HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

10 March 2010

QUASYM MR 10 mg, modified-release hard capsule
Box of 30 (CIP: 377 618-4)

QUASYM MR 20 mg, modified-release hard capsule
Box of 30 (CIP: 377 620-9)

QUASYM MR 30 mg, modified-release hard capsule
Box of 30 (CIP: 377 622-1)

Applicant: SHIRE FRANCE S.A.

Methylphenidate

ATC code: N06BA04

List I
Narcotic.
Prescription limited to 28 days.
Prescription must comply with the specifications laid down in the decree of 31 March 1999.
Initial annual hospital prescription restricted to specialists and/or departments specialising in neurology, psychiatry and paediatrics and to sleep centres.

Date of Marketing Authorisation: 27 December 2006 (mutual recognition)

Reason for request: inclusion on the list of medicines reimbursed by National Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Methylphenidate.

1.2. Indication

"Methylphenidate is indicated as part of a comprehensive treatment programme for attention-deficit/hyperactivity disorder (ADHD) in children over 6 years of age 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.

Additional information on the safe use of the medicinal product

The specific aetiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical, psychological, educational and social resources.
A comprehensive treatment programme typically includes psychological, educational and social measures and is aimed at stabilising children with a behavioural syndrome characterised by symptoms which may include chronic history of 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 is not indicated in all children with this syndrome and the decision to use the medicinal product must be based on a very thorough assessment of the severity of the child's symptoms."

1.3. Dosage

"QUASYM MR consists of an immediate-release component (30% of the dose) and an extended-release component (70% of the dose). Hence, QUASYM MR 10 mg yields an immediate-release dose of 3 mg and an extended-release dose of 7 mg. The extended-release portion is designed to maintain a treatment response through the afternoon without the need for a midday dose. It is designed to deliver therapeutic plasma levels for a period of approximately 8 hours, which is consistent with the school day rather than the whole day (see section 5.2 of the SPC).
For example, 20 mg of QUASYM MR is intended to take the place of 10 mg of immediate-release methylphenidate at breakfast and at lunchtime.

Adults: not applicable.

Elderly: not applicable.

Children (over 6 years and adolescents):

Titration
Careful dose titration is necessary at the start of treatment. This is normally achieved using an immediate-release formulation of methylphenidate taken in divided doses. The recommended starting daily dose is 5 mg once daily or twice daily (e.g. at breakfast and lunch), increasing if necessary by weekly increments of 5-10 mg in the daily dose according to tolerability and degree of efficacy observed.
QUASYM MR 10 mg once daily may be used in place of immediate-release methylphenidate 5 mg twice daily from the beginning of treatment where the treating physician considers that twice daily treatment administration is impracticable.

For doses not realisable with this strength, other strengths of this medicinal product and other methylphenidate-containing products are available.

Patients currently using methylphenidate: patients stabilised on an immediate-release methylphenidate formulation may be switched to the equivalent daily dose of QUASYM MR.
If the effect of the medicinal product wears off too early in the late afternoon or evening, disturbed behaviour and/or inability to go to sleep may recur. A small dose of an immediate-release methylphenidate late in the day may help to solve this problem. In that case, it could be considered that adequate symptom control might be achieved with a twice-daily immediate-release methylphenidate regimen. Treatment should not continue with QUASYM MR if an additional late dose of immediate-release methylphenidate is required, unless it is known that the same extra dose was also required for a conventional twice-daily immediate-release regimen at equivalent breakfast/lunchtime dose. The regimen that achieves satisfactory symptom control with the lowest daily dose must be used.

The maximum daily dose of methylphenidate is 60 mg.

QUASYM MR is not indicated for children under 6 years due to a lack of data on efficacy and safety in this population.

QUASYM MR should be given in the morning before breakfast. The capsules may be swallowed whole with the aid of liquids. Alternatively, the capsule may be opened and the capsule contents sprinkled onto a tablespoon of applesauce and given immediately; the mixture must not be stored for future use. Drinking some fluid, e.g. water, should follow the intake of the sprinkles with applesauce. The capsules and the capsule contents must not be crushed or chewed.

