet	Oral use

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Portugal		Beecham Portuguesa, Produtos Farmacêuticos e Químicos, Lda., Rua Dr. António Loureiro Borges, n.º 3, Arquiparque - Miraflores, 1495-131 Algés	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Portugal		Beecham Portuguesa, Produtos Farmacêuticos e Químicos, Lda., Rua Dr. António Loureiro Borges, n.º 3, Arquiparque - Miraflores, 1495-131 Algés	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Slovakia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Slovakia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Slovakia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Slovakia		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use

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Slovenia		GSK d.o.o., Ljubljana, Knezov stradon 90, 1000 Ljubljana, Slovenia	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Slovenia		GSK d.o.o., Ljubljana, Knezov stradon 90, 1000 Ljubljana, Slovenia	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Slovenia		GSK d.o.o., Ljubljana, Knezov stradon 90, 1000 Ljubljana, Slovenia	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Slovenia		GSK d.o.o., Ljubljana, Knezov stradon 90, 1000 Ljubljana, Slovenia	ADARTREL	2.0 mg	Film-coated tablet	Oral use
Spain		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Spain		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Spain		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Spain		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use

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Sweden		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
Sweden		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
Sweden		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use
Sweden		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use
UK		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.25 mg	Film-coated tablet	Oral use
UK		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	0.5 mg	Film-coated tablet	Oral use
UK		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	1.0 mg	Film-coated tablet	Oral use

<u>Member state</u>	<u>Marketing authorisation Holder</u>	<u>Applicant</u>	<u>Invented name</u>	<u>Strengths</u>	<u>Pharmaceutical form</u>	<u>Route of administra tion</u>
UK		Laboratoire GlaxoSmithKline, 100 Route de Versailles, 78163 Marly-le-Roi Cedex, France	ADARTREL	2.0 mg	Film-coated tablet	Oral use

ANNEX II

SCIENTIFIC CONCLUSIONS AND GROUNDS FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET PRESENTED BY THE EMEA

SCIENTIFIC CONCLUSIONS

OVERALL SUMMARY OF THE SCIENTIFIC EVALUATION OF ADARTREL (see Annex I)

Ropinirole has been granted a marketing authorisation by France on 30 June 2004. Before the end of a mutual recognition procedure, Spain and the Netherlands, presented to the EMEA a referral considering that this medicinal product might present a risk to public health since they were of the opinion that safety and efficacy in long-term treatment of ropinirole in restless legs syndrome had not been demonstrated.

The issues discussed included the efficacy data provided in the clinical trials, particularly in the subset of patients having a functional impact and the long-term efficacy and safety as well as the benefit-risk ratio.

The MAH has defined severe idiopathic RLS as those patients who have an International Restless Legs Syndrome Rating Scale (IRLS) baseline score of 24 points or more. However, for the CHMP, this population of patients should be defined as moderate to severe idiopathic RLS.

According to the literature, the tolerability profile of ropinirole in this population of patients must be analysed in the context of a physical condition that significantly affects the quality of life of patients mainly due to the fact that RLS patients suffer with chronic insomnia. In this context the clinical trial safety data demonstrate that ropinirole has an acceptable tolerability and safety profile in RLS patients over the dose range 0.25 - 4mg/day. Whilst the adverse events of nausea, vomiting, dizziness and somnolence occurred more frequently with ropinirole treatment than with placebo, the majority of patients had events that were mild to moderate in severity. These events were generally first reported during the initial two weeks of treatment and the rate of discontinuation from ropinirole treatment was low and similar to that from placebo treatment. The nature of these events is consistent with the established safety profile of ropinirole and the dopamine agonist class of drugs. A detailed assessment of the most common adverse events in the target population (IRLS baseline score 24-40 points) has been provided. The adverse events that are specific to RLS patients, such as augmentation and rebound effects have been discussed.

The analysis of Serious Adverse Events (SAE) was unremarkable in the overall group of patients enrolled in the ropinirole clinical studies.

A recent study has been conducted by the MAH in healthy volunteers on the effects of ropinirole on cardiac conduction. No clinically significant effect on the QT interval was observed.

The data generated from the ropinirole clinical trial programme with studies of up to 52-week duration of ropinirole treatment is reassuring as far as the clinical significance of potential episodes of augmentation reported. The reported rates in the literature of augmentation associated with dopamine agonists including ropinirole are generally lower than the ones reported for levodopa. More importantly the majority of the ropinirole episodes of augmentation had limited clinical significance as generally patients continued on ropinirole treatment without discontinuation and, in the majority of the events the investigators did not increase the dose of ropinirole as a result of the augmentation.

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.

The MAH agreed to revise the SPC, sections 4.2 and 5.1, to specify that ropinirole is indicated in moderate to severe idiopathic restless legs syndrome.

The MAH agreed to revise also section 5.1, to specify that ropinirole treated patients had higher IRLS scores at follow up assessment compared to placebo treated patients.

In the moderate to severe RLS population the benefit of treating with ropinirole is seen in all outcomes measured in a consistent way. The safety profile although pledged by uncomfortable adverse events like nausea and vomiting is mostly a problem in the early phase of the treatment and is considered

manageable. The benefit-risk assessment is considered favourable for the moderate to severe RLS as defined in the SPC.

