CERIS 20 mg, film-coated tablet
B/30 (CIP code: 351 615-8)

Applicant: ROTTAPHARM
trospium chloride

List I
ATC code: G04BD09

Date of Marketing Authorisation (national procedure): 28 June 1999

National Health Insurance (35%) – hospitals

Reason for request: Re-assessment of the Improvement in Actual Benefit (IAB).
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Trospium chloride

1.2. Indication

“Symptomatic treatment of urinary incontinence and/or pollakiuria and urgency as may occur in patients with overactive bladder (e.g. idiopathic or neurologic detrusor overactivity).”

See annex

1.3. Dosage

“One film-coated tablet twice a day (corresponding to 40 mg of trospium chloride daily). The film-coated tablet should be taken whole on an empty stomach with a large glass of water before meals. In patients with severe kidney dysfunction (creatinine clearance between 10 and 30 ml/min/1.73 m²) the recommended dosage is one film-coated tablet once a day or every second day (corresponding to 20 mg of trospium chloride every day or every second day). The necessity of continuing the treatment should be reassessed at regular intervals of 3-6 months. As no corresponding data are available, the use of this product in children under the age of 12 is not recommended.”
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC classification (2010)

G Genito-urinary system and sex hormones
G04 Urologicals
G04B Other urologicals, incl. antispasmodics
G04BD Urinary antispasmodics
G04BD09 Trospium

2.2. Medicines in the same pharmaco-therapeutic category

Other anticholinergics:
- DITROPAN 5 mg, scored tablet and its generics (oxybutynin), indicated in “urinary incontinence, urgency and pollakiuria in unstable bladder conditions due to idiopathic overactive bladder or neurogenic bladder disorders (detrusor overactivity)”. The most recent available Opinion on this product is that of 18 March 2009 (Opinion on renewal of listing) in which a moderate ACB was ascribed.

- URISPAS 200 mg, film-coated tablet (flavoxate), indicated in “urinary urgency in women with or without incontinence, with detrusor instability only, excluding those with stress incontinence.” The most recent available Opinion on this product is that of 28 March 2001 (re-evaluation Opinion) in which a low ACB was ascribed.

- DETRUSITOL 1 mg and 2 mg, film-coated tablet (tolterodine), indicated in the “symptomatic treatment of urinary incontinence and/or pollakiuria and urgency as may occur in patients with overactive bladder”. This product has yet to be evaluated by the Committee. It is on the market, but is not refundable.

- VESICARE 5 mg and 10 mg, film-coated tablet (solifenacin), indicated in the “symptomatic treatment of urinary incontinence and/or pollakiuria and urgency as may occur in patients with overactive bladder”. The most recent available Opinion on this product is that of 7 October 2009 (Opinion on listing) in which a moderate ACB was ascribed.

2.3. Treatments with a similar therapeutic aim

Behavioural treatments, surgery (sacral root neuromodulation in cases refractory to drug therapy), palliative treatments (protective devices, collecting bags, etc.).
3. SUMMARY OF THE TRANSPARENCY COMMITTEE’S OPINIONS

Opinion of the Committee of 20 October 1999
Inclusion on the list of medicines refundable by National Health Insurance and approved for use by hospitals

CERIS has been shown to be effective.
CERIS provides no improvement in actual benefit compared to oxybutynin (level V).
The transparency Committee recommends inclusion on the list of products refundable by National Health Insurance and on the list of products approved for hospital use in all the indications and at the dosages in the marketing authorisation.
Reimbursement rate: 35%

The Committee had at that time two controlled studies versus oxybutynin. It had judged that “the results of the studies did not demonstrate a statistically significant difference between the two treatments. From a small-scale meta-analysis of the two studies, a very small difference in the incidence of adverse effects was concluded between those treated with trospium (69% of patients) and those given oxybutynin (77% of patients). The clinical relevance of this difference is uncertain.”

Opinion of the Committee of 16 April 2008
Renewal of listing

The actual benefit remains moderate.
The transparency Committee recommends maintaining inclusion on the list of medicines refundable by National Health Insurance in the indications and at the dosages in the marketing authorisation.
4. ANALYSIS OF AVAILABLE DATA SINCE THE PREVIOUS OPINION

In support of its request, the company has submitted literature data. These data relate only to those studies published since the last Committee Opinion and to the indications of the marketing authorisation of CERIS.