Maintenance/extended treatment
The long-term use of methylphenidate has not been systematically evaluated in controlled clinical trials. The physician who elects to use QUASYM MR for extended periods in patients 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. Improvement may be sustained when the drug is either temporarily or permanently discontinued.
Note: If improvement of symptoms is not observed after appropriate dosage adjustment over a one-month period, the medicinal product should be discontinued. Methylphenidate should be discontinued periodically to assess the child’s condition. Medicinal product treatment is usually discontinued during or after puberty."

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)

N06BA04:

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

2.2. Medicines in the same therapeutic category

2.2.1. Strictly comparable comparator medicines

Other extended-release (MR) methylphenidate-based medicinal products with the same indication:

CONCERTA MR 18 mg, 36 mg and 54 mg, tablet
RITALINE MR 20 mg, 30 mg and 40 mg hard capsules

2.2.2. Not strictly comparable comparator medicines

Other immediate-release methylphenidate-based medicinal product:

RITALINE 10 mg, tablet.

2.3. Medicines with a similar therapeutic aim

Methylphenidate is the only medicinal product to have been awarded marketing authorisation in France for the treatment of ADHD.

3 ANALYSIS OF AVAILABLE DATA

The pharmaceutical company has submitted three main studies in support of its request:

- One randomised, double-blind study versus placebo
- One placebo-controlled randomised, double-blind non-inferiority study versus immediate-release RITALINE
- One randomised, double-blind crossover study versus CONCERTA MR.

3.1. Efficacy

Study versus placebo:
This was a randomised, double-blind study lasting three weeks which compared the efficacy of QUASYM MR with that of a placebo in 321 children aged between 6 and 16 years suffering from ADHD according to the DSM IV criterion (combined sub-type or predominantly hyperactive/impulsive sub-type).
Patients who did not respond to methylphenidate or who required a third daily dose of methylphenidate in the afternoon or evening, and those who responded to the placebo in the wash-out phase, were excluded.

The patients were given either QUASYM MR (20 mg in week one then adjusted if necessary to 40 and 60 mg) or the placebo for three weeks.

Results in respect of the primary efficacy endpoint: TCGI questionnaire[1] completed by teachers with a combined morning + afternoon assessment recorded three days a week for three weeks (ITT analysis taking the last value available into account).

The TCGI score fell in the group treated with QUASYM MR but remained unchanged in the placebo group. A statistically significant difference between the groups was observed after three weeks of treatment (p = 0.0001, see Table 1).

[1] "Teacher version of 10 items Conners' Global Index": questionnaire containing 10 items relating to child behaviour disorders. Each item is scored from 0 (never-rarely) to 3 (very often-vastly). The maximum score is 30 points.

Table 1: Change in the TCGI score (combined morning and evening assessment) after three weeks of treatment

TCGI score	**QUASYM MR N =155**	**Placebo N =159**	**p**
Baseline	**12.7 ± 7.24**	**11.5 ± 7.35**	NS
3 weeks	**4.9 ± 4.66**	**10.3 ± 6.92**	**0.0001**

Study versus immediate-release RITALINE:
This was a randomised, double-blind, placebo-controlled non-inferiority study comparing QUASYM MR to immediate-release (IR) RITALINE in 318 children aged from six to twelve with ADHD according to DSM IV criteria after three weeks of treatment.
The children had to have been stabilised by methylphenidate given at a consistent dose for at least three weeks. Children who had previously been unresponsive to methylphenidate were excluded.
The patients were given either QUASYM MR (20 mg, 40 mg or 60 mg/d) or RITALINE IR (10 mg dose) twice a day or the placebo for three weeks.

