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TRANSPARENCY COMMITTEE

APPENDIX

Re-assessment of methylphenidate-based proprietary medicinal products in attention-deficit hyperactivity disorder in response to a request from the Directorate-General for Health

OPINION

3 October 2012

Proprietary medicinal products concerned:
- RITALINE 10 mg, tablet
- RITALINE LP 10 mg, 20 mg, 30 mg, 40 mg, capsule
- CONCERTA LP 18 mg, 36 mg, 54 mg, tablet
- QUASYM LP 10 mg, 20 mg, 30 mg, capsule

Methylphenidate
ATC Code: N06BA04 (psychostimulants and nootropics)

Narcotic.
Prescription restricted to 28 days.
Prescription on form meeting the requirements laid down in the decree of 31 March 1999.
Initial annual hospital prescription restricted to neurology, psychiatry and paediatric specialists and/or specialist services.

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BACKGROUND AND INTRODUCTION

Methylphenidate has been available in France for the treatment of attention-deficit hyperactivity disorder (ADHD) since 1995.

ADHD is defined mainly by signs of hyperactivity, inattention and impulsivity. It is usually associated with other disorders (oppositional defiant disorder, learning disabilities, anxiety, depression, tics and Tourette's syndrome). According to the DSM-IV classification, there are three subtypes:

- the predominantly inattentive type, which is mainly defined by difficulty sustaining attention, difficulty organising, and being forgetful;
- the predominantly hyperactive-impulsive type (where the main symptoms are constant fidgeting with the hands or feet, and frequently getting up and talking in the classroom);
- the combined type (inattention and hyperactivity/impulsivity).

ADHD may lead to substantial impairment of interpersonal relationships and performance at school.

Methylphenidate is a psychostimulant with an amphetamine-like chemical structure. Three proprietary medicinal products are currently marketed: RITALINE, CONCERTA and QUASYM. These medicines are listed as narcotics and subject to prescription and dispensing restrictions.

In 2007, at the request of the European Commission, the European Medicines Agency (EMA) re-evaluated the safety profile of drugs containing methylphenidate. The risk of cardiovascular and neurological adverse effects, risk of psychiatric disorders, effect on growth and sexual maturation, long-term effects and risk of inappropriate use were examined.

In January 2009, the EMA concluded that the risk/benefit ratio of products containing methylphenidate in the treatment of ADHD in children aged over six years remained favourable. However, it was recognised that more data were needed on the long-term effects of methylphenidate, in particular the incidence of cardiovascular, cerebrovascular and psychiatric events. Following this re-evaluation, the information on methylphenidate safety was consolidated and harmonised in SPCs and package leaflets. A European risk management plan (RMP) covering all these proprietary medicinal products was implemented.

In France, the National Agency for the Safety of Medicines and Health Products (ANSM) has been running a pharmacovigilance and drug abuse monitoring programme since 2006.

In 2011, a status report on pharmacovigilance and drug dependence data was presented to the National Narcotics and Psychotropic Drugs Committee and the National Pharmacovigilance Committee, which highlighted the lack of data on the long-term effects of methylphenidate and the significant risk of abuse and dependence. Several initiatives aiming to limit the risks associated with methylphenidate use are currently in progress at ANSM (information for families and prescribers, requests for further studies, etc.).

I. SUBJECT OF THE REQUEST

In view of concerns about the long-term effects of methylphenidate and the risk of inappropriate use, the Director-General for Health requested on 22 May 2012 that the Transparency Committee re-assess the actual benefit of proprietary medicinal products containing methylphenidate and give its opinion on the conditions for use of these medicines in ADHD.

II. DESCRIPTION OF THE PRODUCTS CONCERNED

II.I. ATC classification

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

II.II. Medicines in the same therapeutic category

Three methylphenidate-based proprietary medicinal products are currently available in France. A fourth product, MEDIKINET, was granted Marketing Authorisation in 2011 but to date has not been marketed. These proprietary medicinal products differ in terms of methylphenidate release kinetics (see Table 1).

Table I: Description of methylphenidate-based proprietary medicinal products

Proprietary Medicinal Product	RITALINE	RITALINE LP	CONCERTA LP	QUASYM LP	MEDIKINET	MEDIKINET LM
Dosage	10 mg tablets	20 mg, 30 mg, 40 mg capsules	18 mg, 36 mg, 54 mg tablets	10 mg, 20 mg, 30 mg capsules	5 mg, 10 mg, 20 mg tablets	5 mg, 10 mg, 20 mg, 30 mg, 40 mg capsules
MA Holder	Novartis Pharma		Janssen Cilag	Shire	HAC Pharma	
Date of MA (Procedure)	31/07/1995 (national)	5/05/2003 (national)	28/03/2003 (mutual recognition)	27/12/2006 (mutual recognition)	18/07/2011 (decentralised)	
Transparency Committee Opinion (Date)	Substantial actual benefit IAB II (22/11/1995)	Substantial actual benefit IAB IV (14/01/2004)	Substantial actual benefit IAB IV (29/10/2003)	Substantial actual benefit IAB V (10/03/2010)	Evaluation in progress	
Proportion of IR/ER Methylphenidate	100% IR	50% IR 50% ER	22% IR 78% ER	30% IR 70% ER	100% IR	50% IR 50% ER
Duration of Action	3-4 hours	~8 hours	~12 hours	~8 hours	3-4 hours	~8 hours
Indication in ADHD	*The wording of the indication in ADHD was standardised for all methylphenidate-based medicines following the EMA re-evaluation in 2009.* "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 symptoms. 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 evaluation 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. Methylphenidate should always be used according to the authorised indication and according to the prescribing/diagnostic guidelines."					
Prescription and Dispensing Conditions	Narcotic. Prescription restricted to 28 days. Prescription on form meeting the requirements laid down in the decree of 31 March 1999. Initial annual hospital prescription restricted to neurology, psychiatry and paediatric specialists and/or specialist services.					

