VESICARE 5 mg, coated tablet  
B/30 (CIP: 365 515-0)  
VESICARE 10 mg, coated tablet  
B/30 (CIP: 365 516-7)

Applicant: ASTELLAS PHARMA SAS Laboratories

solifenacine (succinate of)  
ATC code: G04BD08

List II

Date of marketing authorisation (mutual recognition procedure): 16 August 2004

Reason for request: inclusion on the list of medicines reimbursed by National Health Insurance and approved for use in hospitals.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active substance
solifenacine (succinate of)

1.2. Indication
« Symptomatic treatment of urinary incontinence due to urgency and/or pollakiuria and urinary urgency in patients suffering from overactive bladder. »

1.3. Dosage
« Adults, including the elderly
The recommended dosage is 5 mg solifenacine succinate once daily.
If necessary, the dose can be increased to 10 mg solifenacine succinate once daily.

Children and adolescents
As safety and efficacy of solifenacine have not yet been established in children, VESICARE must not be prescribed to children.

Special populations
Renal insufficiency
No dose adjustment is necessary in mild to moderate renal insufficiency (creatinine clearance > 30 mL/min). In severe renal insufficiency (creatinine clearance ≤ 30 mL/min), treatment should be given with caution and the daily dose of 5 mg not exceeded.

Hepatic insufficiency
No dose adjustment is necessary in mild hepatic insufficiency. In moderate hepatic insufficiency (Child-Pugh score 7-9), treatment should be given with caution and the daily dose of 5 mg not exceeded.

Potent inhibitors of iso-enzyme 3A4 of cytochrome P450
The maximum dose of VESICARE must be limited to 5 mg in the event of concomitant administration of ketoconazole or another potent inhibitor of the iso-enzyme CYP3A4 administered at therapeutic doses; for example ritonavir, nelfinavir, itraconazole.

Method of administration
The 10 mg or 5 mg VESICARE tablet must be taken orally and swallowed whole with water without chewing. The medication can be taken with or without food.

1 A few definitions:
Overactive bladder: clinical syndrome characterised by urgency, with or without incontinence, most frequently associated with pollakiuria and nocturia, in the absence of urinary infection or an evident local organic pathology likely to cause these symptoms.
Pollakiuria: increase in frequency of micturition (generally ≥ 8 times per 24h).
Urgency: sudden, urgent and often uncontrollable desire to urinate.
Urinary incontinence: sudden and involuntary loss of urine.
2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Class (2009)
G   Urogenital system and sex hormones
G04   Urological medications
G04B  Other urological medications, including antispasmodics
G04BD Urinary antispasmodics
G04BD08 Solifenacine

2.2. Medicines in the same therapeutic category

Other anticholinergics:
- DITROPAN 5 mg, scored tablet and its generics (oxybutynine), indicated in “urinary incontinence, urinary urgency and pollakiuria in unstable bladder which may result from an idiopathic instability of the detrusor (muscle) or neurogenic bladder.”
  *The last opinion available for this medicinal product is that of 18 March 2009 (opinion about renewal of inclusion on list of reimbursable pharmaceutical products) in which DITROPAN was attributed a moderate actual medical benefit.*

- CERIS 20 mg, coated tablet (trospium), indicated in the « symptomatic treatment of urinary incontinence due to urgency and/or pollakiuria and urinary urgency in patients suffering from overactive bladder (for example idiopathic or neurological hyperreflexia of the detrusor muscle) ».
  *The last opinion available for this medicinal product is that of 16 April 2008 (opinion about renewal of inclusion on list of reimbursable pharmaceutical products) in which CERIS was attributed a moderate actual medical benefit.*

- DETRUSITOL 1 mg and 2 mg, coated tablet (tolterodine), indicated in the « symptomatic treatment of urinary incontinence due to urgency and/or pollakiuria and urinary urgency in patients suffering from overactive bladder ».  
  *This medicinal product has never been evaluated by the Transparency Committee. It is commercially available but not reimbursable.*

2.3. Medicines with a similar therapeutic aim

These are behavioural treatments, surgery (neuromodulation of the sacral roots in the event of resistance to drug treatments), palliative treatments (pads, collection pouches, pouch for the penis (comprising urinary receptacle) etc.).

3. ANALYSIS OF AVAILABLE DATA

The company has submitted a dossier comprising:
- the marketing authorisation studies previously evaluated by the Committee (see opinion of 15 February 2006).

These are four phase III studies, two of which have been published\(^2\,^3\). All are randomised, double-blind, multicentre studies comparing the efficacy and tolerability of 2 doses (5 and 10 mg) solifenacine with that of placebo in the treatment of overactive bladder. One study (study 905-CL-015\(^2\)) included a comparator arm (tolterodine) at a dose of 2mgx2 /day.


\(^3\) Cardozo L et al. Randomized, double blind placebo controlled trial of the once daily antimuscarinic agent solifenacin succinate in patients with overactive bladder. J Urol 2004; 172: 1919-1924
new data – five clinical and three observational studies:

- The SUNRISE\(^4\) study, a comparative, randomised, double-blind study, whose main objective was to demonstrate the efficacy and tolerability of solifenacine compared with placebo, after 16 weeks of treatment, in 728 patients.
- The VOLT\(^5\) study, a non-comparative study, whose objective was the subjective evaluation of efficacy by the patient as regards discomfort and quality-of-life, after 12 weeks of treatment in 2,225 patients.
- The SOLAR study, a comparative, randomised, double-blind study, whose main objective was to evaluate the contribution of behavioural reeducation associated with solifenacine after 16 weeks of treatment in 643 patients.
- The VERSUS\(^6\) study, a non-comparative study whose objective was to evaluate the efficacy of solifenacine after failure of previous treatment with tolterodine after 12 weeks of treatment in 606 patients.
- The VECTOR\(^7\) study, a comparative study versus oxybutynine, whose objective was to evaluate tolerability after 8 weeks of treatment in 132 patients.
- The VESIQUAL study, an observational study whose objective was to describe the evolution in hyperactivity symptoms under treatment associated with an accompanying programme after 12 weeks of treatment in 427 (female) patients.
- The MICHEL\(^8\) study, an observational study, whose objective was to describe cardiovascular tolerability of solifenacine after 12 weeks of treatment in 4,450 patients.
- And the DSRU (Drug Safety Research Unit) study, a prescribing study.