Primary efficacy endpoint results: inattention/overactivity score (I/O) on the IOWA questionnaire measured by the teacher[2] on D21 (overall morning and afternoon score). QUASYM MR was to be regarded as not inferior to RITALINE IR if the lower limit of the 97.5% confidence interval of the difference between the treatments was greater than (-1.5).

285 of the 318 patients treated completed the study. The reasons for discontinuing the study were: worsening of ADHD, an adverse effect, protocol violation, withdrawal of consent by the patient or his/her legal representative, investigator's decision, contact with the patient lost.
The analysis was carried out on the per-protocol (PP) population defined as patients who received the treatment and had at least one measurement of efficacy after the first dose and without a major deviation from the protocol. The PP population comprised 279 patients, 120 of whom received QUASYM, 120 RITALINE IR and 39 placebo.

On D21 the I/O score had improved in the QUASYM MR groups but not in the placebo group. QUASYM MR was shown to be not inferior to RITALINE IR (see Table 2): the lower limit of the 97.5% CI of the difference between treatments of (-1.06) was greater than the predetermined non-inferiority threshold (-1.5). QUASYM MR was not inferior to RITALINE IR at the other measurement points, D7 and D14. This result was confirmed when the ITT population was taken into account.

Table 2: Inattention/overactivity (I/O) score of the IOWA questionnaire measured by teachers on D21 (PP population)

I/O score	**QUASYM MR** N =120	**RITALINE IR** N =120	**Placebo** N =39
Baseline (mean, SD)	**5.8 ± 3.59**	**6.1 ± 3.74**	**6,0 ± 3.64**
D21 (mean, SD)	**4.5 ± 0.29**	**4. 3 ± 0.29**	**7.7 ± 0.50**
Lower limit of the 97.5% CI of the difference between QUASYM MR and RITALINE IR	**-1.06**		**-**

[2] "Overall teacher's inattention/overactivity with aggression Conners ratings scale": questionnaire comprising 10 items split into two categories, I/O (inattention/overactivity) and O/D (opposition/defiance). Each item is graded on a scale of 0 (not at all) to 3 (considerably). This is an assessment scale validated for forms of ADHD that can be assessed.

Secondary endpoint results:
QUASYM MR was also non-inferior to RITALINE IR in respect of the opposition/defiance (O/D) category of the IOWA questionnaire completed by teachers at all visits.
When parents completed the version of the IOWA questionnaire for parents, QUASYM MR was non-inferior to RITALINE IR on the O/D score at D14 and on the I/O score at D7 and D14.

Study versus CONCERTA MR:
Randomised, double-blind crossover study comparing QUASYM MR with CONCERTA MR and placebo in 184 children aged six to twelve with ADHD according to DSM IV criteria, of the "inattentive", "hyperactive-impulsive" or "combined" sub-type.
The patients had to have been responsive to methylphenidate at a stable dose of 10 to 60 mg/day, in one to three doses, for at least two weeks.
They were given successive weekly courses of QUASYM MR (20 mg, 40 mg or 60 mg/day), CONCERTA MR (18 mg, 36 mg or 54 mg/day) and placebo, with no wash-out period between regimens.
Primary efficacy endpoint: average score of the « behaviour » element on the SKAMP questionnaire[3] assessed by teachers for the first five 1.5-hour sessions after administration of the treatment (periods H0 – H1.5; H1.5 – H3; H3 – H 4.5; H4.5 – H6 and H6 – H7.5). The clinical significance threshold was set at a difference of at least 0.225. The analysis was carried out on the ITT population.
Results:
157 of the 184 patients randomised took the three treatments and participated in all the sessions.

A total of 13 patients withdrew from the study prematurely: five because of withdrawal of consent, three due to a (non-serious) adverse event, one because of an exclusion criterion, one for protocol violation, one for an administrative reason and two for other reasons. No premature withdrawal from the study occurred in the QUASYM MR group.