Therefore the CHMP has recommended that there are no objections for the granting of the Marketing Authorisation for Adartel, in the treatment of symptomatic treatment of moderate to severe idiopathic restless legs syndrome. This Marketing Authorisation is subject to conditions considered essential for the safe and effective use of the medicinal product, which are that a long-term, double-blind, placebo controlled trial should be conducted as a post-marketing commitment (see Annexe IV). The amended SPC is endorsed by the CHMP.

GROUND FOR AMENDMENT OF THE SUMMARY OF PRODUCT CHARACTERISTICS

Whereas,

- the scope of the referral was that the safety and efficacy in long-term treatment of ropinirole in restless legs syndrome should be demonstrated,
- based on the documentation submitted and the scientific discussion within the Committee, the Summary of Products Characteristic proposed by the applicant has been amended as set out in Annexe III.

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE LEAFLET

A. SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ADARTREL 0.25 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.25 mg of ropinirole (as hydrochloride).

Excipient(s):

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White oval-shaped, marked "GS" on one side and "MLE" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADARTREL is indicated 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.

Adults

Individual dose titration against efficacy and tolerability is recommended. 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 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 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 re-initiated by dose titration carried out as above.

Children and adolescents

ADARTREL 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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe renal impairment (creatinine clearance <30 ml/min)

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Ropinirole should not be used to treat neuroleptic akathisia, dyskinesia (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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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 major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

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

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

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) 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 known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. 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 maybe required.

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

No pharmacokinetic interaction has been seen between ropinirole and domperidone (a medicinal product used to treat nausea and vomiting) 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 with ropinirole should be avoided.

4.6 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 fetus.

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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common ($>1/10$) or common ($>1/100$, $<1/10$) or uncommon ($>1/1,000$, $<1/100$).

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 $\geq 1.0\%$ 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)

<i>Psychiatric disorders</i>	
Common	Nervousness
Uncommon	Confusion
<i>Nervous system disorders</i>	
Common	Syncope, somnolence, dizziness (including vertigo)
<i>Vascular disorders</i>	
Uncommon	Postural hypotension, hypotension
<i>Gastrointestinal disorders</i>	
Very common	Vomiting, nausea
Common	Abdominal pain
<i>General disorders and administration site conditions</i>	
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.

Other experience 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.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

<i>Psychiatric disorders</i>	
Common	Hallucinations, confusion
Uncommon	Increased libido
<i>Nervous system disorders</i>	
Very common	Syncope, dyskinesia, somnolence
<i>Gastrointestinal disorders</i>	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
<i>General disorders and administration site conditions</i>	
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.

Very rare cases of hepatic reactions ($<1/10,000$), mainly increase of liver enzymes, have been reported.

4.9 Overdose

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

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Clinical efficacy

ADARTREL 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with C_{max} reached on average 1.5 hours after the dose. In the presence of food, C_{max} is delayed by about 2.6 hours and the peak plasma level is reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution, which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination

Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

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

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 a high dose (50 mg/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 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film coating:

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Polysorbate 80 (E433).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.

Packs of 2 or 12 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex

France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1 NAME OF THE MEDICINAL PRODUCT

ADARTREL 0.5 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg of ropinirole (as hydrochloride).

Excipient(s):

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Yellow oval-shaped, marked "GS" on one side and "TES" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADARTREL is indicated 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.

Adults

Individual dose titration against efficacy and tolerability is recommended. 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 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 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 re-initiated by dose titration carried out as above.

Children and adolescents

ADARTREL 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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe renal impairment (creatinine clearance <30 ml/min)

Severe hepatic impairment.

4.4 Special warnings and precautions for use

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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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 major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

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

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

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) 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 known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. 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.

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

No pharmacokinetic interaction has been seen between ropinirole and domperidone (a medicinal product used to treat nausea and vomiting) 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 with ropinirole should be avoided.

4.6 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

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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1,000, <1/100).

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 $\geq 1.0\%$ 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)

<i>Psychiatric disorders</i>	
Common	Nervousness
Uncommon	Confusion
<i>Nervous system disorders</i>	
Common	Syncope, somnolence, dizziness (including vertigo)
<i>Vascular disorders</i>	
Uncommon	Postural hypotension, hypotension
<i>Gastrointestinal disorders</i>	
Very common	Vomiting, nausea
Common	Abdominal pain
<i>General disorders and administration site conditions</i>	
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.

Other experience 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.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

<i>Psychiatric disorders</i>	
Common	Hallucinations, confusion
Uncommon	Increased libido
<i>Nervous system disorders</i>	
Very common	Syncope, dyskinesia, somnolence
<i>Gastrointestinal disorders</i>	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
<i>General disorders and administration site conditions</i>	
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.

Very rare cases of hepatic reactions ($<1/10,000$), mainly increase of liver enzymes, have been reported.

4.9 Overdose

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

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Clinical efficacy

ADARTREL 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with C_{max} reached on average 1.5 hours after the dose. In the presence of food, C_{max} is delayed by about 2.6 hours and the peak plasma level is

reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution, which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination

Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

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

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 a high dose (50 mg/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 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film coating:

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.

Packs of 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1 NAME OF THE MEDICINAL PRODUCT

ADARTREL 1 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of ropinirole (as hydrochloride).

