HAUTE AUTORITÉ DE SANTÉ

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TRANSPARENCY COMMITTEE

Opinion

3 October 2012

RITALIN 10 mg, tablet

B/30 (CIP code: 34009 339 294 0-4)

RITALIN LP 10 mg, sustained-release tablets

B/28 (CIP code: 34009 416 865 3-5)

RITALIN LP 20 mg, sustained-release tablets

B/28 (CIP code: 34009 365 349 3-3)

RITALIN LP 30 mg, sustained-release tablets

B/28 (CIP code: 34009 365 350 1-5)

RITALIN LP 40 mg, sustained-release tablets

B/28 (CIP code: 34009 365 351 8-3)

Applicant: NOVARTIS PHARMA

INN	Methylphenidate
ATC Code (2012)	N06BA04 (psychostimulants)
Reasons for the review	▪ **Re-assessment of methylphenidate-based proprietary products in attention-deficit hyperactivity disorder in response to a request from the Directorate-General for Health** ▪ **Renewal of inclusion**
Lists concerned	**National Health Insurance (French Social Security Code L.162-17)**
Indications concerned	▪ **Attention-deficit hyperactivity disorder in children aged six years and over when remedial measures alone prove insufficient.** ▪ **Narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (national procedure)	RITALIN 10 mg, tablet: 31/07/1995 RITALIN LP 20 mg, 30 mg, 40 mg, sustained-release tablet: 05/05/2003 RITALIN LP 10 mg, sustained-release tablets: 01/08/2011
General classification for supply / special status	List I

ATC Classification	2012	
	N	Nervous system
	N06	Psychoanaleptics
	N06B	Psychostimulants, agents used for ADHD and nootropics
	N06BA	Centrally acting sympathomimetics
	N06BA04	Methylphenidate

02 BACKGROUND

- Examination of the medicinal products included again on the list of medicines refundable by National Health Insurance for a 5-year period starting on 17 August 2007 (Official Gazette of 29 April 2009).

- Re-assessment of the actual benefit and conditions of use of proprietary products containing methylphenidate in attention-deficit hyperactivity disorder (ADHD) in response to a request from the Directorate-General for Health of 22 May 2012.

03 THERAPEUTIC INDICATIONS

“Attention-deficit hyperactivity disorder in children aged six years and over.
Methylphenidate is indicated as part of the comprehensive management of attention-deficit Hyperactivity Disorder (ADHD) in children aged 6 years and over when remedial measures alone prove insufficient. Treatment must be under the supervision of a specialist in childhood behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the patient. The diagnosis cannot be made solely on the presence of one or more symptom.
The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and psychological, educational and social resources.
A comprehensive treatment programme typically includes psychological, educational and social measures as well as pharmacotherapy and is aimed at stabilising children with a behavioural disorder characterised by symptoms which may include: history of attention-deficit disorders (short attention span), distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and abnormal EEG. Learning may or may not be impaired.
Methylphenidate treatment is not indicated in all children with ADHD and the decision to use the drug must be based on a very thorough assessment of the severity and the chronicity of the child’s symptoms in relation to the child’s age.
Appropriate educational placement is essential, and psychosocial intervention is generally necessary. Where remedial measures alone prove insufficient, the decision to prescribe a psychostimulant must be based on rigorous assessment of the severity of the child’s symptoms. The use of methylphenidate should always be used according to the authorised indication and according to the prescribing/diagnostic guidelines.

Narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years."

04 SUMMARY OF PREVIOUS ASSESSMENTS

The conclusions of the previous assessments were as follows:

Opinion of the Committee of 8 and 22 November 1995 – RITALIN 10 mg, tablet

Reason for request: New active ingredient.
Conclusion: Improvement in actual benefit (IAB) type II (substantial) in terms of efficacy in attention-deficit hyperactivity disorder in children aged over six years, with no upper age limit.

Opinion of the Committee of 1999 – RITALIN 10 mg, tablet

Reason for request: Request for renewal on the list of medicines refundable by National Insurance.
Conclusion: Substantial actual benefit in attention-deficit hyperactivity disorder in children aged over six years, with no upper age limit.

Opinion of the Committee of 10 and 24 May 2000 – RITALIN 10 mg, tablet

Reason for request: Extension of indication to the treatment of narcolepsy with or without cataplexy, where modafinil is ineffective in adults and children aged over 6 years.
Conclusion: Substantial AB/ IAB II in the strategy for managing narcolepsy with or without cataplexy as second-line therapy.

Opinion of the Committee of 12 June 2002 – RITALIN 10 mg, tablet

Reason for request: Request for renewal of inclusion on the list of medicines refundable by National Insurance.
Conclusion: Substantial AB in attention-deficit hyperactivity disorder in children aged over 6 years, with no upper age limit.
Substantial AB in narcolepsy with or without cataplexy, where modafinil is ineffective in adults and children aged over 6 years.

Opinion of the Committee of 14 January 2004

Proprietary products:
RITALIN LP 20 mg, capsule, hard (B/30)
RITALIN LP 30 mg, capsule, hard (B/30)
RITALIN LP 40 mg, capsule, hard (B/30)
Reason for request: Inclusion on list of products refundable by National Insurance and approved for hospital use.
Conclusion: IAB IV (minor) in terms of convenience of use compared with immediate-release methylphenidate in attention-deficit hyperactivity disorder in children aged over 6 years, with no upper age limit.

Opinion of the Committee of 16 March 2005

Proprietary products:
RITALIN LP 20 mg, sustained-release tablet (Bottle of 28),
RITALIN LP 30 mg, sustained-release tablet (Bottle of 28),
RITALIN LP 40 mg, sustained-release tablet (Bottle of 28),
Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for use by hospitals and various public services.
Conclusion: Substantial AB/No IAB compared with packs of 30 in bottles, in attention-deficit hyperactivity disorder in children aged over 6 years, with no upper age limit.

