HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

18 March 2009

REQUIP LP 2 mg extended-release tablet
Box of 21 tablets (CIP: 379 214-8)
Box of 28 tablets (CIP: 379 215-4)
Box of 84 tablets (CIP: 379 217-7)

REQUIP LP 4 mg extended-release tablet
Box of 28 tablets (CIP: 379 221-4)
Box of 84 tablets (CIP: 379 222-0)

REQUIP LP 8 mg extended-release tablet
Box of 28 tablets (CIP: 379 223-7)
Box of 84 tablets (CIP: 379 224-3)

Applicant: GlaxoSmithKline

Ropinirole hydrochloride

ATC code: N04BC04

List I

Date of Marketing Authorisation (MA): 28 March 2007

Reason for request: reassessment of the IAB level following the submission of new clinical data.

Medical, Economic, and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
Ropinirole hydrochloride

1.2. Indication(s)

"Parkinson's disease under the following conditions:
- First-line treatment as monotherapy to delay the introduction of levodopa.
- In combination with levodopa as the disease progresses and levodopa becomes less effective or less consistently effective, and when fluctuations in the therapeutic effect start to appear ("end-of-dose" fluctuations or "on-off" effects)."

1.3. Dosage

"The dosage must be titrated based on individual therapeutic response and tolerability.
REQUIP LP extended-release tablets must be taken once daily at the same time each day. The extended-release tablets may be taken with or without food.
REQUIP LP extended-release tablets must be swallowed whole. The tablets must not be chewed, crushed or divided.

Initiation of treatment

The starting dose of ropinirole extended-release tablets is 2 mg taken in a single daily dose for the first week. The dose is then increased to 4 mg taken in a single daily dose starting the second week of treatment. A therapeutic response can be observed as soon as patients start taking ropinirole extended-release tablets at a dose of 4 mg/day.

Continuation of treatment

Patients must be kept on the lowest possible dose of ropinirole extended-release tablets that control their symptoms.
If the 4 mg once-daily dose does not sufficiently or consistently control the symptoms, the daily dose of ropinirole extended-release tablets can be increased by 2 mg per week at one-week (or longer) intervals up to a single daily dose of 8 mg of ropinirole extended-release tablets.
If the 8 mg once-daily dose of ropinirole extended-release tablets still does not sufficiently or consistently control the symptoms, the daily dose of REQUIP LP can be increased by 2 mg or 4 mg every two weeks at least. The maximum daily dose of ropinirole extended-release tablets is 24 mg/day.

Practitioners are advised to prescribe patients the smallest number of extended-release tablets needed to obtain the optimal dosage by using the highest possible strength of REQUIP extended-release tablets.

If this treatment is interrupted for one day or longer, retitration of therapy may be warranted according to the initiation regimen described above.

If REQUIP LP extended-release tablets are being administered as adjunct therapy to levodopa, the levodopa dose can be gradually reduced as tolerated. In clinical trials, the levodopa dose was gradually reduced by approximately 30% in patients who were concurrently taking REQUIP LP extended-release tablets. Patients with advanced Parkinson's disease who are also taking levodopa may experience dyskinesia when they are in the initial phase of treatment with REQUIP LP extended-release tablets. The levodopa dose can be reduced in this situation.

When ropinirole is used to replace another dopamine agonist, the latter must be discontinued according to the marketing authorisation holder's recommendations before introducing ropinirole.

As with other dopamine agonists, ropinirole treatment should be discontinued gradually by reducing the daily dose over a one-week period.

Switching from REQUIP immediate-release tablets to REQUIP LP extended-release tablets

REQUIP immediate-release tablets can be directly replaced with REQUIP LP extended-release tablets. The dose of REQUIP LP extended-release tablets must be selected on the basis of the daily dose of REQUIP immediate-release tablets that the patient was previously taking according to the dose equivalence table below:

Total daily dose of REQUIP immediate-release tablets (mg)	**Total daily dose of REQUIP LP extended-release tablets (mg)**
0.75 - 2.25	2
3 - 4.5	4
6	6
7.5 – 9	8
12	12
15 – 18	16
21	20
24	24

Following the conversion to REQUIP LP, the dose can be titrated according to therapeutic response (see "initiation of treatment" and "continuation of treatment" above).