Excipient(s):

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Green oval-shaped, marked "GS" on one side and "SJG" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADARTREL is indicated 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.

Adults

Individual dose titration against efficacy and tolerability is recommended. 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 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 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 re-initiated by dose titration carried out as above.

Children and adolescents

ADARTREL 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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe renal impairment (creatinine clearance <30 ml/min)

Severe hepatic impairment.

4.4 Special warnings and precautions for use

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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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 major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

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

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

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) 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 known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. 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.

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

No pharmacokinetic interaction has been seen between ropinirole and domperidone (a medicinal product used to treat nausea and vomiting) 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 with ropinirole should be avoided.

4.6 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

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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1,000, <1/100).

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 $\geq 1.0\%$ 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)

<i>Psychiatric disorders</i>	
Common	Nervousness
Uncommon	Confusion
<i>Nervous system disorders</i>	
Common	Syncope, somnolence, dizziness (including vertigo)
<i>Vascular disorders</i>	
Uncommon	Postural hypotension, hypotension
<i>Gastrointestinal disorders</i>	
Very common	Vomiting, nausea
Common	Abdominal pain
<i>General disorders and administration site conditions</i>	
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.

Other experience 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.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

<i>Psychiatric disorders</i>	
Common	Hallucinations, confusion
Uncommon	Increased libido
<i>Nervous system disorders</i>	
Very common	Syncope, dyskinesia, somnolence
<i>Gastrointestinal disorders</i>	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
<i>General disorders and administration site conditions</i>	
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.

Very rare cases of hepatic reactions ($<1/10,000$), mainly increase of liver enzymes, have been reported.

4.9 Overdose

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

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Clinical efficacy

ADARTREL 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with C_{max} reached on average 1.5 hours after the dose. In the presence of food, C_{max} is delayed by about 2.6 hours and the peak plasma level is

reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution, which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination

Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

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

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 a high dose (50 mg/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 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film coating:

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Indigo carmine aluminium lake (E132).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.

Packs of 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

1 NAME OF THE MEDICINAL PRODUCT

ADARTREL 2 mg film-coated tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient(s):

Lactose

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

Pink oval-shaped, marked "GS" on one side and "GYG" on the other.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ADARTREL is indicated 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.

Adults

Individual dose titration against efficacy and tolerability is recommended. 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 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 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 re-initiated by dose titration carried out as above.

Children and adolescents

ADARTREL 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

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance between 30 and 50 ml/min).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Severe renal impairment (creatinine clearance <30 ml/min)

Severe hepatic impairment.

4.4 Special warnings and precautions for use

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.

In Parkinson's disease, ropinirole has been associated uncommonly with somnolence and episodes of sudden sleep onset (see section 4.8) however, in Restless Legs Syndrome, this phenomenon is very rare. Nevertheless, patients must be informed of this phenomenon 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 major psychotic disorders should not be treated with dopamine agonists unless the potential benefits outweigh the risks.

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

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

Due to the risk of hypotension, patients with severe cardiovascular disease (in particular coronary insufficiency) should be treated with caution.

4.5 Interaction with other medicinal products and other forms of interaction

Ropinirole is principally metabolised by the cytochrome P450 isoenzyme CYP1A2. A pharmacokinetic study (with a ropinirole dose of 2 mg, three times a day) 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 known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study between ropinirole (at a 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. 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.

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

No pharmacokinetic interaction has been seen between ropinirole and domperidone (a medicinal product used to treat nausea and vomiting) 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 with ropinirole should be avoided.

4.6 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

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 effects have resolved (see also Section 4.4).

4.8 Undesirable effects

Adverse drug reactions are listed below by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common (>1/10) or common (>1/100, <1/10) or uncommon (>1/1,000, <1/100).

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 $\geq 1.0\%$ 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)

<i>Psychiatric disorders</i>	
Common	Nervousness
Uncommon	Confusion
<i>Nervous system disorders</i>	
Common	Syncope, somnolence, dizziness (including vertigo)
<i>Vascular disorders</i>	
Uncommon	Postural hypotension, hypotension
<i>Gastrointestinal disorders</i>	
Very common	Vomiting, nausea
Common	Abdominal pain
<i>General disorders and administration site conditions</i>	
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.

Other experience 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.

Table 3 Adverse drug reactions reported in Parkinson's disease clinical trials at doses up to 24 mg/day

<i>Psychiatric disorders</i>	
Common	Hallucinations, confusion
Uncommon	Increased libido
<i>Nervous system disorders</i>	
Very common	Syncope, dyskinesia, somnolence
<i>Gastrointestinal disorders</i>	
Very common	Nausea
Common	Vomiting, abdominal pain, heartburn
<i>General disorders and administration site conditions</i>	
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.

Very rare cases of hepatic reactions ($<1/10,000$), mainly increase of liver enzymes, have been reported.

4.9 Overdose

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

Pharmacotherapeutic group: Dopamine agonist, ATC code: N04BC04.

Mechanism of action

Ropinirole is a non ergoline D2/D3 dopamine agonist which stimulates striatal dopamine receptors.

Clinical efficacy

ADARTREL 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.

