HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

OPINION

9 March 2011

ADARTREL 0.25 mg film-coated tablet
B/12 (CIP code: 391 839-4)

ADARTREL 0.5 mg film-coated tablet
B/28 (CIP code: 391 840-2)

ADARTREL 1 mg film-coated tablet
B/28 (CIP code: 364 452-5)

ADARTREL 2 mg film-coated tablet
B/28 (CIP code: 391 844-8)

Applicant : GLAXOSMITHKLINE

Ropinirole (hydrochloride)
ATC code: N04BC04

List I

Date of Marketing Authorisation: 30 June 2004 (mutual recognition procedure)
(Reference Member State: France)
Date of last revision: 1 July 2009

Current reimbursement conditions

Refundable by National Health Insurance at 65% in very severe forms of restless legs syndrome:

- patients experiencing substantial disturbances of sleep and/or a significant negative impact on their everyday family, social, and/or work life, and an IRLS (idiopathic restless legs syndrome) score of 31 or above.
- on condition that initial medical prescription is conducted by a neurologist or a specialist physician practicing in a sleep centre.

Not refundable in the moderate or severe forms of the condition.

Included on the list of medicines approved for hospital use and various public services: under the same conditions.

Reason for request: Reassessment of the actual benefit in accordance with the request made by the Directorate General for Health on 14 June 2010 following the re-inclusion opinion dated 10 March 2010.

Medical, Economic and Public Health Assessment Division

Therapeutic indications:

"Symptomatic treatment of moderate to severe idiopathic restless legs syndrome (cf. Pharmacodynamics)."
The Pharmacodynamics section states that "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."

N.B.: reminder of the wording of 2004: "Treatment of moderate to severe idiopathic restless legs syndrome (RLS) that interferes with sleep and/or has a negative impact on everyday family, social and/or work life."

Dosage: See SPC (Summary of Product Characteristics).

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 Pharmacodynamics). 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 dosage 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 clinical response.

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

New data since the Committee's last opinion

A - Efficacy data

A -1 In its first opinion (22 December 2004) the Transparency Committee approved the inclusion of ADARTREL proprietary medicinal products on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use and various public services,

- in very severe forms of restless legs syndrome: patients experiencing substantial disturbances of sleep and/or a significant negative impact on their everyday family, social and/or work life, and an IRLS score of 31 or above.

- on condition that initial medical prescription is conducted by a neurologist or a specialist physician practicing in a sleep centre.

Since the Committee's first opinion, issued in 2004, new clinical efficacy data have been incorporated into the "pharmacodynamics" section of the SPC. The "Pharmacodynamic properties" section cites four randomised studies of efficacy (as opposed to two evaluated in the last opinion of the Committee):

"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)."

The SPC also states that:
- "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.

A -2 The pharmaceutical company has not submitted any new clinical studies on efficacy for the population eligible for reimbursement since the Committee's previous opinion (re-inclusion opinion dated 10 March 2010).

The results of the post-marketing authorisation study (ROR104836) requested by the CHMP (Europe) as part of an arbitration procedure have already been described and discussed in the opinion dated 10 March 2010 (see appendix 1). Overall, the results of this study show ropinirole to be superior to placebo. But the extent of this superiority appears to be low, and the question of its clinical relevance arises. The results suggest that this advantage could

decline over time. In the sub-group of patients most severely affected, no long-term benefit was shown (it should be borne in mind that this population is small). Consequently, this study did not confirm the benefit of the medicinal product for patients with the most severe form of the condition.

A meta-analysis of 6 trials (including trials 190, 191, 194 and 188, Hansen et al, 2009) was conducted in order to assess ropinirole compared to placebo on the sleep scale (MOS Sleep) and on the overall clinical assessment scale (CGI-I) used in these studies. This meta-analysis does not document the clinical efficacy in the very severe forms.