Elderly patients

Since a decline in ropinirole clearance is observed after the age of 65, dose increases should be more gradual and titrated based on symptomatic response. A slower dose increase can be considered during treatment initiation for very elderly patients.

Patients with renal impairment

Dose adjustment is not necessary for Parkinson's patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 ml/min), since there have been no observed changes in ropinirole clearance in this population.

Children and adolescents

Since no safety or efficacy data is available, REQUIP LP is not recommended for children and adolescents under 18 years of age."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2008)

N: NERVOUS SYSTEM
N04: ANTI-PARKINSON DRUGS
N04B: DOPAMINERGIC AGENTS
N04BC: DOPAMINE AGONISTS
N04BC04: Ropinirole

2.2. Medicines in the same therapeutic category

Dopamine agonists indicated **as monotherapy or in combination** with levodopa:

Ergot derivatives:
- bromocriptine
  PARLODEL 2.5 mg tablets and generic (BROMO-KIN 2.5 mg tablets)
  PARLODEL 5 mg and 10 mg capsules and generics (BROMO-KIN 5 mg and 10 mg capsules)

- lisuride
  DOPERGINE 0.2 mg and 0.5 mg scored tablets

Non-ergot derivatives:
- piribedil
  TRIVASTAL 20 mg and TRIVASTAL LP 50 mg coated tablets

- pramipexole
  SIFROL 0.18 mg and 0.7 mg tablets

- ropinirole
  REQUIP 0.25 mg, 0.5 mg, 1 mg, 2 mg and 5 mg film-coated tablets

Dopamine agonists indicated for **second-line treatment** alone or in combination with levodopa:

- pergolide
CELANCE 0.05 mg, 0.25 mg and 1 mg, scored tablets

- apomorphine
APOKINON, solution for injection

2.3. Medicinal products with a similar therapeutic aim

All medicinal products indicated in the treatment of Parkinson's disease.

3. ANALYSIS OF AVAILABLE DATA

3.1. Efficacy

The Applicant submitted two phase III, randomised, double-blind, controlled studies (PREPARED and SK & F-101468/228).

PREPARED study

The objective of the PREPARED study was to compare the superiority of efficacy of extended-release ropinirole (LP) to immediate-release ropinirole (LI) in combination with L-dopa in patients with advanced Parkinson's disease whose symptoms are not fully controlled by L-dopa (end-of-dose akinesia, "on/off" fluctuations). The dose was gradually increased for the first four weeks and then adjusted until the maximum dose of 24 mg/day was reached (if this dose was regarded as necessary by the investigator).

The study took place in three stages:
- a two-week reference stage, in which patients were treated with a fixed dose of L-dopa;
- a 24-week stage, in which patients were given ropinirole LP or ropinirole LI. The dose was gradually increased over the first four weeks until the maximum dose of 24 mg/day was reached, then was adjusted at the investigator's discretion. The L-dopa dose could be reduced, but this was always done in conjunction with an increase in the dose of ropinirole. Finally, ropinirole doses were reduced in the last week of this stage;
- a two-week follow-up stage (L-dopa alone).

The primary inclusion criteria were:
- idiopathic Parkinson's disease (diagnosed according to stages II-IV of the modified Hoehn and Yahr staging scale) inadequately controlled by L-dopa, i.e., end-of-dose akinesia and on/off fluctuations;
- L-dopa dose stable for at least four weeks before the reference stage;
- at least three hours of awake "off" time as indicated by the patient log completed every day during the reference stage.

The primary efficacy endpoint was the proportion of patients with a reduction of ≥ 20% (compared with the baseline time value) in the awake "off" phase at week 24, whereas the reduction had been maintained during the previous two consecutive appointments (defined as "maintained reduction in "off" time").

The main secondary endpoints were:
- the variation in "off" time (as a percentage and in absolute terms) compared with the reference stage;

- the proportion of patients recorded as “significantly improved” or “very significantly improved” on the CGI-I scale;
- the variation (compared with the reference stage) of UPDRS, EQ5, PDSS, AIMS, PD-NMS and ADL scores;
- the percentage of patients requiring reintroduction of L-dopa;
- the variation in the dosage of L-dopa compared with the reference stage.