5.2 Pharmacokinetic properties

Absorption

The bioavailability of ropinirole is about 50% (36% to 57%), with $C_{\max}$ reached on average 1.5 hours after the dose. In the presence of food, $C_{\max}$ is delayed by about 2.6 hours and the peak plasma level is

reduced by 25%, with no effect on the bioavailable quantity. The bioavailability of ropinirole varies greatly between individuals.

Distribution

The binding of ropinirole to plasma proteins is not high (<40%), with no effect on the distribution, which is very extensive (volume of distribution in the order of 7 l/kg).

Metabolism

Ropinirole is mainly metabolised by the isoform CYP1A2 of cytochrome P450. None of the many metabolites formed are involved in the resulting activity of the product and the main metabolite is 100 times less potent than ropinirole in animal models examining dopaminergic function.

Elimination

Unchanged ropinirole and the metabolites are mainly excreted through the kidneys. The elimination half-life of ropinirole is 6 hours on average.

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

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 a high dose (50 mg/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 15 times the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg (approximately 25 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg (approximately 40 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg (approximately 30 times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet cores:

Lactose monohydrate
Microcrystalline cellulose
Croscarmellose sodium
Magnesium stearate.

Film coating:

Hypromellose
Macrogol 400
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Do not store above 25 °C.

Store in the original package.

6.5 Nature and contents of container

PVC/PCTFE/Aluminium blister.

Packs of 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

8 MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

{DD month YYYY}

[To be completed nationally]

10 DATE OF REVISION OF THE TEXT

{MM/YYYY}

[To be completed nationally]

B. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

ADARTREL 0.25 mg film-coated tablets
Ropinirole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.25 mg of ropinirole (as hydrochloride)

3. LIST OF EXCIPIENTS

This product contains lactose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

2 film-coated tablets
12 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be taken as directed by your doctor.

8. EXPIRY DATE

exp {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France

{See Annex I- to be completed nationally}

12. MARKETING AUTHORISATION NUMBER(S)
--

{To be completed nationally}

13. BATCH NUMBER

{To be completed nationally}

14. GENERAL CLASSIFICATION FOR SUPPLY
--

{To be completed nationally}

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{To be completed nationally}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ADARTREL 0.25 mg film-coated tablets
Ropinirole

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Laboratoire GlaxoSmithKline

{See Annex I- to be completed nationally}

3. EXPIRY DATE

exp {MM YYYY}

4. BATCH NUMBER

lot {XXXXXX}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

ADARTREL 0.5 mg film-coated tablets
Ropinirole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg of ropinirole (as hydrochloride)

3. LIST OF EXCIPIENTS

This product contains lactose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be taken as directed by your doctor.

8. EXPIRY DATE

exp {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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100, route de Versailles
78163 Marly-le-Roi Cedex
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{See Annex I- to be completed nationally}

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{To be completed nationally}

13. BATCH NUMBER

{To be completed nationally}

14. GENERAL CLASSIFICATION FOR SUPPLY
--

{To be completed nationally}

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{To be completed nationally}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ADARTREL 0.5 mg film-coated tablets
Ropinirole

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Laboratoire GlaxoSmithKline

{See Annex I- to be completed nationally}

3. EXPIRY DATE

exp {MM YYYY}

4. BATCH NUMBER

lot {XXXXXX}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

ADARTREL 1 mg film-coated tablets
Ropinirole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg of ropinirole (as hydrochloride)

3. LIST OF EXCIPIENTS

This product contains lactose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be taken as directed by your doctor.

8. EXPIRY DATE

exp {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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100, route de Versailles
78163 Marly-le-Roi Cedex
France

{See Annex I- to be completed nationally}

12. MARKETING AUTHORISATION NUMBER(S)
--

{To be completed nationally}

13. BATCH NUMBER

{To be completed nationally}

14. GENERAL CLASSIFICATION FOR SUPPLY
--

{To be completed nationally}

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{To be completed nationally}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ADARTREL 1 mg film-coated tablets
Ropinirole

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Laboratoire GlaxoSmithKline

{See Annex I- to be completed nationally}

3. EXPIRY DATE

exp {MM YYYY}

4. BATCH NUMBER

lot {XXXXXX}

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**CARTON****1. NAME OF THE MEDICINAL PRODUCT**

ADARTREL 2 mg film-coated tablets
Ropinirole

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 2 mg of ropinirole (as hydrochloride)

3. LIST OF EXCIPIENTS

This product contains lactose
See leaflet for further information

4. PHARMACEUTICAL FORM AND CONTENTS

28 film-coated tablets
84 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

To be taken as directed by your doctor.

8. EXPIRY DATE

exp {MM YYYY}

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C
Store in the original package

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Not applicable

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France

{See Annex I- to be completed nationally}

12. MARKETING AUTHORISATION NUMBER(S)
--

{To be completed nationally}

13. BATCH NUMBER

{To be completed nationally}

14. GENERAL CLASSIFICATION FOR SUPPLY
--

{To be completed nationally}

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{To be completed nationally}

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS
--

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

ADARTREL 2 mg film-coated tablets
Ropinirole

2. NAME OF THE MARKETING AUTHORISATION HOLDER
--

Laboratoire GlaxoSmithKline

{See Annex I- to be completed nationally}

3. EXPIRY DATE

exp {MM YYYY}

4. BATCH NUMBER

lot {XXXXXX}

5. OTHER

C. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADARTREL 0.25 mg film-coated tablets Ropinirole (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ADARTREL is and what it is used for
2. Before you take ADARTREL
3. How to take ADARTREL
4. Possible side effects
5. How to store ADARTREL
6. Further information

1 WHAT ADARTREL IS AND WHAT IT IS USED FOR

ADARTREL belongs to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine.