The data provided are:
- a meta-analysis\(^1\)\(^,\)\(^2\) comparing the efficacy and tolerance of antimuscarinic treatments versus placebo in overactive bladder.
- Two clinical studies carried out in the USA\(^3\) evaluating the efficacy and tolerance of a sustained-release trospium chloride product given as a single daily dose of 60 mg versus placebo in the treatment of overactive bladder. These studies included analyses of various patient subgroups (elderly, multiply medicated patients, etc.).
- A study\(^4\) comparing the efficacy and tolerance of anticholinergic treatment with galantamine with or without antimuscarinic treatment with trospium chloride given at a daily dosage of 45 to 60 mg in patients aged over 65 years with Alzheimer’s disease and/or overactive bladder symptoms.
- A systematic review\(^5\) of the pharmacological and clinical effects and tolerance of trospium chloride given at a daily dosage of 45 mg.

The following four studies are not described in this document, as the evaluated dosage regimen does not correspond to that of the marketing authorisation granted in France for the product CERIS 20 mg given at a dosage of 2 tablets/day.
- A cohort study\(^6\) carried out in the USA with the objective of determining the effects on cognitive function and/or the changes in daily activities in patients aged over 65 years, living in a care home and a beneficiary of the Indiana Medicaid programme, treated either with an anticholinergic and a cholinesterase inhibitor or with cholinesterase inhibitors alone.
  The anticholinergics evaluated in this study were oxybutynin and tolterodine. Since trospium chloride was not evaluated, this study is not described. Moreover, the transposability of the data is not guaranteed.
- A pharmaco-epidemiological study\(^7\) of the duration of anticholinergic treatments based on Danish prescription data between 1999 and 2006. This study is not described because of the non-transposability of the data.
- The data from the Periodic Safety Update Reports (PSUR) covering the period from 27 December 2007 to 26 December 2009.
- A report by the Amiens Regional Pharmacovigilance Centre (CRPV) on the neuropsychiatric effects of CERIS since market launch, written in response to a request by the French Health Products Safety Agency (AFSSAPS) (dated 5 March 2010).

There are no new data versus active treatment.

In this document we present:
- the data from the Chapple meta-analysis,
- the data from the PSUR,
- the conclusions of the CRPV report,
- and, for information purposes, a long-term study versus active treatment\(^8\) that was already available at the time of the previous assessment by the transparency Committee of the product CERIS for the purposes of renewal of inclusion on the list of products refundable by National Health Insurance and was included in the meta-analysis by Chapple, for which a check of the comprehensive inclusion of all the available individual studies was carried out.

### 4.1. Efficacy results

The meta-analysis by Chapple\(^5\), which covered 73 studies, compared the efficacy of antimuscarinic treatments versus placebo in overactive bladder based on the following criteria: absence of incontinence, number of episodes of urinary urgency, frequency of urination. This meta-analysis contains some bias: the data search was not exhaustive, no adjustment was made for multiple comparisons, and there was no test of heterogeneity.

The only result available for CERIS concerns the criterion “absence of incontinence” compared with placebo (RR = 2.0, 95% CI [1.4; 2.9], \(p < 0.01\)). This result is close to that observed for the comparators\(^9\) (RR 1.3 to 3.5; \(p < 0.01\)).

The randomised (3:1), double-blind Halaska study\(^8\) compared the efficacy and tolerance of trospium chloride given at a dose of 20 mg twice daily with that of oxybutynin given at a dosage of 5 mg twice daily for 52 weeks in 357 patients with overactive bladder (267 in the trospium chloride group, 90 in the oxybutynin group) with an average age of 53.7 years.

No hypothesis was formulated. No endpoint was defined. The analysis of efficacy and tolerance was descriptive. The results are therefore presented for information purposes, but no conclusion can be formally drawn.