Of the 430 subjects calculated to be necessary, 350 patients were recruited. In light of previous studies assessing ropinirole LI, it was estimated that 344 subjects (172 per group) would be needed to show a 17% difference between ropinirole LP and ropinirole LI in the proportion of subjects with a sustained reduction in “off” time of at least 20% by W24 (LOCF).

Results:

The characteristics of the patients in both groups were comparable.

Primary efficacy endpoint: the percentage of patients treated with ropinirole LP who had a reduction of at least 20% in “off” time at week 24 (analysis conducted using the last observation carried forward [LOCF] technique) was 64% *versus* 51% for patients treated with ropinirole LI (p=0.009) (see table 1).

Table 1: results for the primary efficacy endpoint.

	N	% responders	Probability of adjusted response	Adjusted OR	95% CI	p
Ropinirole LP	174	110/172 (64%)	0.657	1.82	(1.16; 2.86)	0.009
Ropinirole LI	169	85/168 (51%)	0.512			

These results, which were obtained with the ITT population (patients who received at least one treatment dose and underwent at least one assessment, i.e., 98% of the patients), were confirmed by the per-protocol analysis.

Secondary endpoints: ropinirole LP was superior to ropinirole LI with respect to:

- the proportion of patients recorded as “significantly improved” or “very significantly improved” on the CGI-I scale;
- the variation in motor score on the UPDRS scale compared with the reference stage;
- the variation in the dosage of L-dopa compared with the reference stage.

There were no statistically significant differences between the two groups of patients for the other secondary criteria.

A major deviation from the protocol was observed in 176 of 343 subjects (51%); these 176 subjects were excluded from the per-protocol analysis. The deviation related to the L-dopa dose reduction regime in 147 subjects (43%) and occurred more frequently with ropinirole LP (47%) than with ropinirole LI (38%).

The average daily dose of ropinirole LP (18.6 mg) at week 24 was higher than that of ropinirole LI (10.4 mg). The superiority of ropinirole LP might be due to this difference between the two groups.

Study SK & F-101468/228

Phase III randomised, double-blind, parallel-group study comparing ropinirole LP (2 to 24 mg/day) with L-dopa (Sinemet at a dose of 50 to 1,000 mg/day) in patients with early-stage Parkinson's disease already being treated with L-dopa.
The aim of this study was to assess the time to onset of dyskinesia over a two-year treatment period.

Note:
The advantage of ropinirole treatment compared with L-dopa treatment in terms of time to onset of dyskinesia was demonstrated in the RASCOL study (see the Transparency Committee's opinion of 16 February 2000). The objective of this new study, SK & F-101468/228, was to demonstrate the benefit of the extended-release form in combination with L-dopa for patients whose existing treatment was not adequately controlling their condition.

The main inclusion criteria were:

- idiopathic Parkinson's disease (stage I to III according to the modified Hoehn and Yahr criteria), in which the symptoms are not optimally controlled by L-dopa (end-of-dose akinesia, "on/off" fluctuations);
- L-dopa dose ≤ 600 mg/d for up to three years and stable for at least four weeks prior to inclusion in subjects not suffering from dyskinesia.