ADARTREL is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping or severe discomfort in their legs or arms.

Restless Legs Syndrome is a condition characterised by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or prickling. These feelings occur during periods of rest or inactivity such as sitting or lying down, especially in bed, and are worse in the evening or at night. Usually the only relief is obtained by walking about or moving the affected limbs, which often leads to problems sleeping.

ADARTREL relieves the discomfort and reduces the urge to move the limbs that disrupt night time sleep.

2 BEFORE YOU TAKE ADARTREL

Do not take ADARTREL

- if you are allergic (hypersensitive) to the active ingredient, ropinirole, or any of the other ingredients of ADARTREL
- if you have serious liver disease
- if you have serious kidney disease

If you are unsure, it is essential that you talk to your doctor.

Take special care with ADARTREL

Tell your doctor before you start to take this medicine if you:

- are pregnant or think you are pregnant
- are breast-feeding
- are intolerant to some sugars (e.g. lactose)

- have liver disease
- have a serious heart complaint
- have a serious mental health problem

In these situations your doctor should carefully supervise the treatment.

During treatment with ADARTREL take special care when you drive or operate machinery. If you suffer from extreme sleepiness or suddenly fall asleep without apparently feeling sleepy, do not drive or use machinery, and contact your doctor.

If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms, you should see your doctor who may adjust the dose of ADARTREL that you are taking.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The effect of ADARTREL may be increased or decreased by other medicines and vice versa. These medicines include:

- ciprofloxacin (an antibiotic)
- enoxacin (an antibiotic)
- fluvoxamine (a drug used to treat depression)
- theophylline (a drug used to treat asthma)
- hormone replacement therapy (also called HRT)
- anti-psychotics and other drugs that block dopamine in the brain (e.g. sulpiride or metoclopramide)

Tell your doctor if:

- you are already receiving any other medicines for Restless Legs Syndrome.
- you give up or start smoking while taking ADARTREL. Your doctor may need to adjust your dose.
- you are taking ADARTREL and the doctor is going to prescribe you any other medicine.

Taking ADARTREL with food and drink

Taking ADARTREL with food may reduce the likelihood of you feeling or being sick.

Pregnancy

The use of ADARTREL during pregnancy is not recommended. ADARTREL should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Tell your doctor immediately if you are pregnant, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

Breast-feeding

ADARTREL should not be used during breast-feeding as milk production may be affected. Tell your doctor immediately if you are breast-feeding or if you are planning to breast-feed. Your doctor will advise you to discontinue this medicine.

Driving and using machines

This medicine does not usually affect people's normal activities. However, ADARTREL can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you suffer from these effects you must not drive or put yourself in a situation where sleepiness or falling asleep may put you at risk of serious injury or death (for example using machinery) until these episodes have been resolved.

Important information about some of the ingredients of ADARTREL

Patients who are intolerant to lactose should note that each ADARTREL tablet contains a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Children

The use of ADARTREL in children with Restless Legs Syndrome has not been studied and therefore ADARTREL is not usually prescribed in patients under 18 years of age.

3 HOW TO TAKE ADARTREL

Always take ADARTREL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take ADARTREL once a day by mouth, every day at about the same time each day. ADARTREL is usually taken just before bedtime, but can be taken up to 3 hours before going to bed.

Swallow the ADARTREL tablet(s) whole with water. You can take ADARTREL with or without food. Taking ADARTREL with food may decrease the occurrence of nausea (feeling sick), which is a possible side effect of ADARTREL. Do not chew the tablet(s).

The exact dose of ADARTREL people take can be different. Your doctor will decide on the dose you need to take each day and you should follow the doctor's instructions. When you first start taking ADARTREL, the dose you take will be increased gradually.

The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose by 0.5mg per week over three weeks to a dose of 2mg per day. In some patients with insufficient improvement, the dose may be increased gradually up to a maximum of 4mg daily. After three months of treatment with ADARTREL, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.

Remember to take your medicine. If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work for you. If you have the impression that the effect of ADARTREL is too strong or too weak, talk to your doctor or pharmacist. Do not take more tablets than your doctor has recommended.

If you take more ADARTREL than you should

Someone who has taken an overdose may experience; feeling or being sick, dizziness (or spinning sensation), feeling drowsy, fatigue (mental or physical tiredness), stomach pain, fainting or nervousness. If you take more ADARTREL than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

If you forget to take ADARTREL

If you find you have forgotten to take your dose of ADARTREL do not take an extra dose to make up for forgotten individual doses.

When you do remember to take ADARTREL, take your next dose of ADARTREL at the usual time. If you have missed taking ADARTREL for more than a few days consult your doctor for advice on restarting ADARTREL.