In terms of efficacy, the results at 52 weeks are as follows:
- for the criterion “episodes of incontinence per 24 h”: a reduction of one episode was observed in each treatment group (at inclusion there were 1.5 episodes in the trospium chloride group and 2.1 episodes in the oxybutynin group).
- for the criterion “episodes of urgency per 24 h”: there were reductions of 3.5 episodes in the trospium chloride group and 3.6 in the oxybutynin group (number of episodes at inclusion: 10.2 in the trospium group and 11.0 in the oxybutynin group).
- for the criterion “mean reduction in the number of micturitions per 24 h”: a reduction of 3.5 episodes per 24 h was observed in the trospium chloride group and of 4.2 in the oxybutynin group (number of micturitions per 24 h at inclusion: 11.4 in the trospium group and 12.5 in the oxybutynin group).

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\(^9\) RR = 1.51, 95% CI [1.26; 1.82] for solifenacin 5 mg RR = 1.60, 95% CI [1.34; 1.93] for solifenacin 10 mg, and RR = 3.53, 95% CI [1.94; 6.41] for oxybutynin.
4.2. Tolerance data

Given the anticholinergic pharmacological action, dry mouth, dyspepsia and constipation may occur during treatment with trospium chloride.

4.2.1. Findings of the meta-analysis by Chapple (2008)

The described adverse effect that was reported most often was dry mouth (29.6% of patients treated with anticholinergics, 7.9% of patients treated with placebo).

Table 3. Adverse events of antimuscarinic drugs compared with placebo

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>All adverse effects</td>
<td>RR = 1.30</td>
<td>[1.15; 1.45]</td>
<td>&lt; 0.01</td>
<td>1409</td>
</tr>
<tr>
<td>Dry mouth (all severities)</td>
<td>RR = 3.17</td>
<td>[2.37; 4.24]</td>
<td>&lt; 0.01</td>
<td>1389</td>
</tr>
<tr>
<td>Discontinuation of treatment due to adverse effects</td>
<td>RR = 1.27</td>
<td>[0.86-1.88]</td>
<td>p NS</td>
<td>1490</td>
</tr>
</tbody>
</table>

No difference was observed between the anticholinergic treatments and placebo in terms of occurrence of serious adverse events or the percentage of patients who stopped treatment for any reason.

Discontinuation of treatment due to adverse effects was significantly higher for treatment with oxybutynin (given at a dosage of 7.5, 10 or 15 mg per day) than with placebo (RR = 1.33, 95% CI [1.01; 1.76], p = 0.04).

This meta-analysis, which compared the tolerance of antimuscarinic treatments in overactive bladder\(^\text{10}\) \(^\text{11}\), suggests that solifenacin has better tolerability than oxybutynin. Indeed, the number of dropouts due to adverse effects in randomised studies versus placebo with solifenacin argues in favour of the better tolerability of solifenacin when compared indirectly with oxybutynin (RR = 1.53 [1.02; 2.3], p = 0.04 for solifenacin 10 mg; RR = 1.91 [1.18; 3.1], p = 0.01 for oxybutynin dosages of 7.5 to 10 mg per day, RR = 1.89 [1.23; 2.9], p < 0.01 for an oxybutynin dosage of 15 mg). This is not the case for trospium chloride, for which no difference was observed in the number of patients discontinuing treatment due to adverse effects in randomised studies versus placebo.


4.2.2 Findings of the PSUR analysis

The analysis of data from the last international PSUR (covering the period from December 2007 to December 2009) on CERIS is consistent with the tolerance information given in the current marketing authorisation. Nevertheless, over this period there were 43 observed adverse events, of which 10 were serious and expected, 14 non-serious and unexpected, and 19 serious and unexpected. Of the 19 serious and unexpected adverse events, 7 were judged to be possibly linked to treatment with trospium chloride. These events were cutaneous (one case of Stevens-Johnson syndrome, one case of Henoch-Schönlein purpura), psychiatric (two cases of mental confusion), neurological (one case of myasthenia), ocular, and renal (one case of urine retention).

4.2.3 Findings of the report by the Amiens CRPV

Following the notification of a case of mental confusion in a patient treated with CERIS, the French Health Products Safety Agency (AFSSAPS) requested harmonisation of section 4.8 Adverse effects of the SPC of CERIS with that of other anticholinergic drugs, particularly as regards CNS effects (confusion, hallucinations, agitation). In the case of CERIS, there is no mention in this section of adverse effects on the central nervous system such as “headache and dizziness”.