The following are presented in this opinion:
- the results of the marketing authorisation dossier studies as analysed by the Committee in February 2006
- the results of the new comparative studies, carried out under the terms of the marketing authorisation, enabling the efficacy and tolerability of solifenacine to be assessed, i.e., the SUNRISE and SOLAR studies
- the results of the VESIQUAL, DSRU and MICHEL observational studies.

The other studies (VOLT and VERSUS) will not be described as their methodology does not enable the efficacy of VESICARE to be assessed. The VECTOR study was performed in Canada according to the oxybutynine dosage guidelines defined by the marketing authorisation granted by the local authorities (i.e. 1 x 5 mg tablet 2-3 times daily, or 10-15 mg daily, with a maximum dosage of 20 mg per day). Since the dosage scheme used did not correspond to that of the marketing authorisation granted in France\(^9\), this study will not be described.

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\(^4\) Cardozo et al., Solifenacin in the treatment of urgency and other symptoms of overactive bladder: results from a randomized, double-blind, placebo-controlled, rising-dose trial. BJU Int 2008; 102(9): 1120-112

\(^5\) Garely et al. Symptom bother and health-related quality of life outcomes following solifenacin treatment for overactive bladder: The VESICare open-label trial (VOLT). Clinical Therapeutics 2006;289(11): 1935-46


\(^7\) Not published, only the abstract is available.

\(^8\) Michel et al. Cardiovascular safety and overall tolerability of solifenacin in routine clinical use. A 12-week, open label, post marketing surveillance study. Drug safety 2008; 31 (6) : 505-14

\(^9\) In France, the SPC recommends an initial dose of 2.5 mg oxybutynine 3 times daily, a routine dose of 5 mg 2 or 3 times daily, with a maximum dose of 20 mg daily.
3.1. Efficacy results

3.1.1. Reminder of results of marketing authorisation studies (derived from the opinion of 15 February 2006)

“Four phase III trials with similar methodology which included a total of 3 098 patients, compared the 5 mg and 10 mg doses of solifenacine versus placebo over 12 weeks.

The inclusion criteria were: male or female aged over 18 years of age with symptoms of overactive bladder (including urgency, incontinence, pollakiuria) for more than 3 months. Those patients presenting, after a two-week period on placebo, with a mean frequency of at least 8 episodes of micturition per day and who had had over the last three days 3 episodes of urgency and/or incontinence were eligible for randomisation. Patients with hyperactivity of the detrusor muscle of neurological origin were excluded from the study.

The population studied in each group was comparable. These were to a large extent women (80%), of a mean age of 58 years, elderly people aged over 75 representing on average 10% of the population. The mean number of daily episodes of micturition was 12.

N.B.: According to the data in the literature, approximately 30% of patients affected with overactive bladder are over 75 years of age\(^\text{10}\).

Primary criterion
Mean reduction in number of episodes of micturition per 24 hours compared with the initial value at inclusion in the treatment group.

Secondary criteria
- Reduction in the number of episodes of urgency per 24 hours
- Reduction in the number of episodes of incontinence per 24 hours
- Reduction in the number of episodes of nocturia per 24 hours
- Increase in the volume evacuated by micturition
- Reduction in the number of pads required per 24 hours
- Impact on quality-of-life of the patients

Results relating to primary criterion:

The results of the 4 trials were summarised for the statistical analysis.

Table 1:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Daily dose</th>
<th>Number of patients</th>
<th>Reduction in number of episodes of micturition over 24 hours</th>
<th>Reduction in number of episodes of micturition daily compared with placebo</th>
<th>( p ) (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>1 138</td>
<td>-1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacine</td>
<td>5 mg</td>
<td>552</td>
<td>-2.3</td>
<td>-0.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>1 158</td>
<td>-2.7</td>
<td>-1.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

The reduction in the number of daily episodes of micturition was significantly greater in the solifenacine group on the 5 mg dosage (\( \Delta = -0.9 \), \( p<0.001 \)) and 10 mg dosage (\( \Delta = -1.3 \), \( p<0.001 \)) than in the placebo group.

\(^{10}\) 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.
Table 2: Results of the 905-CL-015 study which included a tolterodine arm

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Daily dose</th>
<th>Number of patients</th>
<th>Reduction in number of episodes of micturition over 24 hours</th>
<th>Reduction in number of episodes of micturition daily compared with placebo</th>
<th>p (vs placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td>253</td>
<td>-1.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solifenacine</td>
<td>5 mg</td>
<td>266</td>
<td>-2.2</td>
<td>-1.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>10 mg</td>
<td>264</td>
<td>-2.6</td>
<td>-1.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>2x2 mg</td>
<td>250</td>
<td>-1.9</td>
<td>-0.7</td>
<td>0.004</td>
</tr>
</tbody>
</table>

The reduction in the number of daily episodes of micturition was significantly greater in the tolterodine arm at a dosage of 2x2mg/day ($\Delta=-0.7$, $p=0.004$) than in the placebo arm, and in the 5 mg solifenacine arm ($\Delta=-1.0$, $p<0.001$) and 10 mg solifenacine arm versus placebo ($\Delta=-1.4$, $p<0.001$).