ER: extended release; IR: immediate release; LM: modified release; LP: extended release.

LITERATURE SEARCHES

Searches for meta-analyses, literature reviews and clinical studies comparing the efficacy of methylphenidate to placebo or to non-drug management in school-age children with ADHD and published between 01/01/2008 and 01/07/2012 were conducted using the following sources:

- MEDLINE database;
- Cochrane Library;
- websites publishing guidelines or evaluation reports;
- the websites of learned societies competent in this field.

The safety data is based on information provided by ANSM, information given on the EMA website and files submitted by the pharmaceutical companies.

The usage data is based on information provided by ANSM and files submitted by the pharmaceutical companies.

CLINICAL DATA

I. NICE META-ANALYSIS, 2009[1]

In 2009, NICE conducted a review of data comparing:
a) the efficacy of methylphenidate versus placebo or versus no psychostimulant treatment;
b) the efficacy of methylphenidate versus combination therapy (methylphenidate + psychosocial interventions).

NICE also compared c) the efficacy of combination therapy versus psychosocial interventions alone and d) the efficacy of psychostimulant treatment alone versus psychosocial interventions alone. These two analyses are primarily based on the results of the MTA study discussed below.

a) Efficacy of methylphenidate versus placebo or versus no psychostimulant treatment

Fourteen studies (1660 children) comparing the effect of methylphenidate to placebo (13 studies) or to no psychostimulant treatment (1 study) in children aged over 5 years with ADHD were included.

The duration of follow-up in these studies ranged from 3 weeks to 3 months. The ADHD endpoints were improvement in ADHD symptoms, conduct problems and overall clinical improvement. In general terms, a more substantial reduction in ADHD symptoms and behavioural disorders and greater overall clinical improvement were observed with methylphenidate than with placebo. However, the great diversity of used scales makes these results difficult to interpret (see detailed table of results in Appendix 1).

b) Efficacy of methylphenidate versus combination therapy (methylphenidate + psychosocial interventions)

Seven studies including 544 children aged 5 to 12 years with ADHD were taken into account. The duration of these studies ranged from 8 weeks to 2 years.

The efficacy of combination therapy and of methylphenidate alone was comparable in terms of ADHD symptoms, emotional outcomes and self-efficacy. Combination therapy was observed to be more effective in terms of parent-rated conduct problems at the end of treatment (3 studies; n = 378; standardised mean difference [SMD] -0.21, 95% CI [-0.41 to -0.01]) (see detailed table of results in Appendix 1).

[1] National Collaborating Centre for Mental Health commissioned by the National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder. Diagnosis and management of ADHD in children, young people and adults. National Clinical Practice Guideline Number 72. Leicester and London: The British Psychological Society and The Royal College of Psychiatrists, 2009.

II. MTA STUDY

a. Methods

The Multimodal Treatment for ADHD study is a randomised trial conducted in the USA in 579 children aged 7 to 10 years with ADHD over a period of 14 months. The children were randomised into four groups:

- treatment with methylphenidate as first-line therapy or another psychostimulant (n = 144);
- behavioural treatment with multiple components (n = 144);
- a combination of these two treatments (n = 145);
- standard community care (control group) (n = 146).

The endpoints were ADHD symptoms, oppositional or aggressive behaviour, deterioration in overall functioning, anxiety and depression, teacher-rated social skills, parent-child relations and reading achievement.

Investigators sought to establish the optimal dose of methylphenidate over a period of 28 days. The children received double-blind treatment in a randomised order with four doses of methylphenidate (5 mg, 10 mg, 15 mg or 20 mg) or a placebo.

The methylphenidate dose for the rest of the study was defined after evaluation of the response to the four doses of methylphenidate and the placebo by parents and teachers. If methylphenidate was not judged satisfactory, other, open-label pharmacological treatments were trialled (dextroamphetamine, pemoline, imipramine).

This titration phase was conducted successfully in 256 of the 289 children treated pharmacologically (144 in the pharmacological treatment group and 145 in the combination therapy group). Of these, 198 were treated with methylphenidate, 26 with dextroamphetamine and 32 with placebo due to a satisfactory placebo response.

After the initial study ended at 14 months, families were able to choose which treatment they wished to pursue.

Observational data were gathered at 24 months, 36 months and 8 years.

b. Results

- *Results at 14 months*[2]

At 14 months, a reduction in symptoms was observed in all four treatment groups. However, treatment with methylphenidate, whether this was combined with behavioural therapy or not, was more effective on the core symptoms of ADHD than standard community care or behavioural therapy alone.