If you stop taking ADARTREL

If your symptoms worsen after you stop treatment with ADARTREL, you should contact your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, ADARTREL can cause side effects, although not everybody gets them. Tell your doctor if you notice any side effects and they worry you. The more common side effects of ADARTREL can happen when some patients first start their therapy and/or when the dose is increased. The side effects are generally mild and may become less after you have taken the medicine for a short time.

The most common side effects are:

- feeling or being sick
- dizziness (or spinning sensation)
- feeling drowsy
- fatigue (mental or physical tiredness)
- stomach pain
- fainting
- nervousness

Uncommon side effects are feeling confused and experiencing hallucinations. Also uncommonly, ADARTREL can reduce blood pressure which may make you feel dizzy or faint especially when standing up from a sitting or lying position.

During treatment with ADARTREL you may experience unusual worsening of symptoms (e.g. symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms). If this occurs, you should see your doctor.

If your symptoms worsen after you stop treatment with ADARTREL, you should contact your doctor.

Very rarely, cases of altered liver function (abnormal blood tests) have been reported.

ADARTREL can cause excessive daytime somnolence (excessive drowsiness) and very rarely sudden sleep onset episodes where patients fall asleep suddenly without apparently feeling sleepy.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist as soon as possible.

5 HOW TO STORE ADARTREL

Keep out of the reach and sight of children.

Do not use ADARTREL after the expiry date, which is stated on the carton.

Do not store above 25°C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What ADARTREL contains

- The active substance is ropinirole (as hydrochloride)
 - The other ingredients are
- Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate
- Film coat: hypromellose, macrogol 400, titanium dioxide (E171), polysorbate 80 (E433).

What ADARTREL looks like and contents of the pack

This medicine is provided as oval, white, film-coated tablets marked "GS" on one side and "MLE" on the other. Each pack contains 2 or 12 tablets. Not all packs may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

Manufacturer: SmithKline Beecham Pharmaceuticals,
Manor Royal, Crawley,
West Sussex RH10 9QJ, United Kingdom

This leaflet was last approved in

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADARTREL 0.5 mg film-coated tablets Ropinirole (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What ADARTREL is and what it is used for
2. Before you take ADARTREL
3. How to take ADARTREL
4. Possible side effects
5. How to store ADARTREL
6. Further information

1 WHAT ADARTREL IS AND WHAT IT IS USED FOR

ADARTREL belongs to a group of medicines called dopamine agonists. Dopamine agonists act like a naturally occurring chemical in your brain called dopamine.

ADARTREL is used to treat the symptoms of moderate to severe idiopathic Restless Legs Syndrome. Moderate to severe Restless Legs Syndrome is typically represented by patients who have difficulty sleeping or severe discomfort in their legs or arms.

Restless Legs Syndrome is a condition characterised by an irresistible urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations such as tingling, burning or prickling. These feelings occur during periods of rest or inactivity such as sitting or lying down, especially in bed, and are worse in the evening or at night. Usually the only relief is obtained by walking about or moving the affected limbs, which often leads to problems sleeping.

ADARTREL relieves the discomfort and reduces the urge to move the limbs that disrupt night time sleep.

2 BEFORE YOU TAKE ADARTREL

Do not take ADARTREL

- if you are allergic (hypersensitive) to the active ingredient, ropinirole, or any of the other ingredients of ADARTREL
- if you have serious liver disease
- if you have serious kidney disease

If you are unsure, it is essential that you talk to your doctor.

Take special care with ADARTREL

Tell your doctor before you start to take this medicine if you:

- are pregnant or think you are pregnant
- are breast-feeding
- are intolerant to some sugars (e.g. lactose)
- have liver disease
- have a serious heart complaint
- have a serious mental health problem

In these situations your doctor should carefully supervise the treatment.

During treatment with ADARTREL take special care when you drive or operate machinery. If you suffer from extreme sleepiness or suddenly fall asleep without apparently feeling sleepy, do not drive or use machinery, and contact your doctor.

If during treatment your symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms, you should see your doctor who may adjust the dose of ADARTREL that you are taking.

Taking other medicines

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. The effect of ADARTREL may be increased or decreased by other medicines and vice versa. These medicines include:

- ciprofloxacin (an antibiotic)
- enoxacin (an antibiotic)
- fluvoxamine (a drug used to treat depression)
- theophylline (a drug used to treat asthma)
- hormone replacement therapy (also called HRT)
- anti-psychotics and other drugs that block dopamine in the brain (e.g. sulpiride or metoclopramide)

Tell your doctor if:

- you are already receiving any other medicines for Restless Legs Syndrome.
- you give up or start smoking while taking ADARTREL. Your doctor may need to adjust your dose.
- you are taking ADARTREL and the doctor is going to prescribe you any other medicine.

Taking ADARTREL with food and drink

Taking ADARTREL with food may reduce the likelihood of you feeling or being sick.

Pregnancy

The use of ADARTREL during pregnancy is not recommended. ADARTREL should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Tell your doctor immediately if you are pregnant, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

Breast-feeding

ADARTREL should not be used during breast-feeding as milk production may be affected. Tell your doctor immediately if you are breast-feeding or if you are planning to breast-feed. Your doctor will advise you to discontinue this medicine.