No significant difference in the efficacy of VESICARE was observed as a function of the age or sex of the patient.

Results relating to secondary criteria
The secondary criteria were significantly improved compared with placebo, except for nocturia.
As far as the secondary criterion «reduction in the number of episodes of incontinence per 24 hours» is concerned, 51% of patients on 5 mg solifenacine, 52% of patients on 10 mg solifenacine and 34% of patients on placebo were continent at the end of the study ($p < 0.001$).

Evaluation of the impact on quality-of-life
Quality-of-life was studied as a secondary criterion in several clinical trials, using two specific scales validated for quality-of-life, the Contilife™ questionnaire and King’s Health Questionnaire. These questionnaires were specifically developed as tools for urinary incontinence.

Results relating to the Contilife™ questionnaire
The Contilife questionnaire was used to evaluate quality-of-life in a phase II clinical trial. It enables evaluation of the impact of all types of urinary incontinence on quality-of-life according to 28 items distributed into five domains (daily activities, effort situation, perception of self, emotional impact, sexuality). Here are the results:

Table 3: quality-of-life according to the 5 domains in the Contilife™ questionnaire

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>5 mg</th>
<th>VESICARE®</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>% Δ mean</td>
<td>-10</td>
<td>-27</td>
<td>-32</td>
<td></td>
</tr>
<tr>
<td>$p^*$</td>
<td></td>
<td>S.</td>
<td>S.</td>
<td></td>
</tr>
<tr>
<td>Effort</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>% Δ mean</td>
<td>-5</td>
<td>-17</td>
<td>-6</td>
<td></td>
</tr>
<tr>
<td>$p^*$</td>
<td></td>
<td>N.S.</td>
<td>N.S.</td>
<td></td>
</tr>
<tr>
<td>Perception of self</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>35</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>% Δ mean</td>
<td>-9</td>
<td>-19</td>
<td>-23</td>
<td></td>
</tr>
<tr>
<td>$p^*$</td>
<td></td>
<td>N.S.</td>
<td>S.</td>
<td></td>
</tr>
<tr>
<td>Emotional impact</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>% Δ mean</td>
<td>-5</td>
<td>-18</td>
<td>-27</td>
<td></td>
</tr>
<tr>
<td>$p^*$</td>
<td></td>
<td>N.S.</td>
<td>S.</td>
<td></td>
</tr>
<tr>
<td>Sexuality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>36</td>
<td>35</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>% Δ mean</td>
<td>+4</td>
<td>-6</td>
<td>-8</td>
<td></td>
</tr>
<tr>
<td>$p^*$</td>
<td></td>
<td>N.S.</td>
<td>S.</td>
<td></td>
</tr>
</tbody>
</table>

*S.: significant versus placebo, N.S.: not significant versus placebo
Solifenacine at the 10 mg dose significantly improved the domains of daily activity, effort situation, perception of self, emotional impact, sexuality, with respect to placebo. At the 5 mg dose, a significant improvement was only seen in the domains daily activities and emotional impact.

Results relating to the King’s Health Questionnaire.
Quality-of-life was evaluated in 2 out of 4 phase III marketing authorisation studies using a specific and validated quality-of-life scale, the KHQ (King’s Health Questionnaire).
Ten domains were analysed. The scores for each of the domains ranged from 0 (best) to 100 (worst), a higher score indicating a greater impact on quality-of-life. On a scale of 100, a difference of 5 is considered to be the minimum difference relevant to the patient. Here are the results:

Table 4: Quality-of-life according to the 10 domains of the King’s Health Questionnaire

<table>
<thead>
<tr>
<th>Domain of King’s Health Questionnaire</th>
<th>Results at 12 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean variations (%)</td>
</tr>
<tr>
<td></td>
<td>/initial state</td>
</tr>
<tr>
<td>General health perception</td>
<td>-11 S.</td>
</tr>
<tr>
<td>Incontinence impact</td>
<td>-32 S.</td>
</tr>
<tr>
<td>Role limitations</td>
<td>-33 S.</td>
</tr>
<tr>
<td>Physical limitations</td>
<td>-29 S.</td>
</tr>
<tr>
<td>Social limitations</td>
<td>-31 N. S.</td>
</tr>
<tr>
<td>Personal relationships</td>
<td>-28 N. S.</td>
</tr>
<tr>
<td>Emotions</td>
<td>-33 S.</td>
</tr>
<tr>
<td>Sleep/energy</td>
<td>-25 S.</td>
</tr>
<tr>
<td>Austerity measures</td>
<td>-26 S.</td>
</tr>
<tr>
<td>Severity of symptoms</td>
<td>-28 S.</td>
</tr>
</tbody>
</table>

An improvement in the KHQ quality-of-life scale was observed in 9 out of 10 domains. Only the « personal relationships » domain did not improve.

Additional data:
Sub-group analyses, which were planned in the protocol\(^{11}\), but not detailed in the previous opinion, were presented by the company in the new dossier. These data, which were intended to be exploratory, are presented for information purposes.
An analysis was carried out of the efficacy of solifenacine\(^{12,13}\) after 12 weeks of treatment, in a sub-group of patients suffering from urinary incontinence (n=1 873), a population originating from the pooled analysis planned at the outset of the 4 phase III marketing authorisation trials.
A reduction of ≥ 50% in the number of episodes of incontinence was observed in approximately 70% of patients treated with solifenacine (71% in the 5 mg solifenacine group, 79% in the 10 mg group) and in 58% of patients in the placebo group (p<0.001). A reduction of ≥ 50% in the number of episodes of urgency was observed in 62% of patients treated with solifenacine and 44% of patients in the placebo group (p<0.001).