The combination therapy was superior to standard community care and to behavioural therapy alone on several endpoints (oppositional/aggressive symptoms, anxiety and depression, teacher-rated social skills, parent-child relations and reading achievement). No difference in efficacy was observed between the group treated with methylphenidate alone and the group receiving combination therapy (methylphenidate + behavioural therapy).

[2] MTA Co-operative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Archives of General Psychiatry 1999; 56: 1073–1086.

- *Observational data at 24 and 36 months and 8 years*[3,4,5]

The observational data from the MTA study are a significant source of information on the development of children with ADHD in childhood. The development of treatment groups was compared at 24 months, 36 months and 8 years. This comparison is based on the treatments assigned at the time of randomisation and does not take into account the treatment pursued by the children at the end of the 14-month initial phase.
At 24 months, 540 children (93%) were evaluated and it was observed that pharmacological treatment, whether this had been combined with behavioural therapy or not, remained superior to other treatment strategies for ADHD symptoms.
At 36 months, 485 children (84%) aged 10 to 13 years were evaluated. No difference in efficacy was observed between the four groups.
At 8 years, 436 children and adolescents (75%) were evaluated. As with the 36-month analysis, no difference was observed between the groups for the variables analysed, in particular school grades, detentions by police and psychiatric hospitalisations.

III. ADVERSE EFFECTS

III.I. Main adverse effects

According to the SPCs, the adverse effects most commonly encountered with methylphenidate (≥ 1/10) are nervousness, insomnia and headaches.
The other common adverse events (≥ 1/100, < 1/10) are:

- anorexia, decreased appetite, moderately reduced weight and height gain during prolonged use in children;
- dizziness, dyskinesia, psychomotor hyperactivity, somnolence;
- affect lability, aggression, agitation, anxiety, depression, irritability, abnormal behaviour;
- changes in blood pressure and heart rate (arrhythmia, palpitations, tachycardia);
- gastrointestinal disorders such as abdominal pain, nausea and vomiting occurring at the beginning of treatment and which may be alleviated by concomitant food intake, dry mouth;
- skin reactions: alopecia, pruritus, rash, urticaria.

More rarely, methylphenidate administration may be associated with the onset or worsening of psychiatric disorders: psychotic or manic symptoms, or motor or verbal tics.

Questions remain as to cardiovascular, neurological and psychiatric events in the long term.

III.II. Re-evaluation by the European Medicines Agency (EMA)

In 2009, the EMA re-evaluated methylphenidate's safety profile because of concerns about the risk of cardiovascular and neurological events (cerebrovascular accident). The risk of psychiatric disorders (depression, psychotic disorders, suicide risk), effect on growth and sexual maturation, and long-term effects were also studied.

[3] MTA Co-operative Group. National Institute of Mental Health multimodal treatment study of ADHD follow-up: 24-month outcomes of treatment strategies for attention-deficit/hyperactivity disorder. Archives of General Psychiatry 2004; 56: 1088–1096.
[4] Jensen, P. S., Arnold, L. E., Swanson, J. M., et al. 3-year follow-up of the NIMH MTA study. Journal of the American Academy of Child and Adolescent Psychiatry 2007; 46: 989–1002.
[5] Molina B. et al. The MTA at 8 Years: Prospective Follow-Up of Children Treated for Combined Type ADHD in a Multisite Study. J Am Acad Child Adolesc Psychiatry 2009; 48: 484–500.

The EMA concluded that the risk/benefit ratio of methylphenidate-based proprietary medicinal products in the treatment of ADHD in children aged six years or over remained favourable and recommended to maintain the Marketing Authorisation.[6]
However, following this evaluation, information on methylphenidate safety in the SPCs and package leaflets was consolidated and harmonised.
The EMA also drew up a list of conditions for the maintenance of Marketing Authorisation ("follow-up measures"), primarily including:

1) a request for further studies of the risks associated with methylphenidate, in particular:
    - cardiovascular and cerebrovascular effects;
    - carcinogenic risk (cytogenetic study);
    - effects on growth, development and sexual maturation;
    - risk of suicide;
    - effects of long-term use, specifically cognitive and psychiatric effects (mood disorders, hostility and psychotic disorders);
    - use of the drug, including off-label use and abuse;
2) the implementation of a risk management plan covering all these proprietary medicinal products. The important identified and potential risks monitored through the risk management plan are listed in Appendix 2;
3) the creation of educational tools for health professionals.

1. Changes to the SPC

The special warnings and precautions for use (section 4.4), undesirable effects and contraindications (sections 4.8 and 4.3) concerning cardiovascular effects, cerebrovascular disorders, psychiatric disorders, the occurrence of tics, effects on growth, convulsions and the risk of abuse and misuse have been updated and consolidated.

The amendments to the SPC also include the addition of restrictions for the initiation and monitoring of methylphenidate treatment (section 4.2):
"Treatment must be initiated under the supervision of a specialist in childhood and/or adolescent behavioural disorders.
Pre-treatment screening
Prior to prescribing, it is necessary to conduct a baseline evaluation of a patient's cardiovascular status including blood pressure and heart rate. A comprehensive history should document concomitant medications, past and present comorbid medical and psychiatric disorders or symptoms, family history of sudden cardiac/unexplained death; in addition, the patient's pre-treatment height and weight should be recorded accurately and noted on a growth chart […].