05 ANALYSIS OF NEW DATA AVAILABLE

05.1 Efficacy

5.1.1 ADHD in children aged 6 years and over when remedial measures alone prove insufficient.

The report of the Transparency Committee is appended.

5.1.2 Narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years (RITALIN, tablet).

The pharmaceutical company has provided no clinical data on methylphenidate.

05.2 Adverse effects/Undesirable effects

See the report of the Transparency Committee, as appended.

05.3 Usage/prescription data

See the report of the Transparency Committee, as appended.

05.4 Therapeutic strategy

5.4.1 ADHD in children aged 6 years and over when remedial measures alone prove insufficient.

See the report of the Transparency Committee, as appended.

5.4.2 Narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years (RITALIN, tablet).

Methylphenidate still has a place as second-line therapy for narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years[1].

[1] Billiard M et al. Management of narcolepsy in adults. Chapter 38. European handbook of neurological management: Volume 1, 2nd edition. 2011.

06 COMMITTEE CONCLUSIONS

Actual benefit:

1) ADHD in children aged 6 years and over when remedial measures alone prove insufficient.

The Transparency Committee conclusions are as follows:

ADHD is defined mainly by signs of lack of attention, hyperactivity and impulsivity. It may occur alongside other disorders such as oppositional defiant disorder, learning disability, anxiety, depression, tic disorder and Tourette syndrome. ADHD may lead to substantial impairment of interpersonal relationships and performance at school.

Methylphenidate-based proprietary products fall under the category of symptomatic treatment.

The efficacy/safety ratio for these medicinal products is moderate.

Management of ADHD is comprehensive. It comprises primarily psychological, educational and social measures which, if they really prove insufficient, can be combined with methylphenidate, as second line therapy.

There are several methylphenidate-based proprietary products.

Public health benefit

In view of its prevalence, estimated to be 2% in the case of school-age children[2], and the impact it has on family, education and social circles, the public health burden of attention-deficit hyperactivity disorder may be considered to be moderate.
Improving the treatment of children with this disorder, frequently combined with other concomitant disorders (language disturbances, psychiatric disorders, sleep disorders etc.) is a public health need which is an established priority (French 2004 Law on Public Health, French Psychiatry and Mental Health Plan).
The response to this need should not be restricted to a drug-related approach (psychological, educational and family-based measures should also be instituted). When drug treatment is recommended, methylphenidate-based medicinal products help meet the public health need identified.
In view of the available data these proprietary products can be considered to have a low impact in terms of morbidity, quality of life and socio-educative effect for the patients treated.
Moreover, it is not certain that clinical trials can be transposed into practice, owing to the remaining uncertainties about the medium- and long-term effects of methylphenidate, particularly in terms of cardiovascular, neurological and psychiatric events.
There is a risk of inappropriate use, misuse or abuse of methylphenidate.
Consequently, in the light of current knowledge, methylphenidate-based proprietary products offer a public health benefit in this indication. This benefit is slight.

The Transparency Committee considers that:
The actual benefit of RITALIN and RITALIN LP is substantial in the context of the comprehensive therapeutic management of ADHD in children aged 6 years and over when psychological, educational and social management alone proves insufficient.

The Committee points out that prescriptions for methylphenidate must comply strictly with the indication authorised by the MA and should be restricted to ADHD, to the exclusion of other behavioural disorders. Diagnosis should be made according to DSM-IV criteria or the guidelines in ICD-10 and should be based on a complete history and evaluation of the child.
The Committee notes the undesirable effects of methylphenidate and is still concerned about its long-term effects, linked to its amphetamine-like structure.

[2] Troubles mentaux : Dépistage et prévention chez l'enfant et l'adolescent. Expertise collective INSERM. Les Editions INSERM 2002

2) Narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years (RITALIN, tablet).

Narcolepsy with or without cataplexy is a disabling chronic disease that has effects on the personal, social and working life of patients.

RITALIN, tablet, falls under the category of symptomatic treatment.

The efficacy/safety ratio for this medicinal product is modest.

This proprietary product is a second-line medicine where modafinil is ineffective.
There are alternative therapies for treating narcolepsy with or without cataplexy.

The Transparency Committee considers that:
The actual benefit of RITALIN, tablet, is still substantial in treating narcolepsy with or without cataplexy where modafinil is ineffective in adults and children aged over 6 years.

The Transparency Committee recommends continued inclusion on the list of medicines refundable by National Health Insurance in the indications in the Marketing Authorisation.

◗ **Proposed reimbursement rate: 65%**

07 COMMITTEE RECOMMENDATIONS

In the indication of ADHD in children aged 6 years and over when remedial measures alone prove insufficient, the Transparency Committee recommends that information resources on methylphenidate be produced for patients, families and healthcare professionals.

◗ Packaging

Methylphenidate comes under narcotics regulations.
The packaging of RITALIN (B/30) and RITALIN LP (B/28) is unsuitable:

- RITALIN 10 mg, tablet: one carton contains 30 tablets arranged on 3 blisters. The batch number and the expiry date on the carton are only printed on one end of each blister, which presents problems when the pharmacist has to remove the packaging.
- RITALIN LP 20 mg, 30 mg, 40 mg, hard capsule: the tablets/hard capsules are packed in a bottle containing one or two desiccants in direct contact with the contents and closed with a "child-resistant" cap. This bulk packaging does not allow the guaranteed preservation, safety and appropriate identification of the medicinal product if removed from the packaging.

This opinion is available on the site of the Haute Autorité de Santé.
http://www.has-sante.fr