The urgency resolved in 29% of patients in the 5 mg solifenacine group, 26% of patients in the 10 mg solifenacine group, 16% of patients in the placebo group.
Normal continence was regained in 51% of patients treated with 5 mg solifenacine, 52% of patients treated with 10 mg solifenacine and 34% of patients on placebo (p<0.001).
Each sub-group of patients showed results in favour of the solifenacine treatment group compared with placebo.

\(^{11}\) Allowance was made for multiple comparisons
\(^{12}\) Cardozo et al. Reductions in overactive bladder-related incontinence from pooled analysis of phase III trials evaluating treatment with solifenacin. Int Urogynecol 2006; 17(5): 512-9
\(^{13}\) Chapple et al. Solifenacin significantly improves all symptoms of overactive bladder syndrome. Int J Clin Pract 2006;60(8):959-66
The company also presented data on patients ≥ 65 years. This was a pooled analysis on this sub-group planned at the outset of the phase III marketing authorisation trials.

The mean age of the patients was 71.9 years (n=1 045) in the placebo group (n=422), 71.4 years in the 5 mg solifenacine group (n=192) and 72.1 years in the 10 mg solifenacine group (n=431). The majority of patients were women. The mean duration of overactive bladder was 7.0 years in the placebo group, 9.2 years in the 5 mg solifenacine group and 8.5 years in the 10 mg group. Fewer than 50% of the patients had received prior treatment.

The mean reduction in number of episodes of micturition per 24 hours (main assessment criterion) was 2.0 (0.17) in the 5 mg solifenacine group (mean difference with respect to placebo: -1.00 [-1.4; -0.6], p<0.001) and 2.5 (0.13) in the 10 mg solifenacine group (mean difference with respect to placebo: -1.42 [-1.7; -1.1], p<0.001).

The urgency resolved in 35% of patients in the 5 mg solifenacine group, 25% of patients in the 10 mg solifenacine group, 17% of patients in the placebo group (p<0.01).

Normal continence was regained in the patients aged over 65 years in 49% of patients on 5 mg solifenacine, 47% on 10 mg solifenacine, 29% on placebo (p<0.001).

3.1.2. Results of the new studies

3.1.2.1. SUNRISE study

Methodology and objective:
Phase III, comparative, randomised, double-blind study whose main objective was to evaluate the reduction in urgency over 24 hours on solifenacine compared with placebo, after 16 weeks of treatment.

Inclusion criteria:
Male or female aged more than 18 years of age with symptoms of overactive bladder (including urgency, incontinence, pollakiuria) for more than 3 months and more than 3 episodes of urgency with or without incontinence over the last three days.
Those patients presenting with a mean frequency of at least 8 episodes of micturition per day and 3 episodes of severe urgency with or without incontinence were eligible for randomisation.

Administration schedule:
The patients were initially randomised to receive for 8 weeks according to a 1:3 ratio either placebo, or solifenacine at a dosage of 5 mg once daily. The dose of solifenacine could be increased to 10 mg, depending on symptoms. 50% of patients initially treated with 5 mg wanted this dose increase.
At week 8, those patients previously treated with 5 mg solifenacine once daily who wished to increase their dose, were randomised once more to receive either solifenacine at a dose of 5 mg daily, or solifenacine at a dose of 10 mg once daily. These patients made up the « solifenacine » group. This group was used to calculate the number of patients to be included.
A total of 728 patients was randomised according to a 1:1 ratio, 505 in the solifenacine group and 223 in the placebo group.

Principal endpoint
Reduction in mean number of episodes of severe urgency over 24 hours after 16 weeks of treatment.

Note: Urgency, the main symptom of overactive bladder, is a symptom that should be differentiated from a normal pressing need. To avoid any bias in evaluation of the main study criterion, episodes of urgency were identified using a validated scale (PPIUS: Patient’s Perception of Intensity of Urgency Scale)\(^{15}\).

This scale ranges from 0 to 4 depending on the intensity of the urgency experienced:
« 0 ». No pressing desire to urinate.
« 1 ». Slightly pressing desire to urinate: long wait possible.
« 2 ». Moderately pressing desire to urinate: small wait possible.
« 3 ». Very pressing desire to urinate: I had to rush to the toilet.
« 4 ». Incontinence due to extremely pressing desire to urinate.

The formal definition of urgency according to the ICS (International Continence Society) corresponds to scores 3 and 4, i.e. severe urgency according to the PPIUS scale.

The protocol planned for the inclusion of 616 patients to demonstrate a difference of 0.9 episodes of urgency\(^{16}\) with a power of 80% and an overall alpha risk of 0.05.

Main secondary endpoints:
- reduction in episodes of urgency, all intensities, according to the PPIUS scale (scores 1-4)
- mean change compared with initial state in number of episodes of micturition per 24 hours, number of episodes of incontinence per 24 hours, incontinence due to urgency per 24 hours
- evaluation of treatment by the patient using:
  - the PPBC\(^{17}\) questionnaire which relates to bladder problems, ranging from 1 (no problem) to 6 (severe problems)
  - a visual analogue scale evaluating the discomfort linked to urgency
  - a visual analogue scale evaluating patient satisfaction.