[6] EMA. Methylphenidate - Article 31 referral - Annex I, II, III, IV. www.emea.europa.eu

Ongoing monitoring

Growth, psychiatric and cardiovascular status should be continuously monitored […].

- Blood pressure and pulse should be recorded on a percentile curve at each adjustment of dose and then at least every 6 months;
- Height, weight and appetite should be recorded at least 6 monthly and noted on a growth chart;
- Development of *de novo* or worsening of pre-existing psychiatric disorders should be monitored at every adjustment of dose and then at least every 6 months and at every visit.

Patients should be monitored for the risk of diversion, misuse and abuse of methylphenidate. […]

Long-term use (more than 12 months) in children and adolescents

The safety and efficacy of long-term use of methylphenidate have not been systematically evaluated in controlled trials. Methylphenidate treatment should not and need not be indefinite. Methylphenidate treatment is usually discontinued during or after puberty. The physician who elects to use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. It is recommended that methylphenidate is dechallenged at least once yearly to assess the child's condition (preferably during school holidays). Improvement may be sustained when the drug is either temporarily or permanently discontinued."

2. Studies conducted as part of the European risk management plan

A status report on studies conducted as part of the European risk management plan is given in Table 2.

Table 2: Status report on studies conducted as part of the European risk management plan

Issue	Status Report (Summer 2012)
Cardiovascular and cerebrovascular effects	In April 2012, the pharmaceutical companies sent the EMA an analysis of the FDA/AHRQ/Vanderbilt University study published in 2011 in the NEJM[7]. This is a retrospective study conducted in the USA from four medical databases. The objective was to compare the incidence of serious cardiovascular events (cardiac arrest and myocardial ischemia) in patients currently or previously treated with psychostimulants versus a population that had never received psychostimulant treatment. In total, 1 200 438 children and young adults aged 2 to 24 years were included, corresponding to 2 579 104 person-years. The patients currently and previously treated with psychostimulants totalled 373 667 and 607 475 person-years respectively. The incidence of cardiovascular events was evaluated over a mean follow-up period of 2.1 years. In total, 81 serious cardiovascular events were listed (3.1 events per 100 000 person-years). The analysis did not demonstrate any increased risk of serious cardiovascular events in the population treated with psychostimulants (currently or previously) in comparison with the population never treated with psychostimulants (currently treated versus never treated population: hazard ratio [HR] 0.75; 95% CI 0.31 to 1.85; previously treated versus never treated population: HR 1.03; 95% CI 0.57 to 1.89). Similarly, no increased risk of cardiovascular events was demonstrated in the population currently treated with methylphenidate versus the population never treated (HR: 0.96; 95% CI 0.31 to 2.97). *The authors conclude that this study does not demonstrate any increased risk of serious cardiovascular events in patients currently receiving psychostimulant treatment, although the upper limit of the 95% confidence interval indicates that a doubling of the risk cannot be ruled out.* The EMA's analysis of these results is in progress.
Carcinogenicity	The pharmaceutical companies have submitted the results of two cytogenetic studies to the EMA. On the basis of these results, the MHRA has recommended that the carcinogenic risk is still mentioned as a potential risk in the risk management plan and is monitored in the context of pharmacovigilance.
Growth, development and sexual maturation	Study of growth and development: in progress. Study of sexual maturation: in progress.
Risk of suicide	A meta-analysis evaluating the risk of suicide associated with methylphenidate use was submitted to the EMA in December 2011. Analysis of the results is in progress.
Effects of long-term use, specifically cognitive and psychiatric effects	To date, no study has been conducted.
Drug utilisation studies, including evaluation of off-label use and abuse	The pharmaceutical companies submit usage data from the IMS Disease Analyser database to the EMA annually (see Usage Data).

[7] Cooper WO et al. ADHD drugs and serious cardiovascular events in children and young adults. NEJM (2011). doi:10.1056/NEJMoa1110212

III.III. Measures implemented by ANSM

ANSM implemented a national pharmacovigilance and addiction monitoring programme in 2006.

In 2011, the National Narcotics Committee and the National Pharmacovigilance Committee declared themselves in favour of the following actions:[8,9]

- National monitoring of methylphenidate to continue, with a new point at one year.
- Pharmaceutical companies to disseminate information approved by ANSM to families and health professionals (prescribers and pharmacists) in order to reiterate the conditions of methylphenidate prescription, dispensing and use, as well as its adverse effects and the recommendations for monitoring these adverse effects.
- ANSM to study the means available in France of strengthening compliance with the prescription and dispensing conditions (e.g. Council of the National Chamber of Pharmacists, National Medical Association, learned societies, regional health authorities, etc.).
- The need to involve the Health Insurance Fund, so that the inappropriate use of methylphenidate can be monitored.
- A request that pharmaceutical companies provide pharmacological data as part of national monitoring, particularly on the affinity of methylphenidate for certain receptors and especially the 5-HT_{2B} receptor, because of the potential cardiovascular risk.
- Ongoing support of the European request for a study evaluating the long-term effects of methylphenidate, to supplement the studies already conducted as part of the European risk management plan.