The SKAMP behaviour score improved more markedly in the QUASYM MR group than in the CONCERTA MR group (statistically significant difference) in respect of the average of the first five 1.5-hour sessions of the day (see Table 3). QUASYM MR was not different from CONCERTA MR at H 7.5 after administration [6.7 versus 7.0, with QUASYM MR still superior to placebo (11.1)], while CONCERTA MR was superior to QUASYM at H 12 after administration. QUASYM MR was not different from placebo at H 12 after administration.

Table 3: SKAMP score – behaviour

SKAMP- behaviour (mean)	**QUASYM MR**	**CONCERTA MR**	**Placebo**	**QUASYM MR vs. CONCERTA MR p**
0 hour after administration	N = 174	N = 174	N = 176	-
	8.4 ± 8.4	8.1 ± 7.9	6.6 ± 6.8	
Average of the first five 1.5-hour sessions of the day	N = 174	N = 175	N = 177	<0.0001
	5.0 ± 5.4	6.7 ± 7.0	10.8 ± 8.2	
H 7.5 after administration	N = 173	N = 174	N = 177	NS
	6.7 ± 7.3	7.0 ± 8.0	11.1 ± 9.2	
H 12 after administration	N = 171	N = 172	N = 175	0.0012
	9.0 ± 8.6*	7.3 ± 8.2	9.6 ± 8.8	

[3] The SKAMP (Swanson, Kopthkin, Atkins, M/Flynn, Pelham) questionnaire comprises a six-item "behaviour" element and a seven-item "attention" element. The responses are scored on a scale of 0 (none) to 3 (considerably).

* : NS versus placebo

3.2. Adverse effects

3.2.1. Adverse effects mentioned in the SPC:

The adverse effects most commonly encountered with methylphenidate (≥ 1/10) are nervousness and insomnia, especially at the start of treatment. These effects are usually controlled by reducing the dosage.
The other common adverse effects (≥ 1/100, < 1/10) are:

- loss of appetite, which is generally transitory,
- cardiac disorders (arrhythmia, palpitations, tachycardia),
- gastrointestinal disorders such as abdominal pain, nausea and vomiting, which occur at the start of treatment and can be attenuated by concomitant food intake, dry mouth,
- disorders of the nervous system (vertigo, somnolence, dyskinesia, headache and hyperactivity),
- skin and subcutaneous tissue disorders (alopecia, pruritus, rash and urticaria),
- changes in blood pressure and heart rate (usually an increase).

3.2.2. Clinical studies

Clinical studies have found the safety profile of QUASYM MR to be similar to that of RITALINE IR with the exception of headaches and anorexia which were more common in patients treated with QUASYM MR (18% vs. 13.5% for headaches and 6.5% vs. 3% for anorexia).

In the study comparing QUASYM MR to CONCERTA MR, the safety profile was similar in both groups except for loss of appetite and headache, which were slightly more common in patients treated with CONCERTA MR (3.3% vs. 1.7% for loss of appetite and 2.9% vs. 1.7% for headache).
Differences were observed in systolic blood pressure, which did not increase in the QUASYM MR group (-0.6 mmHg) compared to placebo (+0.9 mmHg) but did increase in the CONCERTA MR group versus placebo (+5.2 mmHg).

3.2.3. Observational studies

In an observational study carried out in the USA among 308 children aged between six and seventeen who had ADHD and had either never been treated with methylphenidate or were already stabilised on methylphenidate, the main adverse effects after three weeks of treatment with QUASYM MR were headache (6%), abdominal pain (5%) and decline or loss of appetite (3%).