Results:
The results are derived from the analysis of all the randomised patients who received at least one dose of treatment, with the initial data and at least one measurement on treatment. At inclusion, the mean age of the patients was 58 years (30.5% of patients in the solifenacine group and 34.5% in the placebo group were aged 65 years or more) and the majority of patients were female (89.1% in the solifenacine group, 85.7% in the placebo group).

In each group:
- the predominant symptom of overactive bladder was urgency with incontinence in 50% of patients
- the overactive bladder dated back 6.4 years on average in the solifenacine group, 5.2 years in the placebo group
- 55.5% of patients in the solifenacine group and 57.4% of patients in the placebo group had not received prior treatment.

<table>
<thead>
<tr>
<th>Table 5: Characteristics of overactive bladder at inclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean daily (SD)</strong></td>
</tr>
<tr>
<td><strong>N=503</strong></td>
</tr>
<tr>
<td>Number of episodes of urgency with scores 3-4</td>
</tr>
<tr>
<td>Number of episodes of urgency with scores 1-4</td>
</tr>
<tr>
<td>Maximum intensity of urgency (max PPIUS score)</td>
</tr>
<tr>
<td>Number of episodes of micturition per 24 hours</td>
</tr>
<tr>
<td>Number of episodes of incontinence per 24 hours</td>
</tr>
<tr>
<td>Number of episodes of incontinence due to urgency</td>
</tr>
</tbody>
</table>


\(^{16}\) The value of 0.9 corresponds to the least significant effect measured in the phase III marketing authorisation studies with one of the two licensed doses of VESICARE.

\(^{17}\) Coyne et al. Validation of the perception of bladder condition in overactive bladder. Value Health 2002, 231
Principal endpoint

Table 6: evolution in number of episodes of severe urgency at 16 weeks:

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Mean number of daily episodes of urgency with scores 3-4 (initial state) (standard deviation SD)</th>
<th>Mean change at 16 weeks (SD)</th>
<th>Mean difference / placebo, CI 95%, p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solifenacine</td>
<td>503</td>
<td>5.1 (3.4)</td>
<td>-2.6 (3.2)</td>
<td>-1.0 ([−1.5; -0.4]; p&lt;0.0001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>216</td>
<td>5.5 (3.9)</td>
<td>-1.8 (3.8)</td>
<td></td>
</tr>
</tbody>
</table>

There was a greater reduction in the number of episodes of urgency in the solifenacine group than in the placebo group (difference between solifenacine and placebo: -1.0 IC95% [-1.5; -0.4], p<0.0001).

Secondary endpoints:
Compared to inclusion, the number of episodes of urgency (all intensities) decreased by 2.3 (3.0) on solifenacine and 1.6 (3.3) on placebo, i.e. a difference versus placebo of -0.8 CI 95% [-1.3; -0.3], p=0.0006.
The number of episodes of micturition per 24 hours decreased by 2.1 (2.6) on solifenacine and 1.3 (2.7) on placebo, i.e. a difference versus placebo of -0.9 CI 95% [-1.3; -0.4], p<0.0001.
The difference versus placebo in the number of episodes of incontinence over 24 hours (evaluated in 329 patients in the solifenacine group, 158 in the placebo group) and incontinence due to urgency over 24 hours (evaluated in 326 patients in the solifenacine group, 158 in the placebo group) was -0.5 CI 95% [-0.9; -0.2], p<0.05.
Statistically significant differences were observed between the solifenacine and placebo groups in the criterion « evaluation of treatment by the patient ».
At inclusion, the score of the PBC questionnaire, a validated questionnaire, was 4.6 (0.8) in each treatment group. After 16 weeks of treatment, this score decreased by 1.5 (1.3) in the solifenacine group and 1.0 (1.3) in the placebo group, i.e. a difference of -0.5 CI 95% [-0.7; -0.3], p<0.0001.

3.1.2.2. SOLAR study

Methodology and objective:
Comparative, randomised, open study, whose main objective was to evaluate the efficacy of solifenacine at a dose of 5 mg compared with that of solifenacine at a dose of 5 mg combined with behavioural treatment after 16 weeks of treatment in patients suffering from overactive bladder.
The behavioural treatment consisted of advice for improving bladder control combined with simple exercises for contracting the pelvic muscles to prevent the desire to urinate.

Inclusion criteria:
Male of female aged over 18 years with symptoms of overactive bladder (including urgency, incontinence) for more than 3 months and more than 3 episodes of urgency with or without incontinence over the last three days.
Those patients presenting with a mean frequency of at least 8 episodes of micturition per day and 3 episodes of urgency or incontinence due to urgency in the last three days were eligible for randomisation.
Administration schedule:
Patients were randomised to receive for 8 weeks either solifenacine at a dose of 5 mg once daily, or solifenacine at a dose of 5 mg once daily combined with behavioural treatment. From week 8, the dosage of solifenacine could be increased to 10 mg once daily.
A total of 643 patients was randomised, 323 in the 5 mg solifenacine group and 320 in the 5 mg solifenacine + behavioural treatment group.

Principal endpoint
Mean reduction in number of episodes of micturition per 24 hours after 8 weeks of treatment

The protocol planned for the inclusion of 510 patients to demonstrate a difference of 0.7 in daily episodes of micturition\(^{18}\) with a power of 80% and an overall alpha risk of 0.05.

This assessment criterion that was planned in the protocol was analysed in the patient subgroups (as a function of whether prior treatment had been given, and the age of the patients). No allowance has been made for multiple comparisons and therefore an overestimate of the effect cannot be excluded. No formal conclusion can be drawn from these exploratory analyses and therefore they have not been presented here.