[8] Report of the meeting of the National Committee of Narcotics and Psychotropic Drugs of 16 June 2011. www.ansm.sante.fr

[9] Report of the meeting of the National Pharmacovigilance Committee of 22 November 2011. www.ansm.sante.fr

IV. ABUSE AND DEPENDENCE

In 2011, a status report on cases of methylphenidate abuse, dependence or misuse was presented to the National Narcotics and Psychotropic Drugs Committee.[8]
The main sources of this status report were:
- clinical data collected by the drug dependence evaluation and information centres (CEIPs);
- the results of a study conducted in 2011 in the PACA-CORSE region;
- ANSM analysis of data from the broad sample of National Health Insurance beneficiaries (EGB).

The National Narcotics and Psychotropic Drugs Committee (CNSP) concluded as follows:
"The three conducted investigations show:
- an increase in the number of cases of inappropriate use between 2000-2006 and 2006-2011 (21 vs. 83), an increase in the doses used and high levels of use in the PACA Corse region;
- this inappropriate use involves an increasingly younger population, in particular students hoping for good academic performance. Methylphenidate is also misused as a weight-loss aid;
- all the proprietary medicinal products (but especially the immediate-release form) are involved and the route of administration is often inappropriate ("snorting" and injection 20%);
- violent behaviour during the "comedown" and burnout syndrome are highlighted by specialist drug addiction treatment services;
- many doctors prescribe methylphenidate off-label;
- there are suggestions, particularly on the internet, that cocaine is being substituted with methylphenidate."

Following this status report, the CNSP made the following recommendations:
"Given the significant risk of abuse and dependence, and of inappropriate prescription and inappropriate dispensing, the CNSP recommends that information be disseminated on the prescription and dispensing of methylphenidate-based medicines.
Health professionals should also be informed of this inappropriate use: AFSSAPS should contact the National Health Insurance Fund and the National Council of the Medical Association, who should then pass on this information at regional level. Communication should also be initiated with the regional health authorities.
The CNSP wishes the Advertising Committee to be made aware of the risks associated with methylphenidate, with particular attention paid to messages intended for health professionals and the general public."

V. CONCLUSION

The NICE review of studies comparing methylphenidate to placebo indicates that methylphenidate is effective on the symptoms of ADHD in school-age children. The duration of follow-up in these studies is generally very short (3 weeks to 3 months).
Few studies have compared the efficacy of methylphenidate to psychosocial interventions or to a combination of both treatments. At present, the American MTA study remains the benchmark study in this field. At 14 months, the MTA study showed that methylphenidate, whether combined with behavioural therapy or not, had superior efficacy to standard community care and to behavioural therapy alone, in terms of ADHD symptoms. Treatment combining methylphenidate and behavioural therapy was superior to standard community care and to behavioural therapy alone on several endpoints (oppositional/aggressive symptoms, anxiety and depression, teacher-rated social skills, parent-child relations and reading achievement).

After several years of marketing (methylphenidate has been available in the USA since 1955), methylphenidate's short-term safety profile is well known. The most common adverse effects of methylphenidate include nervousness, insomnia and headaches, decreased appetite, gastrointestinal disorders (abdominal pain, nausea, vomiting, dry mouth) and cardiovascular disorders (changes in blood pressure, palpitations, arrhythmia, tachycardia). Skin disorders such as alopecia, pruritus, rash and urticaria may also occur. More rarely, methylphenidate administration may be associated with the onset or worsening of psychotic of manic symptoms.
Despite these years of use, concerns persist about the long-term consequences of methylphenidate treatment, particularly in terms of cardiovascular, neurological and psychiatric events. The risk of inappropriate use is also a concern.
The EMA has re-evaluated the safety profile of methylphenidate-based proprietary medicinal products and concluded in January 2009 that the risk/benefit ratio of methylphenidate-based medicines in the treatment of ADHD in children aged six years and over remains favourable. However, the information on methylphenidate safety in SPCs and package leaflets was consolidated and harmonised and a list of conditions for the maintenance of Marketing Authorisation was drawn up, including requests for studies of the risks of methylphenidate.
In France, several initiatives aiming to limit the risks associated with methylphenidate use are currently in progress at ANSM (information for families and prescribers, requests for further studies, etc.).

Therapeutic use of methylphenidate in ADHD in school-age children[1,10,11]

Methylphenidate is indicated "as part of the comprehensive management of ADHD in children aged 6 years and over when remedial measures alone prove insufficient".
The prescription of methylphenidate is aimed at school-age children for whom psychological, educational and family interventions alone prove insufficient, in cases where the chronicity and severity of symptoms justify drug treatment. Treatment should be initiated by a specialist in childhood behavioural disorders.
A well-supported diagnosis is essential before starting drug treatment. 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. Adequate diagnosis requires the use of medical, psychological, educational and social resources.
Treatment should form part of an overall management strategy that includes psychological, educational and social interventions for the child and his or her family circle.

It is strongly recommended that patients are followed up through hospital consultations with the initial prescriber for the first two months, in order to monitor the efficacy of treatment and check the dosage.
Once treatment has been started, growth, mental health and cardiovascular health must be monitored regularly (see detailed methods in the products' SPC).
Patients should also be monitored for the risk of inappropriate use, misuse and abuse of methylphenidate.