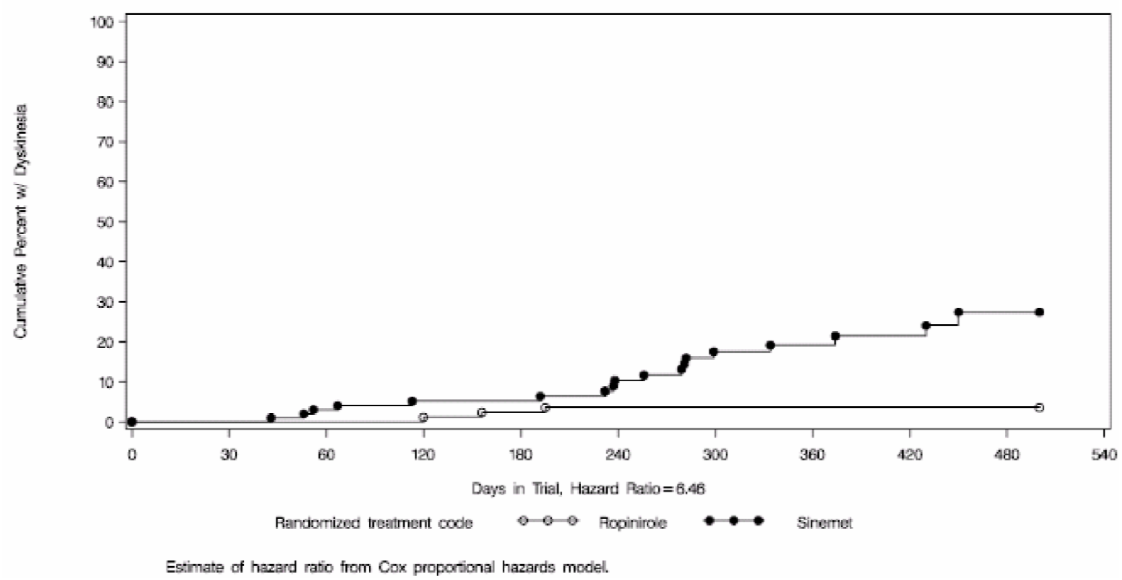
The primary efficacy endpoint was the time to onset of dyskinesia.
The main secondary assessment endpoints were four of the six sections of the UPDRS scale (Section II: activities of daily living, Section III: motor examination, Section IV: complications of therapy, Section V: Hoehn and Yahr staging).

Out of the 350 subjects calculated to be necessary (175 per group), only 209 patients were included. The ITT population comprised 208 subjects. The analysis of the results was carried out for 104 subjects in each of the two groups (ropinirole LP and Sinemet).
The patient characteristics on inclusion were comparable in both groups.
At week 28, 165 patients (84 in the ropinirole LP group and 81 in the Sinemet group) had received the study medication. By week 52 there were only 56 patients left in the ropinirole LP group and 52 in the Sinemet group.

Results:

A total of 21 patients developed dyskinesia: 3 in the ropinirole LP group and 18 in the Sinemet group. The times to onset are presented in figure 1 (Cox model).

Figure 1: Times to onset of dyskinesia according to randomisation group



The time to onset of dyskinesia was significantly longer ($p<0.001$) for ropinirole LP subjects than for Sinemet subjects.
No differences were observed between the two treatment groups (ropinirole LP versus Sinemet) with respect to the UPDRS and the four sections of this scale that were examined.

3.2. Adverse events

During the treatment phase of the PREPARED study, 57% of patients in the ropinirole LP and 42% of patients in the ropinirole LI group experienced adverse events considered to be treatment-related. The most commonly reported adverse effect was nausea (14% in the ropinirole LP group and 16% in the ropinirole LI group). The other adverse events experienced by at least 5% of patients were dyskinesia (10% versus 6%), somnolence (7% versus 6%), vertigo (7% versus 4%), hallucinations (6% versus 1%) and headache (5% versus 2%).
Severe adverse events were observed in two patients in the REQUIP LP group (hypotension leading to fall and pulmonary granuloma) and in one patient in the ropinirole LI group (hypertension).

The adverse events experienced by at least 5% of patients were nausea (20% in the ropinirole LP group versus 12% in the L-dopa group), vertigo (14% versus 9%), somnolence (13% versus 6%), insomnia (13% versus 4%), constipation (5% versus 2%), fatigue (6% versus 5%) and peripheral oedema (6% versus 0%). There were no serious adverse events.

The adverse events observed in both these studies were broadly comparable to those mentioned in the MA for REQUIP LP (except for the pulmonary granuloma and hypertension observed in the PREPARED study). In these studies, the adverse events were more common in patients taking ropinirole LP than in those taking ropinirole LI or L-dopa.

3.3. Conclusion

The Applicant submitted two new studies. The PREPARED study showed REQUIP LP to have superior efficacy compared with ropinirole LI in reducing "off" time by at least 20% at week 24 (p=0.009); the relative reduction was 64% in the ropinirole LP group *versus* 51% in the ropinirole LI group.
In the SK & F-101468/228 study, which was an add-on study conducted in early-stage Parkinson's patients who were already being treated with L-dopa, the time to onset of dyskinesia in the REQUIP LP group was significantly prolonged.
Patients being treated with ropinirole LP experienced more frequent adverse events than those being treated with immediate-release ropinirole.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

The actual benefit of this proprietary medicinal product in the treatment of Parkinson's disease (as monotherapy in the early stages of the disease and in combination with L-dopa) remains substantial.