Main secondary endpoints:
- Mean change compared with initial state in frequency of episodes of urgency per 24 hours, number of episodes of incontinence per 24 hours, incontinence due to urgency per 24 hours
- Perception of treatment by the patient, quality-of-life.

Results:
The results are based on analysis of all the randomised patients who received at least one dose of treatment, with the initial data and at least one measurement on treatment.

At inclusion, the mean age of the patients was 58 years (21.4% of patients in the solifenacine group and 27.5% in the solifenacine + behavioural treatment group were aged 65 years or more) and the majority of patients were female (84.8% in the solifenacine group, 86.6% in the solifenacine + behavioural treatment group). In each group:
- the predominant symptom of overactive bladder was urgency with incontinence in 50% of patients, urgency without incontinence in 25% of patients
- the overactive bladder dated back 4 years on average
- 69.5% of patients in the solifenacine group and 66.3% of patients in the solifenacine + behavioural treatment group had not received prior treatment.

\(^{18}\) The value of 0.7 corresponds to that observed in a study that compared tolterodine to tolterodine + behavioural treatment. Mattiasson et al., Simplified bladder training augments the effectiveness of tolterodine in patients with an overactive bladder BJU International 2003;91(1): 54-60
Main endpoint:
Table 7: mean reduction in number of episodes of micturition per 24 hours after 8 weeks of treatment

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>Means number of episodes of micturition per 24 hours – initial state (standard deviation SD)</th>
<th>Mean change adjusted at 8 weeks</th>
<th>Difference/ mean comparator, 95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>solifenacine alone</td>
<td>305</td>
<td>11.50 (2.99)</td>
<td>-2.18</td>
<td>-0.69 [-1.04; -0.35]; p&lt;0.0001</td>
</tr>
<tr>
<td>solifenacine + behavioural</td>
<td>297</td>
<td>11.49 (3.00)</td>
<td>-2.87</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After 8 weeks of treatment, there was a slightly greater reduction in the number of episodes of micturition per 24 hours in the patients on solifenacine + behavioural treatment than in those on solifenacine alone (difference: -0.69, IC95% [-1.04; -0.35]; p<0.001).

Secondary endpoint: no statistically significant difference was observed between the 2 treatment groups.

3.1.2.3. Observational studies

The objective of the VESIQUAL study, an observational study carried out in France on 427 (female) patients, was to describe the evolution in symptoms of overactive bladder on treatment combined with an accompanying programme, Vesiguide, after 12 weeks of treatment.

Results: maintainance of the patients on treatment was considered to be acceptable by the doctor in 70.6% of patients. As far as quality-of-life is concerned (Ditrovie Questionnaire), the negative effects of overactive bladder on everyday activities of the patients appear to be less common after implementation of VESICARE + Vesiguide (accompanying programme). As this study only evaluates the effect of treatment associated with an accompanying programme, it is not possible to assess the impact on morbidity or quality-of-life of the VESICARE treatment specifically.

The DSRU study, a prescription study carried out in the United Kingdom on 5 330 patients, enabled the authors to conclude that the dosages used complied with recommendations (the 5 mg dose was sufficient for the majority of patients) and that 67% of patients were still on treatment at 6 months.

Maintenance of treatment appears to be quite high at 6 months. Since this study was performed in the United Kingdom, its results cannot necessarily be transposed to France. In addition, these data do not allow any conclusions to be drawn about the impact on morbidity/quality-of-life of VESICARE treatment.
3.2. Adverse events
Given its pharmacological effect, the adverse effects of solifenacine (mild to moderate, with a dose-dependent frequency) correspond to those of the class of anticholinergics.

3.2.1 Results of marketing autorisation studies
The tolerability results of the four phase III trials are presented in the table below:

| Tolerability results during four controlled phase III trials: 12 weeks of treatment |
|---|---|---|---|
| Number of patients (%) | Placebo | VESICARE® 5 mg | VESICARE® 10 mg |
| Number of patients | 1 216 | 578 | 1 233 |
| Adverse events (%) | 634 (52.1) | 265 (45.8) | 773 (62.7) |
| Premature termination due to AE (%) | 66 (5.4) | 21 (3.6) | 85 (6.9) |
| AE linked to treatment (%) | 281 (23.1) | 171 (29.6) | 588 (47.7) |
| Dry mouth (%) | 51 (4.2) | 63 (10.9) | 340 (27.6) |
| Constipation (%) | 35 (2.9) | 31 (5.4) | 165 (13.4) |
| Blurred vision (%) | 22 (1.8) | 22 (3.8) | 59 (4.8) |

The adverse events collected during the 905-CL-015 study that included a tolterodine arm are presented below:

<table>
<thead>
<tr>
<th>Placebo</th>
<th>VESICARE® 5 mg</th>
<th>VESICARE® 10 mg</th>
<th>Tolterodine 2 x 2 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>267</td>
<td>279</td>
<td>168</td>
</tr>
<tr>
<td>Dry mouth (%)</td>
<td>13 (4.9)</td>
<td>40 (14.3)</td>
<td>57 (21.3)</td>
</tr>
<tr>
<td>Constipation (%)</td>
<td>5 (1.9)</td>
<td>20 (7.2)</td>
<td>21 (7.8)</td>
</tr>
<tr>
<td>Blurred vision (%)</td>
<td>7 (2.6)</td>
<td>10 (3.6)</td>
<td>16 (6.0)</td>
</tr>
</tbody>
</table>

The incidence of adverse events appeared to be dose-dependent. The incidence was greater in the 10 mg solifenacine group.