The efficacy and safety data for long-term methylphenidate use are limited. Methylphenidate treatment should not and need not be indefinite. Treatment is usually discontinued during or after puberty. Physicians who use methylphenidate for extended periods (over 12 months) in children and adolescents with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trial periods off medication to assess the patient's functioning without pharmacotherapy. Methylphenidate should be dechallenged at least once yearly to assess the child's condition (preferably during school holidays).

[10] SPC of methylphenidate-based proprietary medicinal products. www.ansm.sante.fr

[11] Bailly D. et Mouren M-C. Les prescriptions médicamenteuses en psychiatrie de l'enfant et de l'adolescent. Ouvrage collectif. Congrès de psychiatrie et de neurologie de langue française. Ed. MASSON. 2007.

USAGE DATA

I. DATA FROM THE BROAD SAMPLE OF HEALTH INSURANCE BENEFICIARIES (EGB)

I.I. Number of people refundable for methylphenidate in 2011

Using the EGB data extrapolated to the French population,[12] the number of people who were refundable for methylphenidate at least once in 2011 is estimated to be **41 557 (95% CI: [37 880; 45 734])**.
The distribution by medicinal product is as follows:

Proprietary medicinal product	n	extrapolated n	95% CI lower limit	95% CI upper limit
RITALINE IR	139	15 201	12 674	17 728
RITALINE LP	180	19 685	16 810	22 560
CONCERTA LP	147	16 076	13 478	18 675
QUASYM LP	55	6 015	4 425	7 604
Total number*	380	41 557	37 380	45 734

* The same individual may have been refundable for several methylphenidate-based proprietary medicinal products in 2011.

The distribution by age is as follows:

Age (years)	n	%	cumulative n	cumulative %
< 6	4	1.05	4	1.05
[6-10]	75	19.74	79	20.79
[10-15]	182	47.89	261	68.68
[15-20]	65	17.11	326	85.79
>=20	54	14.21	380	100.00

I.II. ANSM analysis of patient characteristics between 2006 and 2009

Detailed results of this analysis are provided in the National Narcotics and Psychotropic Drugs Committee's report of 16 June 2011.[8]

1. Objective and methods

ANSM studied the characteristics of patients newly treated with methylphenidate from the EGB data.[12]
Patients starting methylphenidate treatment between October 2006 and October 2009 were selected and their treatment pathway was reconstructed (reimbursements for medication, medical consultations, hospitalisations).
A total of 250 patients were included.

2. Results

One hundred and forty-eight patients (59.2%) were refundable for methylphenidate at least five times during period studied.

[12] The EGB is a representative sample of French people covered by national insurance. It contains anonymous information about the demographic characteristics of those persons, the benefits paid and chronic (long-term) conditions since 2003. The extrapolation of EGB data to the French population was done by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01.01.2011 (n = 594 370) in relation to the French population on 01.01.2011 (n = 65 001 181). The extrapolation coefficient obtained is 1/109.36.

Of these, 137 (92.7%) stopped treatment (no reimbursements for methylphenidate in the first 6 months of 2011).
The median patient age was 9 years and patients were primarily boys (76%). “Doctor shopping” occurred in 7.4% of patients and “pharmacy hopping” in 2% of patients. The median number of medical consultations was 11, with a mean treatment duration of 25 months. In 80% of cases, methylphenidate was prescribed by doctors practising in a healthcare institutions (medical specialism not specified).
Prescriptions associated with methylphenidate prescriptions were primarily drugs for benign ENT conditions. According to the ANSM analysis, two groups of patients, corresponding in total to 7.5% of the patients, were identified as having potentially deviant behaviour in terms of methylphenidate use:

- The first group (6.1%) was made up of patients with a mean age of 18 years, primarily men, with “pharmacy shopping” in 11% of cases and a moderate dispensing interval (40 days), using methylphenidate at high daily doses (greater than 60 mg).
- The second group (1.4%) comprised one 6 years aged child and one 59 years old man using very high doses (227 mg) with a very short period of time between prescriptions (25 days), with no “doctor shopping” or “pharmacy shopping” and using only the modified-release form.

II. DATA FROM THE IMS DATABASE

Since 2009, in the context of the actions required for the maintenance of Marketing Authorisation, the pharmaceutical companies marketing methylphenidate-based medicines send every year to European health authorities an analysis of methylphenidate use in Europe from the IMS databases.
The results given here are for 2010.

1. European data

In 2010, it was estimated that more than 5 million methylphenidate prescriptions were issued in the 21 countries included in the analysis. The majority of prescriptions (78%) were for patients aged 6 to 18 years. The most common diagnosis associated with these prescriptions was the ICD-10 diagnosis “hyperkinetic disorders” (F90) (74%). The mean daily dose ranged from 23.92 mg/day to 36.65 mg/day depending on the analysed county. The weighted mean was 29.30 mg/day.

