HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
17 NOVEMBER 2021

The legally binding text is the original French opinion version

methylphenidate
RITALIN LP 10 mg, 20 mg, 30 mg and 40 mg prolonged-release hard capsules

New indication

Key points

Favourable opinion for reimbursement in the treatment of attention-deficit hyperactivity disorder (ADHD) in adults for whom a moderate to severe functional impairment in at least two settings (academic, and/or occupational, social including familial), is demonstrated and when the pre-existence of childhood ADHD has been clearly established, taking into consideration that pharmacological treatment is part of a comprehensive treatment programme.

What therapeutic improvement?

No clinical added value in the therapeutic strategy for ADHD in adults.

◗ Role in the care pathway?

A European expert consensus on the diagnosis and treatment of adults with ADHD has recently been updated (2019). Management must be multimodal and multidisciplinary and initially be based on non-medicinal remedial measures, including educational, familial, rehabilitative and psychotherapeutic approaches (psychoeducation, cognitive behavioural therapy (CBT), etc.). These measures may be combined with methylphenidate-based pharmacological treatment as a second-line approach when non-medicinal measures are insufficient. The presence of comorbidities must be considered in the overall management of ADHD in adults.

Role of RITALIN LP (methylphenidate) in the care pathway:

Pharmacological treatment with RITALIN LP (methylphenidate) may be initiated as second-line therapy in the treatment of ADHD in adults or continued in the event of initiation during childhood or adolescence in strict accordance with the MA criteria and when remedial psychological, educational, social and familial measures alone prove insufficient.

Pharmacological treatment is therefore integrated into the overall management strategy, coordinated between the various players involved in the treatment of ADHD, **with continuation of psychological, educational and social measures concomitantly with the pharmacological treatment**.

The principle of time-limited prescription must be systematically adopted when initiating treatment.

Treatment must be initiated in accordance with the MA:

- following complete pre-treatment screening, in view of the safety profile of methylphenidate, with thorough assessment of the patient's cardiovascular status, including measurement of blood pressure and heart rate. **In adults, the opinion of a cardiologist is necessary prior to treatment initiation to verify, in particular, the absence of any cardiovascular contraindications.** Heart rate and blood pressure should be monitored at each prescription renewal, i.e. every month,

- under the supervision of an ADHD specialist in adults,

- at the lowest possible dose, then gradually increased in weekly increments.

Regular ongoing monitoring of patients on methylphenidate is required in order to reassess the efficacy of treatment, identify any adverse effects - particularly cardiovascular and cerebrovascular - and ensure compliance with treatment and the absence of any misuse or abuse,

Beyond 12 months of treatment, the efficacy and safety data is limited, meaning that systematic reassessment of the continuation of treatment beyond this period is necessary, with methylphenidate-free periods in order to assess the patient's functioning.

It is reiterated that information documents aimed at patients and/or their families and a website for use by healthcare professionals to support the initiation and prescription of methylphenidate and patient monitoring (http://methylphenidate-guide.eu/fr/welcome.php) are available.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Attention-deficit hyperactivity disorder (ADHD) can impair numerous aspects of a patient's life and that of their families (social, familial, occupational and academic), due to its symptoms as well as its indirect consequences and associated comorbidities.
◗ The proprietary medicinal product RITALIN LP (methylphenidate) is a symptomatic medicinal product.
◗ The efficacy/adverse effects ratio is moderate in the short term and still inadequately established in the long term.
◗ The first-line treatment of ADHD in adults is based on non-medicinal remedial measures. When these prove to be insufficient, there is no medicinal alternative for the initiation of treatment in adults with ADHD; however, medicinal alternatives are available for the continuation of treatment initiated during childhood or adolescence if symptoms persist into adulthood.
◗ Methylphenidate is indicated as second-line therapy in the treatment of ADHD in adults or continued in the event of initiation during childhood or adolescence in strict accordance with the MA criteria and when remedial psychological, educational, social and familial measures alone prove insufficient, as part of a comprehensive, coordinated treatment programme.

Public health impact
Considering:

- the seriousness of the disorder and its impact on the quality of life of patients and their families,
- the partially met medical need,
- the lack of response to the identified need with
    - the absence of an additional impact on morbidity in view of a moderate efficacy demonstrated on the symptoms of ADHD in adults compared to placebo, as well as a safety profile identified in the short term and inadequately established in the long term, in a context of persistent uncertainties concerning the prescription of the treatment in the event of failure or otherwise of remedial measures,
    - a demonstrated impact on the quality of life of patients in terms of functional improvement of ADHD in adults, although with a low effect size,
    - the absence of any demonstrated impact on the organisation of care and the patient's care or life pathway despite the prescription of methylphenidate being part of a multidisciplinary and comprehensive treatment programme combined with educational, psychological and social measures.
      The prescription of methylphenidate is supervised at present in terms of prescribing and dispensing, with:
        - a narcotic status, with prescription limited to 28 days,
        - initial annual prescription reserved for specialists and/or specialised departments in neurology, psychiatry or paediatrics, in a hospital or community setting,
        - unrestricted prescription renewal,
        - funding by the French national health insurance system subject to requirement of the doctor to indicate the name of the pharmacist who will dispense the prescription, with the need to present the initial prescription or the prescription of another physician accompanied by an initial prescription issued within the past year,
- since methylphenidate continues to contribute to cover of the medical need in this condition, RITALIN LP (methylphenidate) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of RITALIN LP (methylphenidate) is substantial in the MA indication extension.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the MA indication extension and at the MA dosages.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- demonstration of a superiority versus placebo in treatment initiation situations:
  - on the change in ADHD rating scale total score (symptomatic improvement) after 9 weeks (first ranked co-primary efficacy endpoint), with a mean difference of between 5.4 points ($CI_{95\%}$ [2.9; 7.8 p<0.0001) and 7.0 points ($CI_{95\%}$ [4.6; 9.4], p<0.0001), depending on the treatment doses, although the clinical relevance threshold is uncertain,
  - on quality of life in terms of the change in SDS rating scale total score (functional improvement) after 9 weeks of treatment (second ranked co-primary efficacy endpoint), with a mean difference of between 1.87 points ($CI_{95\%}$ [1.33; 4.39], p = 0.0176) and 3.44 points ($CI_{95\%}$ [1.91; 4.97], p<0.0001), depending on the treatment doses, compared to placebo, with a modest effect size, however,
- demonstration of a superiority versus placebo for the percentage of treatment failures in a situation of continuation of treatment for 6 months versus a switch to placebo (third ranked co-primary efficacy endpoint) with a mean difference of 28.3% in favour of methylphenidate (OR=0.3; $CI_{95\%}$ [0.2; 0.4], p<0.0001).

but in view of:

- uncertainty as to whether the treatment in the study was initiated in a situation of failure of non-medicinal remedial measures,
- the inadequately established long-term safety profile, with continued uncertainties with respect to the long-term effects, particularly in terms of neuropsychiatric, cardiovascular and cerebrovascular adverse events,

the Committee deems that RITALIN LP (methylphenidate) provides no clinical added value (CAV V) in the treatment of ADHD in adults for whom a moderate to severe functional impairment in at least two settings (academic, and/or occupational, social including familial), is demonstrated and when the pre-existence of childhood ADHD has been clearly established, taking into consideration that pharmacological treatment is part of a comprehensive treatment programme.