B - Updating of pharmacovigilance data (post-marketing)

- According to the international pharmacovigilance data for the period covered by the latest PSUR (Periodic Safety Update Report), 9 January 2010 to 8 July 2010, a total of 72 observations were reported. Considering the cases according to the ICH criteria, 32 observations were submitted to the pharmaceutical company, and 11 of these presented a seriousness criterion for the RLS indication. Exposure during this period was estimated at approximately 49.1 million patient days. The events most commonly reported were neurological disorders (19%), general disorders and abnormalities at the administration site (15%) and gastrointestinal disorders (8%).
- In addition to the adverse effects which are already known (in particular, nausea, vomiting, hypotension, hallucinations, drowsiness or suddenly falling asleep), it should be remembered that the SPC for ADARTREL has been amended since the first review in 2004; the "Warnings and adverse effects" sections of the SPC now contain the following information:
  - “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 should be considered”.
  - Impulse control disorders including pathological gambling and hypersexuality, and increased libido, have been reported in patients treated with dopamine agonists, including ropinirole, principally for Parkinson's disease. Those disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases.

    N.B.: Dopamine agonists were the subject of a letter sent to prescribers by AFSSAPS in July 2009 about an adverse effect common to the class of dopamine agonists: impulse control disorder[1]. This adverse effect was mainly observed in patients treated for Parkinson's disease with high dosages or on concomitant use of several dopaminergic medicines. The indication exceptionally concerned the treatment of endocrine disease.
  - Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).
  - Psychotic reactions (other than hallucinations) including delirium, delusion, and paranoia have been observed.

C - Usage data

Reminder: when the first opinion on ADARTREL was issued (22 December 2004), a post-registration study was requested: “The Transparency Committee requests the pharmaceutical company to conduct a study to assess the gap between the target population and the population actually treated because of the potential existence, in particular, of:

- a medicalisation of patients in whom the severity of the condition has not been thoroughly assessed
- an inappropriate medical management of patients for whom this condition is a somatic expression of a psychiatric disorder requiring specific treatment.

[1] Lévodopa, agonistes dopaminergiques et troubles du contrôle des impulsions [Levodopa, dopamine agonists and impulse control disorder]. Afssaps – letter to healthcare professionals – pharmacovigilance – 29 July 2009

It would be desirable to repeat this data gathering in order to describe the development of practice.

The Committee wishes to re-examine these proprietary medicinal products in the light of the results from the study after 1 year."

Despite a reminder letter being sent by the Committee on 15 October 2008, the pharmaceutical company has not set up this study which the Committee requested. The ISPEP [Public Health Interest and Post-Registration Studies] group would like to point out that the post-registration study requested has never been set up even though the protocol was validated in 2008.

Data from the study of the Echantillon Généraliste des Bénéficiaires (EGB) [permanent representative sample of the population covered by French statutory health insurance]

- A study on the conditions under which ADARTREL is used, based on the Echantillon Généraliste des Bénéficiaires (EGB) covered by the general statutory health insurance scheme was submitted by the pharmaceutical company. The request for a review was suspended until 5 January 2011 while awaiting these additional data.
- In the light of the results presented, it can be noted that:
  - according to the EGB data extrapolated to the French population, the population treated with ADARTEL remains within the target population estimates;
  - more than a third of initial prescriptions are not issued by neurologists or physicians practicing in a sleep centre, as the Committee recommended in its 2004 opinion;
  - the standard dosage of 1 mg is lower than the average dose used in the trials (2 mg) and is at the lower limit indicated in the SPC (maximum dosage 4 mg).
  - the ISPEP group points out that the EGB data submitted does not respond to either of the two issues raised in the request.
  - these data are insufficient to determine the level of severity of the condition suffered by patients being treated with ADARTREL for RLS (variable not included in this sample) and are too fragmented to allow a proper assessment of the management or not of an underlying psychiatric disorder in these patients.