2. French data

French data were collected from a sample of 435 general practitioners and specialists in private practice from the IMS Disease Analyser database.
For the year 2010 in France, only 58 prescriptions including methylphenidate could be analysed. The restrictions on the distribution of the product, and particularly the requirement for the initial prescription to be issued by a hospital specialist, probably explain the low number of prescriptions in community medicine.
Because of these restrictions on methylphenidate prescribing, and because only private practice physicians are included in the IMS sample group, a pertinent analysis of methylphenidate use in France is not possible.

TRANSPARENCY COMMITTEE CONCLUSIONS

I. RE-ASSESSMENT OF ACTUAL BENEFIT

Attention-deficit hyperactivity disorder (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's syndrome. ADHD may lead to substantial impairment of interpersonal relationships and integration at school.

These proprietary medicinal products fall within the category of symptomatic treatment.

The efficacy/adverse effects 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 medicinal products.

Public health benefit

In view of its prevalence, estimated to be 2% in the case of school-age children,[13] 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 disorders, 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 implemented).

When drug treatment is recommended, methylphenidate-based medicinal products help to meet identified need for public health.

In view of the available data these medicinal products can be considered to have a low impact in terms of morbidity, quality of life and socio-educative effect in the patients treated.

Moreover, it is not certain whether data from 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 medicinal products have a public health benefit in this indication.The benefit is slight.

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

The Transparency Committee considers that:
The actual benefit of methylphenidate-based proprietary medicinal products (RITALINE, RITALINE LP, CONCERTA LP, QUASYM LP) remains 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 Marketing Authorisation and should be restricted to ADHD, excluding 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 adverse effects of methylphenidate and is still concerned about its long-term effects, linked to its amphetamine-like structure.

II. TRANSPARENCY COMMITTEE RECOMMENDATIONS

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

As a result of these conclusions, the Transparency Committee recommends that educational tools for methylphenidate are put into place for patients, families and healthcare professionals.

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

- RITALINE 10 mg tablets: one box contains 30 tablets in three blisters. The batch number and the expiry date for the box are only printed on one end of each blister, which presents problems when the pharmacist has to remove the packaging.
- RITALINE LP 20 mg, 30 mg, 40 mg capsules and CONCERTA LP 18 mg, 36 mg, 54 mg tablets: the tablets/capsules are packaged 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.

Reimbursement rate: 65%

APPENDICES

APPENDIX 1. RESULTS OF META-ANALYSIS OF STUDIES COMPARING METHYLPHENIDATE TO PLACEBO OR TO NO PSYCHOSTIMULANT TREATMENT IN SCHOOL-AGE CHILDREN (NICE, 2009)

	Methylphenidate versus placebo		**Methylphenidate versus wait-list**
	Mixed comorbidity	**Specific comorbidity (developmental reading disorder)**	**Mixed comorbidity**
Total no. of trials (total no. of participants)	12 (1582)	1 (58)	1 (20)
Study ID	BUTTER1983 CONNERS1980 FINDLING2006 GITTELMANKLEIN1976A GREENHILL2002 GREENHILL2006 IALONGO1994 KOLLINS2006 KURLAN2002 LERER1977 PLISZKA2000 WILENS2006	KUPIETZ1988	BROWN1985
Diagnosis	ADD with hyperkinesis, ADHD, hyperkinetic disorder, hyperkinetic reaction of childhood, MBD (common coexisting conditions: oppositional defiant disorder and/or conduct disorder)	ADD with hyperactivity and developmental reading disorder	ADHD symptoms
Baseline severity (mean range)	CRS range: 35.48 to 42.05	CPRS: 20.55 (4.69)	CTRS (Abbrev): 18.55 (4.30)
Dose	Low: ≤0.4 mg/kg/day Medium: > 0.4 < 0.8 mg/kg/day High: ≤0.8 mg/kg/day	Low: 0.3 mg/kg Medium: 0.5 mg/kg High: 0.7 mg/kg	0.3 mg/kg/day
Treatment length (mean range)	7–112 days	196 days	84 days

	Methylphenidate versus placebo		**Methylphenidate versus wait-list**
	Mixed comorbidity	**Specific comorbidity (developmental reading disorder)**	**Mixed comorbidity**
Benefits			
ADHD core symptoms (mean at endpoint) (teacher-rated)	Various measures: Low dose: SMD -0.40 (-0.95 to 0.15) Quality: High K: 2, N: 78 High dose: SMD -0.84 (-1.06 to -0.62) Quality: High K: 5, N: 806	CTRS (hyperactivity): Low dose: SMD -1.61 (-2.69 to -0.53) Quality: High K: 1, N: 58 Medium dose: SMD -1.35 (-2.29 to -0.40) Quality: High K: 1, N: 58 High dose: SMD -2.37 (-3.54 to -1.20) Quality: High K: 1, N: 58	CTRS: SMD -111 (-2.07 to -0.15) Quality: High K: 1, N: 20
ADHD core symptoms (mean change) (teacher-rated)	CATQ: Medium dose: SMD -1.69 (-2.24 to -1.14) Quality: High K: 1, N: 136	–	–
ADHD core symptoms (mean at endpoint) (parent-rated)	CPRS: Low dose: SMD 0.66 (-0.06 to 1.37) Quality: high K: 1, N: 48 High dose: SMD -0.79 (-1.14 to -0.45) Quality: High K: 4, N: 747	–	CPRS: SMD -1.29 (-2.27 to -0.3) Quality: Moderate K: 1, N: 20
ADHD core symptoms (mean change) (parent-rated)	Various measures: Medium dose: SMD -1.34 (-3.26 to 0.58) Quality: High K: 2, N: 186	–	–
ADHD core symptoms (mean at endpoint) (investigator-rated)	–	–	–
ADHD core symptoms (mean at endpoint) (self-report)	–	–	–
Conduct problems (mean at endpoint) (teacher-rated)	Various measures: Low dose: SMD -0.43 (-1.13 to 0.27) Quality: Moderate K: 1, N: 48 High dose: SMD -0.58 (-0.84 to -0.31) Quality: High K: 4, N: 485	–	–
	Methylphenidate versus placebo		**Methylphenidate versus wait-list**