In a second observational study carried out in Germany, 852 children aged between six and seventeen with ADHD, in whom symptoms were "usually present", and who had either never been treated with methylphenidate or were already stabilised on methylphenidate were monitored for six to twelve weeks while undergoing treatment with QUASYM MR. The most common adverse events were psychiatric disorders: 125 events (mainly tics, aggressivity, depressive mood, difficulty getting to sleep), 118 of which were treatment-related.
Three cases of cardiovascular disorders were reported: tachycardia, moderate palpitations and one case of severe arrhythmia, though it was not possible to determine whether or not this case was treatment-related. Severe adverse events were reported, including psychiatric disorders (26 adverse events such as tics, affective disorders, aggressivity, anger, bipolar disorder, encopresis, difficulty in controlling impulsivity, onychophagia, sleep disorder, exaggerated tendency to crying, apathy, moroseness and anxiety), nervous system disorders (5) (headache, poor quality of sleep, somnolence), gastrointestinal disorders (6) and metabolic and nutritional disorders (3).

3.2.4. CHMP assessment

In 2007 the European Commission asked the EMEA to conduct an assessment of the risk/benefit ratio for medicinal products containing methylphenidate under article 31 of Directive 2001/83/EC in view of the possible cardiovascular and cerebrovascular risks associated with the use of methylphenidate.

In January 2009 the CHMP concluded that the risk/benefit ratio for products containing methylphenidate to treat ADHD in children over six was still favourable. In the light of the conclusions of this assessment, the CHMP suggested harmonising the SPC texts to include monitoring before and after treatment, an update of the sections covering contraindications and warnings, harmonisation of information on adverse effects, checking the dosages and uses, and updating information on use by pregnant and breastfeeding women.

In particular, the CHMP made the following comments on the French SPC dated 7 August 2008:

- analysis of data from clinical trials with methylphenidate among children and adolescents shows fluctuations of more than 10 mmHg in diastolic and systolic blood pressure. The short-term and long-term consequences of these cardiovascular effects are not known, but complications cannot be ruled out, especially for patients with pre-existing cardiac disease.
- cases of cerebral vasculitis appear to be a very rare idiosyncratic reaction.
- psychiatric disorders of the manic type (manias, COD) can develop or worsen at methylphenidate doses normally used to treat children and can lead to the treatment being discontinued.

Finally, the CHMP points out that the long-term effects of methylphenidate treatment on child growth and development are little understood. A small number of studies indicate that long-term use of methylphenidate (21 and 36 months) has no clinically significant impact on child growth.

Consequently, the CHMP recommends:

- that methylphenidate should be contraindicated for patients suffering from underlying cardiopathy or cerebrovascular disease of the cerebral hemiplegic paralysis type
- that methylphenidate should be contraindicated for patients with anorexia of mental origin
- that the cardiovascular history of patients and their families should be investigated and that a cardiovascular examination should be carried out before starting methylphenidate treatment if any heart condition is suspected
- that a neurological examination should be carried out prior to starting methylphenidate treatment to detect any cerebrovascular pathology
- that the patient's blood pressure, heart rate and psychiatric condition should be checked every six months and whenever the dose is adjusted
- that the child's height and weight should be checked every six months
- that methylphenidate treatment should be interrupted once a year.

Following these recommendations, the pharmaceutical company has submitted a request for amendment of the QUASYM MR SPC in line with the CHMP recommendations.

3.3. Conclusion

The efficacy of QUASYM MR (20 mg, 40 mg or 60 mg/day) has been assessed versus placebo in a randomised double-blind study conducted over three weeks among 321 children aged between six and sixteen with ADHD according to the DSM IV criterion (combined sub-type or predominantly hyperactive/impulsive sub-type). The TCGI score fell in the group being treated with QUASYM MR but remained unchanged in the placebo group, and the difference observed between the groups (5.4 points) was statistically significant ($p = 0.0001$).

The efficacy of QUASYM MR was also assessed against active comparators: immediate release (IR) RITALINE and CONCERTA MR in two randomised double-blind studies.

The study versus RITALINE IR (10 mg/day) included 318 children aged six to twelve with ADHD according to the DSM IV criterion. After three weeks treatment QUASYM MR was not inferior to RITALINE IR in terms of reduction of the overall "inattention/overactivity" score on the IOWA questionnaire measured by the teacher in the morning and in the afternoon.
QUASYM MR was not compared to RITALINE MR as the latter medicinal product was not yet available at the time.