Driving and using machines

This medicine does not usually affect people's normal activities. However, ADARTREL can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you suffer from these effects you must not drive or put yourself in a situation where sleepiness or falling asleep may put you at risk of serious injury or death (for example using machinery) until these episodes have been resolved.

Important information about some of the ingredients of ADARTREL

Patients who are intolerant to lactose should note that each ADARTREL tablet contains a small amount of lactose. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicinal product.

Children

The use of ADARTREL in children with Restless Legs Syndrome has not been studied and therefore ADARTREL is not usually prescribed in patients under 18 years of age.

3 HOW TO TAKE ADARTREL

Always take ADARTREL exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Take ADARTREL once a day by mouth, every day at about the same time each day. ADARTREL is usually taken just before bedtime, but can be taken up to 3 hours before going to bed.

Swallow the ADARTREL tablet(s) whole with water. You can take ADARTREL with or without food. Taking ADARTREL with food may decrease the occurrence of nausea (feeling sick), which is a possible side effect of ADARTREL. Do not chew the tablet(s).

The exact dose of ADARTREL people take can be different. Your doctor will decide on the dose you need to take each day and you should follow the doctor's instructions. When you first start taking ADARTREL, the dose you take will be increased gradually.

The starting dose is 0.25 mg once daily. After two days your doctor will probably increase your dose to 0.5 mg once daily for the remainder of your first week of treatment. Then your doctor may increase your dose by 0.5mg per week over three weeks to a dose of 2mg per day. In some patients with insufficient improvement, the dose may be increased gradually up to a maximum of 4mg daily. After three months of treatment with ADARTREL, your doctor may adjust your dose or discontinue your treatment depending on your symptoms and how you feel.

Remember to take your medicine. If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work for you. If you have the impression that the effect of ADARTREL is too strong or too weak, talk to your doctor or pharmacist. Do not take more tablets than your doctor has recommended.

If you take more ADARTREL than you should

Someone who has taken an overdose may experience; feeling or being sick, dizziness (or spinning sensation), feeling drowsy, fatigue (mental or physical tiredness), stomach pain, fainting or nervousness. If you take more ADARTREL than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

If you forget to take ADARTREL

If you find you have forgotten to take your dose of ADARTREL do not take an extra dose to make up for forgotten individual doses.

When you do remember to take ADARTREL, take your next dose of ADARTREL at the usual time. If you have missed taking ADARTREL for more than a few days consult your doctor for advice on restarting ADARTREL.

If you stop taking ADARTREL

If your symptoms worsen after you stop treatment with ADARTREL, you should contact your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, ADARTREL can cause side effects, although not everybody gets them. Tell your doctor if you notice any side effects and they worry you. The more common side effects of ADARTREL can happen when some patients first start their therapy and/or when the dose is increased. The side effects are generally mild and may become less after you have taken the medicine for a short time.

The most common side effects are:

- feeling or being sick
- dizziness (or spinning sensation)
- feeling drowsy
- fatigue (mental or physical tiredness)
- stomach pain
- fainting
- nervousness

Uncommon side effects are feeling confused and experiencing hallucinations. Also uncommonly, ADARTREL can reduce blood pressure, which may make you feel dizzy or faint especially when standing up from a sitting or lying position.

During treatment with ADARTREL you may experience unusual worsening of symptoms (e.g. symptoms become worse, start earlier in the day or after less time at rest, or affect other parts of your body such as your arms). If this occurs, you should see your doctor.

If your symptoms worsen after you stop treatment with ADARTREL, you should contact your doctor.

Very rarely, cases of altered liver function (abnormal blood tests) have been reported.

ADARTREL can cause excessive daytime somnolence (excessive drowsiness) and very rarely sudden sleep onset episodes where patients fall asleep suddenly without apparently feeling sleepy.

If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist as soon as possible.

5 HOW TO STORE ADARTREL

Keep out of the reach and sight of children.

Do not use ADARTREL after the expiry date which is stated on the carton.

Do not store above 25°C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What ADARTREL contains

- The active substance is ropinirole (as hydrochloride)
- The other ingredients are

Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate
Film coat: hypromellose, macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172), indigo carmine aluminium lake (E132).

What ADARTREL looks like and contents of the pack

This medicine is provided as oval, yellow, film-coated tablets marked "GS" on one side and "TES" on the other. Each pack contains 28 or 84 tablets. Not all packs may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

Manufacturer: SmithKline Beecham Pharmaceuticals,
Manor Royal, Crawley,
West Sussex RH10 9QJ, United Kingdom

This leaflet was last approved in

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADARTREL 1 mg film-coated tablets Ropinirole (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.

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- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
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ADARTREL relieves the discomfort and reduces the urge to move the limbs that disrupt night time sleep.

2 BEFORE YOU TAKE ADARTREL

Do not take ADARTREL

- if you are allergic (hypersensitive) to the active ingredient, ropinirole, or any of the other ingredients of ADARTREL
- if you have serious liver disease
- if you have serious kidney disease

If you are unsure, it is essential that you talk to your doctor.

Take special care with ADARTREL

Tell your doctor before you start to take this medicine if you:

- are pregnant or think you are pregnant
- are breast-feeding
- are intolerant to some sugars (e.g. lactose)
- have liver disease
- have a serious heart complaint
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In these situations your doctor should carefully supervise the treatment.