Reassessment of actual benefit

- Restless legs syndrome is a condition classified as organic chronic insomnia. It is not a life-threatening condition and does not cause severe complications or disability. It is typically characterised by paraesthesia and dysaesthesia in the legs associated with motor agitation. These disorders, which are aggravated at rest and improved by activity, normally occur in the evening when the patient goes to bed. Sleep disorders can sometimes have a severe impact on quality of life. In about 80% of cases the patient's legs move at intervals while he or she is asleep. This can cause the patient to wake up briefly and contribute to sleep disorders.

- ADARTEL is intended for symptomatic treatment.

- The efficacy of ropinirole in the treatment of restless legs syndrome has been demonstrated versus placebo in respect of subjective and objective criteria. The population of patients included in the studies had a severe form of the syndrome (average score on the IRLS scale of around 24/40). The extent of the effect was regarded as modest (ropinirole produced an improvement approximately 3 points greater than placebo on the 0 to 40 severity scale; the improvement in quality of life was partial, with results varying according to the studies conducted and scales used; improvement in sleep disorders was partial). The observed effect in patients with a very severe form of the syndrome (severity score of 31 or above) seemed to be more pronounced (ropinirole led to a score gain 6 points higher than placebo). However, comparative data versus placebo obtained from the post-marketing authorisation study requested by the CHMP (Europe) did not confirm this result; they suggest that the extent of the effect would be

minor at best. Consequently, clinical relevance is not clearly established at this degree of severity of this syndrome.

The adverse effects of ropinirole are those known from Parkinson's disease. The lower dosage used in this indication (doses three to four times weaker) had led to the hope that it would be better tolerated. However, this expectation was not confirmed by pharmacovigilance data (see changes to the SPC).

Overall, the efficacy/adverse effects ratio of ropinirole for patients with very severe RLS is not clearly established. Furthermore, the pharmaceutical company has not conducted the post-registration study that would have ensured that ADARTREL is being used correctly and validated the treatment strategy proposed by the Committee (that the medicinal product could be useful only for managing patients with a very severe form of the syndrome). In March 2010 the Committee drew the attention of the DGS, DSS, and CEPS to the fact that this study, requested in December 2004, had not been performed, something which it regards by the Committee as a failure which could be harmful to patients.

- There is no alternative drug treatment since ADARTREL is the only proprietary medicinal product indicated for use in this condition (and eligible for reimbursement). Non-drug alternatives (advice on ways of improving sleep in particular) are appropriate for all forms of the condition and are generally adequate to deal with the mildest forms.

Public health benefit: as the nosology of restless legs syndrome (RLS) is unclear and in view of the lack of data on the epidemiology and severity of forms described as idiopathic, and on the natural course of RLS, it is impossible to assess the importance of the burden condition in terms of public health.
However, the benignity of the condition in the vast majority of cases and the impact on quality of life, which could be only moderate for the most severe forms, suggest that the burden of the disease is minor.
Management of RLS is not a public health need.
The results presented indicate that ADARTREL has a minor impact on morbidity. A negative impact cannot be ruled out in view of the potential adverse effects (paradoxical aggravation of symptoms and impulse control disorders in particular).
It is doubtful whether the results of trials can be transposed to real conditions, particularly because of the difficulty in identifying patients likely to benefit from drug treatment. The data available are insufficient to rule out the risk that RLS manifestations may be the expression of other conditions, particularly psychiatric disorders that require specific treatment.
The EGB data show that the co-prescription of all classes of drugs used to treat conditions of the central nervous system is stable, and so the argument that ADARTEL reduces the use of psychotropic substances is not upheld.

Consequently, ADARTEL offers no public health benefit for RLS.

Conclusion: the actual benefit of this proprietary medicinal product is insufficient to justify its reimbursement in the symptomatic treatment of idiopathic restless legs syndrome, including very severe forms.

Committee recommendations: the Transparency Committee does not recommend continued inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use.