A sub-group analysis (< 65 years, ≥ 65 years and ≥ 75 years) showed a greater incidence of adverse events (dry mouth, constipation, urinary infection, asthenia) in the over 65 year and over 75 year age groups than in the under 65 year age group. No tolerability data is available on cognitive function.

3.2.2. Results of new studies
The main adverse events were:
- dry mouth in 80/505 patients in the solifenacine group and 6/223 patients in the placebo group in the SUNRISE study, 41/323 patients in the solifenacine group and 33/320 patients in the solifenacine + behavioural treatment group in the SOLAR study
- constipation in 35/505 patients in the solifenacine group and 5/223 patients in the placebo group in the SUNRISE study, 8/323 patients in the solifenacine group and 17/320 patients in the solifenacine + behavioural treatment group in the SOLAR study.
19 patients in the solifenacine group and 6 patients in the placebo group terminated treatment prematurely due to adverse effects in the SUNRISE study, 13 patients in the solifenacine group and 8 patients in the solifenacine + behavioural treatment group in the SOLAR study.

In these studies, the incidence of adverse events appeared to be dose-dependent. The incidence was greater in the 10 mg solifenacine group.

In the MICHEL study, an observational study over 12 weeks, carried out on 4 450 patients aged from 51 to 80 years, whose objective was to evaluate cardiovascular tolerability, no change in cardiac parameters (heart rate, blood pressure) was observed. Tolerability of the product was considered to be «good» to «very good» by 95% of patients. One should note that at inclusion 12% of patients had coronary heart disease, 1.6% a history of myocardial infarction and 7% chronic heart failure.

Analysis of data in the last international VESICARE PSUR (covering the period June 2007 – June 2008) agrees with the risk information as stated in the current marketing authorisation. The SPC was amended on 23 February 2009 and mentions new adverse events of the product that occurred post-marketing that are very rare. These are vomiting, erythema, pruritis, urticaria, hallucinations, dizziness and headache.

3.3. Conclusion
The company provided studies used in the marketing authorisation (previously evaluated by the Committee) and new data including only the comparative studies, performed under the terms of the marketing authorisation, enabling assessment of the efficacy and tolerability of solifenacine were used, i.e. the SUNRISE and SOLAR studies.

The four phase III marketing authorisation trials, whose methodology was similar, including a total of 3 098 patients, compared the 5 mg and 10 mg solifenacine doses with placebo over 12 weeks in the treatment of overactive bladder.

The reduction in number of daily episodes of micturition (main assessment criterion) was significantly greater in the solifenacine groups with the 5 mg dose (difference of -0.9, p<0.001) and 10 mg dose (difference of -1.3, p<0.001) than the placebo group. At inclusion, the mean number of daily episodes of micturition was 12. The size of the effect is modest, of the same order as that of other medications in this class.

The Committee regretted in its previous opinion that the studies presented did not include a proportion of elderly subjects more representative of the population affected by overactive bladder. The company therefore provided the results of the sub-group of patients ≥ 65 years. In this population, the mean reduction in number of episodes of micturition per 24 hours was 2.0 (0.17) in the 5 mg solifenacine group (mean difference compared to placebo: -1.00 [-1.4; -0.6], p<0.001) and 2.5 (0.13) in the 10 mg solifenacine group (mean difference compared to placebo: -1.42 [-1.7; -1.1], p<0.001).

A positive impact on quality-of-life of the patients was observed in the majority of domains evaluated.

In the SUNRISE study, a randomised, double-blind, placebo-controlled study, carried out on 728 patients, the observed difference on solifenacine with respect to placebo on the reduction in mean number of episodes of severe urgency over 24 hours after 16 weeks of treatment (main criterion of assessment), was 1.0 (IC95% [-1.5; -0.4], p<0.0001).

Statistically significant differences were observed in all secondary criteria.

The main objective of the SOLAR study, a comparative, randomised, open study, was to evaluate the efficacy of solifenacine at a dose of 5 mg compared with that of solifenacine at a dose of 5 mg combined with behavioural treatment after 16 weeks of treatment on 643 patients suffering from overactive bladder (The Committee regretted in its opinion of 15
February 2006 the lack of comparison with other types of therapy, in particular behavioural
treatments).
After 8 weeks of treatment, the addition of a behavioural treatment to the solifenacine
treatment enabled the number of episodes of micturition per 24 hours to decrease (main
assessment criterion) from 0.69 [-1.04; -0.35]; p<0.001, compared with treatment with
solifenacine alone.

The number of effects observed in all the studies was low and the main adverse events
dose-dependent and corresponding to those of the antimuscarinics) were dry mouth and
constipation.

The Committee does not have any study that directly compares solifenacine with another
drug treatment. None can be recommended in preference.
According to the public evaluation report by the Affssaps (French Health Products Safety
Agency) of 1st November 2004, the risk/benefit ratio of the product is favourable, however
the measured effect remains modest of the order of at least one micturition episode per 24
hours compared with placebo. The effect of solifenacine on the symptoms of overactive
bladder does not appear to be different to that measured for other treatments in the class.
One should point out that oxybutynine has a mediocre tolerability profile mainly dry mouth,
constipation, cognitive disorders etc... despite definite efficacy.
A meta-analysis that compared tolerability of the antimuscarinic treatments in overactive
bladder\textsuperscript{19, 20}, suggests better tolerability of solifenacine compared with oxybutynine. In fact,
treatment withdrawals due to adverse effects in placebo-controlled randomised studies with
solifenacine suggest better tolerability of solifenacine when compared indirectly with
oxybutynine (\textit{RR} =1.16, NS for 5 mg solifenacine, \textit{RR} = 1.53 [1.02; 2.3], p=0.04 for 10 mg
solifenacine; \textit{RR} = 1.91 [1.18; 3.1], p=0.01 for 7.5 mg to 10 mg daily doses of oxybutynine,
\textit{RR} = 1.89 [1.23; 2.9], p<0.01 for a 15 mg dose of oxybutynine).