4.2. Improvement in actual benefit (IAB)

REQUIP LP offers a minor improvement in actual benefit (level IV) compared with immediate-release REQUIP in terms of efficacy (shown by a reduction of at least 20% in "off" time at six months) in patients whose condition is not controlled by L-dopa in the indication of combined administration with levodopa as the disease progresses and levodopa becomes less effective or less consistently effective.

4.3. Target population

It is estimated that 110,000 to 145,000 people suffer from Parkinson's disease.
Of these people, 80 to 90% are treated with levodopa, and in 30% of these cases levodopa is administered as monotherapy. Dopatherapy alone is believed to be sufficient to control the condition in 26,000 to 40,000 patients.

The target population for this proprietary medicinal product can be estimated at 84,000 to 105,000 patients.

4.4. Therapeutic use[1,2,3]

There is currently no curative treatment for degenerative Parkinson's syndromes.

In the early stages of the disease

Therapeutic choices are made based on patient age at the onset of the disease and the degree of functional impairment. The aims of treatment are to correct motor (and non-motor) symptoms, prevent complications (especially falls), attenuate the impact on daily living, limit the adverse effects of treatment, improve quality of life and allow the patient to continue living at home.
Drug treatment is not essential if there are no motor symptoms, and the reasons for not giving treatment will be explained to the patient.

Where functional impairment is minimal, practitioners may prescribe a dopamine agonist, a monoamine oxidase B (MAO-B) inhibitor or an anticholinergic agent. The choice will depend on the predominant symptom and patient age:

- In younger patients, dopamine agonists are used for as long as possible. Dopatherapy may be used when patients do not tolerate dopamine agonists or if the therapeutic response is inadequate. The dose of L-dopa should remain as low as possible and be given according to an optimised administration schedule.

- In elderly subjects, L-dopa can be used as first-line treatment. Practitioners must use the lowest effective doses if the patient's cognitive function starts to decline.

After a number of years, the variable-length "honeymoon period", in which patients' symptoms are well controlled by treatment, comes to an end. At this time, the patient's condition worsens due to the onset of dopa-induced motor disturbances (motor fluctuations and dyskinesia) as well as of signs of the disease itself (dysautonomia, cognitive disorders and psychobehavioural disorders), which are usually dopa-resistant.

At the advanced stage of the disease

In view of the motor complications associated with dopamine treatment, the use of drugs that might aggravate "off" periods and dyskinesia should be questioned. Practitioners must constantly optimise dopatherapy by dividing the daily dose into sub-doses, adjusting the times at which medication is taken and prescribing different galenic formulations, since the dopamine stimulation achieved fluctuates considerably.

These motor complications can also justify the addition of other medicinal products to L-dopa:

- dopamine agonist: rye ergot derivatives and agents not derived from rye ergot (the latter have a longer plasma half-life);
- catechol-O-methyltransferase (COMT) inhibitors;
- MAOB Inhibitors (selegiline, rasagiline).

These drugs are preferred to amantadine and apomorphine.

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[1] National Collaborating Centre for Chronic Conditions. Parkinson's Disease: national clinical guideline for diagnosis and management in primary and secondary care. London, Royal College of Physicians, 2006
[2] Pahwa et al. Treatment of Parkinson Disease with motor fluctuations in dyskinesia (an evidence-based review): Report of the quality standards subcommittee of the American Academy of Neurology. Neurologie 2006 ; 66: 983-995.
[3] La Maladie de Parkinson: critères diagnostiques et thérapeutiques (Parkinson's Disease: diagnostic and therapeutic criteria). ANAES Conférence de consensus (Consensus Conference) - 3 March 2000

Rehabilitation is an important aspect of Parkinson’s patient treatment. The rehabilitation methods must adapt to the uncertainties and fluctuations of the condition, even in the short term.

Stereotactic surgery is an effective option in the treatment of severe motor disorders associated with advanced Parkinson’s disease and refractory tremor.