The study versus CONCERTA MR (18 mg, 36 mg or 54 mg/day) was a crossover study conducted on 184 children aged six to twelve with ADHD according to the DSM IV criteria, of the "inattentive", "hyperactive-impulsive" or "combined" sub-type. The children were given successive one-week courses of QUASYM MR, CONCERTA MR or placebo, with no wash-out between the three periods.
The SKAMP-behaviour score improved significantly more with QUASYM MR than with CONCERTA MR as measured by the average of the first five 1.5-hour sessions after administration of the treatment (5.0 versus 6.7 points with CONCERTA MR, $p<0.0001$; placebo: 10.8 points) but not at H7.5 after administration, while at H12 after administration CONCERTA MR (7.3 points) was found to be superior to QUASYM MR (9.0 points, $p = 0.0012$). QUASYM MR was not different from placebo at H 12 after administration (9.6 points).

The safety profile of QUASYM MR is similar to those of RITALINE IR and CONCERTA MR. Following a review of the risk/benefit ratio of methylphenidate by the CHMP (January 2009), the SPC needs to be harmonised with those of other methylphenidate-based medicinal products in order to:
- point out the risks of fluctuations in diastolic and systolic blood pressure in excess of 10 mmHg, of cerebral vasculitis, of the development or worsening of psychiatric disorders of the manic type (manias, COD) which can occur at a methylphenidate dose normally used to treat children;
- introduce contraindications and recommendations related to these risks.

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Attention deficit and hyperactivity disorder (ADHD) leads to significant impairment in the patient's emotional life and school performance.

These medicines are intended for use as part of symptomatic therapy.

Public health benefit:

As the prevalence of this condition is estimated at 2% for children of school age,[4] and given the impact it can have on family life, education and social life, the public health burden caused by attention deficit and hyperactivity disorder can be regarded as moderate.

[4] Troubles mentaux : *Dépistage et prévention chez l'enfant et l'adolescent*. INSERM expert group review. Les Editions INSERM 2002

Improving the management of children suffering from this disorder, which is commonly associated with other co-morbidities (language disorders, psychiatric disorders, sleep disorders, etc.) is a public health need that is part of established priorities (Public Health Act 2004, Psychiatry and Mental Health Plan).

The response to this need must not be limited to a medication-based approach (psychological, educational and familial measures also need to be adopted), but where drug treatment is recommended, QUASYM MR should, like other methylphenidate-based medicines, help to meet the identified public health need.
In view of the clinical data available and the findings of studies versus active comparators, QUASYM MR is not expected to have any additional impact on the morbidity or quality of life of patients undergoing treatment.

Consequently, in the light of the other treatments available (including extended-release forms), QUASYM MR is not expected to benefit public health in this indication.

The efficacy/adverse effects ratio of these medicinal products is high when psychological, educational and social measures used alone are inadequate.

Administration of an extended-release form avoids the practical difficulties associated with administering two or three tablets a day, especially in respect of the dose due to be taken at school during the lunch break. It is likely to improve compliance and prevent the child being stigmatised.

ADHD requires an overall approach to management. Methylphenidate is the reference medicinal treatment, and the only treatment currently authorised in France. It is a second-line treatment.

There are other extended-release medicinal products based on methylphenidate.

The actual benefit of QUASYM MR 10 mg, 20 mg and 30 mg is substantial.

4.2. Improvement in actual benefit (IAB)

QUASYM MR 10 mg, 20 mg and 30 mg do not offer any improvement in actual benefit (IAB V) compared to other immediate-release or extended-release methylphenidate-based medicinal products.

4.3. Therapeutic use

4.3.1. Treatment strategy

Methylphenidate is intended for prescription to children who have recently started school and for whom psychological, educational and familial measures alone prove inadequate, as soon as their symptoms become sufficiently chronic and severe to justify medication.