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Tell your doctor if:

- you are already receiving any other medicines for Restless Legs Syndrome.
- you give up or start smoking while taking ADARTREL. Your doctor may need to adjust your dose.
- you are taking ADARTREL and the doctor is going to prescribe you any other medicine.

Taking ADARTREL with food and drink

Taking ADARTREL with food may reduce the likelihood of you feeling or being sick.

Pregnancy

The use of ADARTREL during pregnancy is not recommended. ADARTREL should only be used during pregnancy after your doctor has considered the benefit to you and the potential risk of harm to your unborn child. Tell your doctor immediately if you are pregnant, you think you might be or are planning to become pregnant. Your doctor will advise you to discontinue this medicine.

Breast-feeding

ADARTREL should not be used during breast-feeding as milk production may be affected. Tell your doctor immediately if you are breast-feeding or if you are planning to breast-feed. Your doctor will advise you to discontinue this medicine.

Driving and using machines

This medicine does not usually affect people's normal activities. However, ADARTREL can cause extreme sleepiness (somnolence) and sudden sleep onset episodes. If you suffer from these effects you must not drive or put yourself in a situation where sleepiness or falling asleep may put you at risk of serious injury or death (for example using machinery) until these episodes have been resolved.

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Remember to take your medicine. If you have trouble remembering when to take your medicine, ask your pharmacist for some hints.

You should continue to take your medicine even if you do not feel better, as it may take a number of weeks for your medicine to work for you. If you have the impression that the effect of ADARTREL is too strong or too weak, talk to your doctor or pharmacist. Do not take more tablets than your doctor has recommended.

If you take more ADARTREL than you should

Someone who has taken an overdose may experience; feeling or being sick, dizziness (or spinning sensation), feeling drowsy, fatigue (mental or physical tiredness), stomach pain, fainting or nervousness. If you take more ADARTREL than you should or if someone else has taken your medicine, tell a doctor or pharmacist immediately. Show them the package.

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If you stop taking ADARTREL

If your symptoms worsen after you stop treatment with ADARTREL, you should contact your doctor.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4 POSSIBLE SIDE EFFECTS

Like all medicines, ADARTREL can cause side effects, although not everybody gets them. Tell your doctor if you notice any side effects and they worry you. The more common side effects of ADARTREL can happen when some patients first start their therapy and/or when the dose is increased. The side effects are generally mild and may become less after you have taken the medicine for a short time.

The most common side effects are:

- feeling or being sick
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- stomach pain
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Uncommon side effects are feeling confused and experiencing hallucinations. Also uncommonly, ADARTREL can reduce blood pressure, which may make you feel dizzy or faint especially when standing up from a sitting or lying position.

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Very rarely, cases of altered liver function (abnormal blood tests) have been reported.

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If any of the side effects become serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist as soon as possible.

5 HOW TO STORE ADARTREL

Keep out of the reach and sight of children.

Do not use ADARTREL after the expiry date which is stated on the carton.

Do not store above 25°C.

Store in the original package.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6 FURTHER INFORMATION

What ADARTREL contains

- The active substance is ropinirole (as hydrochloride)
- The other ingredients are

Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate

Film coat: hypromellose, macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), indigo carmine aluminium lake (E132).

What ADARTREL looks like and contents of the pack

This medicine is provided as oval, green, film-coated tablets marked "GS" on one side and "SJG" on the other. Each pack contains 28 or 84 tablets. Not all packs may be available.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: Laboratoire GlaxoSmithKline
100, route de Versailles
78163 Marly-le-Roi Cedex
France
tel +33 1 39 178000

[See Annex I- to be completed nationally]

Manufacturer: SmithKline Beecham Pharmaceuticals,
Manor Royal, Crawley,
West Sussex RH10 9QJ, United Kingdom

This leaflet was last approved in

PACKAGE LEAFLET: INFORMATION FOR THE USER

ADARTREL 2 mg film-coated tablets Ropinirole (as hydrochloride)

Read all of this leaflet carefully before you start taking this medicine.

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What ADARTREL contains

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- The other ingredients are
- Tablet core: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate
- Film coat: hypromellose, macrogol 400, titanium dioxide (E171), iron oxide yellow (E172), iron oxide red (E172).

What ADARTREL looks like and contents of the pack

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Manufacturer: SmithKline Beecham Pharmaceuticals,
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ANNEX IV

CONDITIONS OF THE MARKETING AUTHORISATION

CONDITIONS OF THE MARKETING AUTHORISATION

The conditions considered essential for the safe and effective use of the Ropinirole are the following Post-Authorisation Commitment requested by the CHMP and to be submitted to the Reference Member State in the timeline are detailed below:

Area	Description:	Due Date
Module 5 – Clinical		
Clinical	To submit the final study report from the clinical study (ROR104836), “A randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of ropinirole for 26 weeks and to further evaluate the incidence of augmentation and rebound for a further 40 weeks open label extension treatment period in subjects suffering from moderate to severe Restless Legs Syndrome.” The study is expected to commence in Feb 06. The expected recruitment period is 18 months. The final study report will be available 6 months after the last patient visit in the study. GlaxoSmithKline expect to submit the final study report by	July 09