	Mixed comorbidity	**Specific comorbidity (developmental reading disorder)**	**Mixed comorbidity**
Conduct problems (mean change) (teacher-rated)	IOWA (oppositional/defiant): Medium dose: SMD -1.21 (-1.72 to -0.71) Quality: High K: 1, N: 136	–	–
Conduct problems (mean at endpoint) (parent-rated)	Various measures: High dose: SMD -0.73 (-1.06 to -0.41) Quality: High K: 2, N: 378	–	–
Clinical improvement (clinician-rated)	Various measures: Medium dose: RR 3.08 (1.40 to 6.78) Quality: High K: 2, N: 186 High dose: RR 1.81 (1.46 to 2.24) Quality: High K: 5, N: 823	–	–
Clinical improvement (parent and teacher)	–	–	–
Adverse Effects			
Insomnia	High dose: NNTH 12 (7 to 33) Quality: High K: 3, N: 318	–	–
Anorexia	High dose: NNTH 16 (11 to 50) Quality: High K: 4, N: 634	–	–
Increased crying	High dose: NNTH 3 (NNTH 1 to ∞ to NNTB 50) Quality: Moderate K: 1, N: 1	–	–
Increased irritability	High dose: NNTH 14 (NNTH 4 to ∞ to NNTB 16) Quality: Moderate K: 2, N: 119	–	–
Moodiness	High dose: NNTH 16 (NNTH 8 to ∞ to NNTB 100) Quality: High K: 2, N: 141	–	–
Thirst	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
Itching	High dose: NNTH 10 (NNTH 4 to ∞ to NNTB 20) Quality: Moderate K: 1, N: 41	–	–
Diarrhoea	High dose: NNTH 50 (NNTH 20 to ∞ to NNTB 100) Quality: High K: 3, N: 318	–	–
Palpitations	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
Stuttering	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
Negativism	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
Reddened eyes	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
	Methylphenidate versus placebo		**Methylphenidate versus wait-list**
	Mixed comorbidity	**Specific comorbidity (developmental reading disorder)**	**Mixed comorbidity**
Incoherent speech	High dose: NNTH 20 (NNTH 5 to ∞ to NNTB 13) Quality: Moderate K: 1, N: 41	–	–
7% decrease in bodyweight	High dose: NNTH 9 (5 to 50) Quality: Moderate K: 1, N: 100	–	–
Decreased appetite	High dose: NNTH 9 (5 to 50) Quality: Moderate K: 1, N: 59	–	–

Leaving study early due to adverse events	Low dose: not estimable Quality: High K: 1, N: 30 Medium dose: NNTB 100 (NNTB 25 to ∞ to NNTH 50) Quality: High K: 2, N: 186 High dose: ∞ (∞ to NNTH 33) Quality: High K: 2, N: 424	–	–
Leaving study early due to any reason	Low dose: NNTB 25 (NNTB 4 to ∞ to NNTH 6) Quality: High K: 2, N: 78 Medium dose: NNTB 8 (4 to 50) Quality: High K: 2, N: 186 High dose: NNTB 11 (6 to 25) Quality: High K: 5, N: 767	NNTB 14 (NNTH 9 to ∞ to NNTB 4) Quality: Moderate K: 1, N: 58	–

APPENDIX 2. SIGNIFICANT IDENTIFIED AND POTENTIAL RISKS MONITORED THROUGH THE EUROPEAN RISK MANAGEMENT PLAN FOR METHYLPHENIDATE-BASED PROPRIETARY MEDICINAL PRODUCTS

Important identified risks
Hypertension
Tachycardia
Raynaud's phenomenon
Psychosis/Mania
Hallucinations (auditory, skin sensation, visual disturbance)
Anorexia
Decreased rate of growth
Aggression
Depression

Important potential risks
QT prolongation
Arrhythmias
Ischaemic cardiac events
Cyanosis
Sudden death
Cerebrovascular disorders
Hostility
Suicidality
Repetitive behaviours
Migraine
Tics/Tourette's syndrome/Dystonias
Effect on final height
Sexual maturation (delayed)
Drug abuse and drug dependence
Withdrawal syndrome
Diversion
Off-label use
Carcinogenicity
Lymphocytic leukaemia
Neonatal cardiorespiratory toxicity
Neonatal effects on growth

Long-term safety (cardiovascular, cerebrovascular, and psychiatric effects) is identified as important missing information.