AFSSAPS requested a report from the Amiens CRPV, the conclusion of which was as follows: “To ensure that healthcare professionals are kept well informed, it would seem important for there to be mention in the SPC of the adverse effects confusion, hallucinations, and agitation inasmuch as the occurrence of these effects has been reported as possibly linked to use of the drug and its discontinuation could be considered. In terms of frequency, the available data allow mention merely of some reported rare cases (frequency not evaluable or not determined).

The information on the seemingly very limited passage across the blood-brain barrier is acceptable and may be included, following the specific request and assessment, in the “Pharmacokinetics” section of the SPC.

This low passage has been demonstrated in experimental models and even in a clinical context, but is not true of very elderly patients with multiple associated pathologies, particularly those with renal impairment (general lack of adequate information). Such factors tend to affect the blood-brain barrier, making it much more permeable, including to substances that under normal conditions would be unable to cross it.”

4.2.4 Findings of the Halaska study (exploratory analysis)

At 26 and 52 weeks, interviews (based on a list of 20 items) were held to identify anticholinergic-type adverse effects (intensity recorded on a scale comprising 4 levels from zero to severe).

At 1 year, the tolerability as judged by doctors was described as “good” in 63% of patients treated with trospium chloride and in 42% of patients given oxybutynin. Adverse events were observed in 64.8% of patients treated with trospium chloride (173/267) and in 76.7% of patients treated with oxybutynin (69/90). The principal adverse events were dry mouth (in 33% of patients treated with trospium chloride and 50% of those given oxybutynin).

Discontinuation of treatment due to adverse events occurred in 25% of patients treated with trospium chloride (n = 67) and 26.7% of patients treated with oxybutynin (n = 24). No information on these adverse effects is available.
The time of occurrence of an adverse effect and the risk of occurrence of an adverse event per patient per week was analysed. For this result, a relative risk with a “p” value is presented only for the time of occurrence of an adverse effect, without a confidence interval. There is no information on the method of analysis for these criteria.

4.3. Conclusion

Since the last transparency Committee Opinion there have been no new clinical studies. The efficacy of all anticholinergics in the treatment of overactive bladder is, however, modest.

The principal adverse event found in the literature data, which corresponds to that of antimuscarinic drugs and is dose-dependent, is dry mouth. The results of the meta-analysis by Chapple, which compared the tolerance of antimuscarinic drugs in overactive bladder, do not suggest that trospium chloride has better tolerability than other antimuscarinic drugs.

Since its last assessment, the Committee has not been provided with any new study in which CERIS is compared directly with another drug therapy. None can be recommended preferentially.

The conclusions that can be drawn from the direct comparisons with oxybutynin and indirect comparisons with solifenacin are not very informative for methodological reasons. On the basis of literature data and clinical experience, the efficacy of CERIS is equivalent to that of solifenacin (VESICARE) and oxybutynin (DITROPAN). As regards adverse CNS effects, indirect comparisons do not allow any conclusions to be drawn as to the benefit of one substance over another. However, based on clinical experience, the products CERIS and VESICARE seem to be associated with better tolerability than DITROPAN.
5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Urinary incontinence is characterised by the involuntary leakage of urine preceded by an urgent and uncontrollable need to urinate resulting in urination that cannot be delayed. Overactive bladder is a condition that results in a marked deterioration in quality of life and can cause social handicap. CERIS comes under the category of symptomatic treatment. The efficacy/adverse effects ratio of CERIS is moderate, as is the case for all other anticholinergic drugs with the same indication. Alternative medicinal products exist.

Public health benefit:
The public health burden of overactive bladder is low.
The therapeutic need is only partially met, given in particular:
- the modest efficacy of anticholinergic drugs and their adverse effects, which can result in the discontinuation of treatment;
- that non-drug alternatives cannot be considered in some patients.
On the basis of the current data, there is no additional populational impact on morbidity and quality of life with the product CERIS compared with other anticholinergic treatments. CERIS does not provide any additional response to the identified need. Consequently, in the current state of knowledge and given that other therapies are already available, there is no benefit public health for the product CERIS.