It is strongly recommended:
- that patients be monitored via hospital appointments with the physician who initially prescribed the treatment for the first two months so as to monitor the efficacy of the treatment and its dosage,
- that treatment be suspended at weekends and during the holidays.

Treatment must be integrated into an overall strategy for the psychotherapeutic and educational management of the patient.

Methylphenidate is the only medicinal product in France to have a validated indication for ADHD.

Two approaches are possible:
- either to introduce treatment with immediate-release methylphenidate in the form of RITALINE 10 mg in two doses per day (at breakfast and lunchtime), perhaps later replaced by an extended-release formulation (RITALINE MR or CONCERTA MR, at the minimum dose of 18 mg/day), since the dosages of immediate-release RITALINE 10 mg and RITALINE MR are directly equivalent,
- or to start straightaway with an extended-release formulation (CONCERTA MR 18 mg) taken once a day in the morning.

It is recommended that patients always be started on the lowest doses, with the dose being increased gradually over four to six weeks until no further improvement in the signs of ADHD are observed, provided that no adverse effects occur which could make continuation of the treatment unjustifiable.

4.3.2. Role of the medicinal product

QUASYM MR is a new extended-release methylphenidate-based medicinal product complementary to RITALINE MR and CONCERTA MR. These three medicinal products have different methylphenidate release kinetics: immediate release of 30% of the dose and extended release of 70% of the dose (30:70 ratio) in the case of QUASYM MR compared to a 50:50 ratio with RITALINE MR and a 22:78 ratio in the case of CONCERTA MR. The practical consequences of these differences are that their efficacy in dealing with symptoms varies according to the time of day. QUASYM MR is more effective in the early part of the day and throughout the eight-hour school day. The choice of treatment must be made on a case-by-case basis according to the child's symptoms and the family's ability to implement educational and corrective measures.

QUASYM MR is the first extended-release methylphenidate-based medication to have a 10 mg dosage. This formulation of QUASYM MR can be used in a titration phase to replace a dose of 5 mg of immediate-release RITALINE given twice a day, if twice-daily administration is impossible, or when first initiating treatment as an alternative to CONCERTA MR 18 mg.
For patients who have already been undergoing treatment and are stabilised on immediate-release RITALINE, the dose of QUASYM MR must not exceed 60 mg per day.

4.4. Target population

There is little French epidemiological data available, apart from an INSERM expert group review published in the second half of 2001.

The prevalence of ADHD varies according to the classification system used to diagnose this syndrome (DSM or ICD 10). Studies using the DSM system usually give prevalence rates for school-age children of between 5% and 10%. Conversely, those using the ICD 10 system give rates ranging from 0.4% to 4.2%.
Overall prevalence appears to decline in adolescence.
The prevalence of ADHD among school-age children (6 to 16 years of age) in the United Kingdom has been estimated by NICE at 1%.
Only a small proportion of patients with the condition (those with the most severe forms) are treated with methylphenidate.

The expert view as to the prevalence of the most severe forms of ADHD in France on the basis of epidemiological studies using the ICD 10 classification, as reflected in the INSERM expert group review, puts the figure at around 2% for school-age children.
It varies according to gender: 3% to 4% among boys and 1% among girls.

Extrapolating this data to the population of children aged six to fourteen gives a figure for children with ADHD of 135,000 to 169,000.

These figures do not take account of the fact that the symptoms gradually abate in adolescence.

4.5. Transparency Committee recommendations

The Transparency Committee recommends inclusion on the list of medicines reimbursed by National Insurance and on the list of medicines approved for use by hospitals and various public services in the indications and at the dosage in the marketing authorisation.

4.5.1. Packaging:

The packaging (box of 30 capsules) is not appropriate for the prescription conditions, which do not allow methylphenidate to be dispensed for a period of more than 28 days (narcotic).
A request for variation of the marketing authorisation for QUASYM MR, to add a 28-capsule box, is being made.

4.5.2. Reimbursement rate: 65%