4. CONCLUSIONS OF THE TRANSPARENCY COMMITTEE

4.1. Actual benefit
Urinary incontinence due to urgency is characterised by the involuntary loss of urine
preceded by an urgent and irrepressible need to urinate leading to micturition that cannot be
delayed.
Overactive bladder is a condition that involves a marked decrease in a patient’s quality-of-life
and may become a social handicap.
VESICARE is a treatment aimed at the symptoms of this condition.
The efficacy/adverse effects ratio of VESICARE is average.
There are therapeutic alternatives to this medicinal product.

Public health benefit:
As far as public health is concerned, the burden of overactive bladder is low.
The therapeutic need is only partially covered, given in particular:
- a modest efficacy of anti-cholinergic medications and their adverse effects that can lead
to treatment withdrawals;
- the fact that non-drug based alternatives can only be considered in a few patients.
VESICARE represents an additional mean of therapy in the management of overactive
bladder. However, since it is also an anti-cholinergic treatment, VESICARE does not a
priori provide an additional response to the therapeutic need.

\textsuperscript{19} Chapple C, et al, The Effects of Antimuscarinic Treatments in Overactive Bladder: A Systematic Review and
Meta-Analysis, European Urology 2005;48: 5–26
\textsuperscript{20} Chapple et al. The Effects of antimuscarinic treatments in overactive bladder: an update of a systematic review
and meta-analysis. European urology 2008;54:543–62
Considering the available data, no additional effect on morbidity or quality-of-life is expected on the population as a whole from the medicinal product VESICARE compared with the other anticholinergic treatments.

As a result, based on current knowledge and given the other treatments available currently, the medicinal product VESICARE is not expected to provide a public health benefit.

The actual benefit provided by VESICARE is moderate.

4.2. Improvement in actual benefit

The Committee does not have any study comparing solifenacine with available treatments that are currently reimbursable in France. However, according to data in the literature and clinical experience, solifenacine appears to be better tolerated than oxybutynine (DITROPAN).

As a result, the Transparency Committee considers that VESICARE provides a minor improvement (IAB IV) in actual benefit compared with DITROPAN as far as tolerability is concerned in patients suffering from overactive bladder.

4.3. Therapeutic use

Several therapies are available for treating urinary incontinence due to urgency. Behavioural treatments (adapting liquid consumption, micturition reprogramming, keeping a micturition diary) and perineal-sphincter reeducation are recommended (grade C). These various methods can be combined to help reeducation of the bladder and inhibiting contractions of the bladder. They can be suggested as first-line therapies.

Anticholinergic drug treatment can also be proposed as first-line treatments or following failure of behavioural and/or reeducation treatment (grade B).

This is prescribed:
- after eliminating urinary infection and urinary retention;
- if there are no contraindications to the use of anticholinergics and provided anticholinesterase treatment is not already in progress.

This can be combined with keeping of a micturition diary and educational measures (distribution of drinks during the day, changing times diuretic medication is taken).

Oxybutynine, tolterodine or trospium chloride are recommended (grade B). These have shown moderate, but significantly greater efficacy than placebo in relieving or making urinary incontinence due to urgency disappear (mean decrease approx. 1 episode of urinary incontinence per 48-hour period). It is probable that tolterodine and trospium chloride are better tolerated than oxybutynine.


22 Prof. François Haab (University of Paris VI, Tenon Hospital, Paris). Rapport sur le thème de l’incontinence urinaire remis à Mr Philippe Bas (Ministère de la Santé et des Solidarités). Avril 2007 (report on the subject of urinary incontinence presented to Mr Philippe Bas – Ministry of Health and Solidarity – April 2007)
Given the risk of urinary retention with oxybutynine, tolterodine and trospium chloride, it is advisable to monitor for the appearance of distended bladder, especially in weak, elderly patients. If an anticholinergic treatment is envisaged, patients must be warned of side-effects (dry mouth, constipation, cognitive disorders), the time-delay until maximum effect (which may be between 5 and 8 weeks) and the need to consult a doctor if there is no effect after this time period (especially in the case of “test” anticholinergic treatment prescribed without prior urodynamic screening) or in the event of urinary infection or urination difficulties.

However, these recommendations prior to the VESICARE marketing authorisation do not cite solifenacine as treatment for urinary incontinence. VESICARE is a new therapeutic option in the management of urinary incontinence and/or pollakiuria and urinary urgency in patients with overactive bladder.

### 4.4. Target population

The target population is all adult patients with overactive bladder. According to a European study\(^{23}\) (Germany, France, United Kingdom, Italy, Sweden, Spain), the mean incidence of overactive bladder is 16.6% in the over-40 age group. In France, the incidence in this population is 12%, i.e. approx. 3.8 million people affected. 60% of patients with this condition consult a doctor i.e. approx. 2.3 million patients. Of these, at the time of the Europe-wide survey, only 27% who had consulted a doctor were on drug treatment.

Applying these results to the French population, the population likely to be treated with drugs for overactive bladder would be of the order of 617 000 patients.

### 4.5. Transparency Committee recommendations

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

- **Packaging**: appropriate for the prescription conditions
- **Reimbursement rate**: 35%

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\(^{23}\) 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.