The actual benefit provided by CERIS is moderate.

5.2. Reassessment of the improvement in actual benefit (IAB)

Since the last assessment by the transparency Committee, there have been no data suggesting that trospium chloride (CERIS) has superior efficacy and/or better tolerability compared with solifenacin (VESICARE). Consequently, the transparency Committee considers that CERIS does not offer any improvement in actual benefit (IAB V) compared with VESICARE in patients with overactive bladder.

5.3. Therapeutic use

There are many available therapeutic options for the treatment of urinary incontinence. Behavioural therapies (modification of fluid intake, bladder retraining, keeping of a urination diary) and perineal/sphincteral rehabilitation are recommended (grade C). These different approaches may be integrated into a rehabilitation programme aimed at inhibiting bladder contractions. They can be proposed as first-line treatment. Drug therapy with an anticholinergic drug can also be proposed as first-line treatment or after failure of behavioural therapy and/or rehabilitation (grade B).

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It is prescribed:
• after elimination of urinary infection and urinary retention,
• provided there are no contraindications to the use of anticholinergic drugs and provided
treatment with a cholinesterase inhibitor is not already underway.

It may be combined with the keeping of a urination diary and rehabilitation measures
(spacing out beverages over the day, changing the times at which diuretic drugs are taken).

Oxybutynin or tolterodine or trospium chloride are recommended (grade B). They have been
found to show moderate efficacy, but to be significantly superior to placebo in eliminating or
relieving urinary incontinence (mean reduction of approximately one episode of urinary
incontinence per 48-hour period). It is probable that tolterodine and trospium chloride are
better tolerated than oxybutynin, though this likelihood is not supported by adequately robust
methodological data.

In view of the risk of urinary retention during treatment with oxybutynin, tolterodine and
trospium chloride, it is advisable to watch out for a distended bladder, particularly in elderly
patients in a weakened state. If treatment with an anticholinergic drug is planned, patients
must be advised about side effects (dry mouth, constipation, cognitive impairment), the delay
in reaching maximum efficacy (which can take as long as 5 to 8 weeks), and of the need to
seek medical advice in the absence of efficacy after this time (particularly if the anticholinergic treatment has been prescribed on a trial basis without a preliminary
urodynamic test) or in the event of urinary tract infection or difficulty urinating.

These recommendations prior to the marketing authorisation of VESICARE consequently do
not mention solifenacin as a treatment for urinary incontinence.

Like VESICARE, CERIS is a treatment option in the management of urinary incontinence
and/or pollakiuria and urgency in patients with overactive bladder.

5.4. Target population

The target population corresponds to all adult patients with an overactive bladder.
According to a European study\textsuperscript{14} (Germany, France, United Kingdom, Italy, Sweden, Spain),
the mean prevalence of overactive bladder is 16.6\% in the population aged over 40. In
France, the prevalence in this population\textsuperscript{15} is 12\%, i.e. approximately 3.8 million affected
individuals.
The proportion of affected individuals seeking medical advice on these grounds is 60\%, i.e.
approximately 2.3 million patients.
Of these, only 27\% had sought treatment and were undergoing drug therapy at the time of
the European cross-sectional survey.
Applying these results to the French population, the population likely to undergo drug therapy
for overactive bladder will be of the order of 625,000 patients.

\textsuperscript{14} Milsom et al. How widespread are the symptoms of an overactive bladder and how are they managed? A
population-based prevalence study. BJU Int 2001; 87: 760-766.
\textsuperscript{15} Population aged 40 years and over on 1 January 2010: 32,122,030. INSEE [French National Institute for
Statistics and Economic Studies] age distribution, 2010
Annex

Some definitions

Overactive bladder: Clinical syndrome characterised by urinary urgency with or without incontinence, usually associated with pollakiuria and nycturia, in the absence of urinary tract infection or an obvious local organic pathology likely to be the cause of these symptoms.

Pollakiuria: Increased urinary frequency (usually ≥ 8 micturitions per 24 h).

Urinary urgency: Sudden urgent, often uncontrollable desire to urinate.

Urinary incontinence: Sudden and involuntary leakage of urine

Figure 1: Schematic representation of overactive bladder syndrome