HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

15 February 2006

Vesicare 10 mg, film-coated tablet
B/30: CIP code 365 516-7

Vesicare 5 mg, film-coated tablet
B/30: CIP code 365 515-0

Applicant: Yamanouchi Pharma

solifenacin succinate

Date of Marketing Authorisation: 16/08/2004

Reason for application: Inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by hospitals

Health Technology Assessment Division

1 CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

solifenacin succinate

1.2. Background

Solifenacin is a competitive, specific muscarinic receptor antagonist. Its sustained duration of action means it can be administered in a single daily intake.

1.3. Indications

Symptomatic treatment of urge urinary incontinence and/or urinary frequency and urinary urgency in patients suffering from an overactive bladder.

1.4. Dosage

Adults, including elderly patients

The recommended dosage is 5 mg of solifenacin succinate in a single daily intake.

If necessary, this dose can be increased to 10 mg solifenacin succinate in a single daily intake.

Children and adolescents

Because the safety of use and of solifenacin have not yet been established for children, Vesicare 10 mg must not be prescribed for children.

Specific populations

Renal failure

No dosage adjustment is necessary in patients with mild to moderate renal failure (creatinine clearance > 30 mL/min). In patients with severe renal failure (creatinine clearance ≤ 30 mL/min), this medicinal product should be used with caution and a dosage of 5 mg in a single daily intake should not be exceeded.

Hepatic failure

No dosage adjustment is necessary in patients with mild hepatic failure. In patients with moderate hepatic failure (Child-Pugh score 7–9), the treatment should be used with caution and the dosage of 5 mg in a single daily intake should not be exceeded.

Method of administration

Vesicare 10 mg or Vesicare 5 mg tablets should be taken orally and swallowed whole with water, without chewing. Vesicare can be taken either with or between meals.

1.5. Pharmacodynamic or pharmacokinetic properties

Potent inhibitors of cytochrome P450 isoenzyme 3A4

The maximum dose of Vesicare 10 mg or Vesicare 5 mg should not exceed 5 mg if it is administered concomitantly with ketoconazole or other potent CYP 3A4 isoenzyme inhibitors used at therapeutic doses, e.g. ritonavir, nelfinavir, or itraconazole.

2 SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification

G : GENITO-URINARY SYSTEM AND SEX HORMONES
G04 : UROLOGICALS
G04B : OTHER UROLOGICAL PREPARATIONS, INCLUDING ANTISPASMODICS
G04BD : URINARY ANTISPASMODICS
G04BD08 : Solifenacin

2.2. Medicines in the same therapeutic category

2.2.1. Comparator drugs

- Ditropan (oxybutynin) 5 mg, scored tablet and its generics
- Ceris (trospium) 20 mg, coated tablet

On the market, as non-refundable products
- Detrusitol (tolterodine) 1 mg, film-coated tablet
- Detrusitol (tolterodine) 2 mg, film-coated tablet

2.2.2. Comparisons that have been carried out

Not applicable

2.3. Medicines with a similar therapeutic aim

These are the medicinal products referred to above.

3 ANALYSIS OF AVAILABLE DATA

The applicant submitted a dossier mainly consisting of:
- Four phase III trials, two of which have been published[1,2].
All four were multicentre randomised double-blind trials comparing the efficacy and safety of 2 doses (5 and 10 mg) of solifenacin with that of placebo in treating overactive bladder. One (Trial *905-CL-015*[1]) included an active comparator drug (tolterodine) at a dosage of 2 mg, twice daily.

- One active comparator-controlled trial (STAR[3] trial).
A double-blind trial comparing the efficacy and safety of solifenacin with that of tolterodine 4 mg LP.

- One study, combining the published data on anticholinergic drugs, compared the efficacy and safety of solifenacin, oxybutynin, tolterodine and trospium (unpublished study).

3.1. Efficacy

3.1.1. Placebo-controlled trials

Four 12-week phase III trials with a similar methodology, including a total of 3098 patients, compared the 5 mg and 10 mg doses of solifenacin with a placebo.

The inclusion criteria were: males or females over the age of 18 with symptoms of overactive bladder (including urgency, incontinence and urinary frequency) for more than 3 months. Patients with an average frequency of at least 8 voids a day after 2 weeks under a placebo, and who had experienced 3 episodes of urgency and/or 3 episodes of incontinence during the previous 3 days, were eligible for randomisation. Patients with detrusor hyperactivity of neurological origin were excluded from the trial.

The populations studied in each arm were comparable. The majority were female (80%), with a mean age of 58, years and an average of 10% of patients over the age of 75 years. The mean frequency of voiding was 12 times a day.

NB: According to published data, around 30% of patients with overactive bladder are over the age of 75 years[4].

Primary endpoint

Mean reduction in number of voids/24 h compared with baseline value at inclusion in the treatment arm.

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[1] Chapple CR *et al*. Randomized, double-blind placebo-and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder *BJU Int* 2004; 93: 303-310.

[2] 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

[3] Chapple CR *et al*; A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. *Eur Urol* 2005, (48); 464-470

[4] 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.

Secondary endpoints
- Reduction in number of urgency episodes per 24 hours
- Reduction in number of incontinence episodes per 24 hours
- Reduction in number of night-time voids per 24 hours
- Increase in volume voided/void
- Reduction in number of protective pads used per 24 hours
- Assessment of impact on patients' quality of life

Results concerning the primary endpoint

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

	Treatment Daily dose	Number of patients	Reduction in number of voids per 24 hours	Reduction in number of voids per day compared with placebo	P (vs. placebo)
Placebo arm	Placebo	1138	-1.4		
Solifenacin arm	5 mg	552	-2.3	-0.9	<0.001
	10 mg	1158	-2.7	-1.3	<0.001

The reduction in number of voids per day was significantly greater in the solifenacin arm at the dosages of 5 mg (Δ= -0.9, p<0.001) and 10 mg (Δ= -1.3, p<0.001) than in the placebo .

Results of trial *905-CL-015* including a tolterodine arm:

	Treatment Daily dose	Number of patients	Reduction in number of voids per 24 hours	Reduction in number of voids per day compared with placebo	P (vs. placebo)
Placebo Arm	Placebo	253	-1.2		
Solifenacin Arm	5 mg	266	-2.2	-1.0	<0.001
	10 mg	264	-2.6	-1.4	<0.001
Tolterodine Arm	2x2 mg	250	-1.9	-0.7	0.004

The reduction in the number of voids per day was significantly greater in the tolterodine arm at a dosage of 2 mg twice daily (Δ= -0.7, p=0.004) than in the placebo arm.

There was no significant difference in the efficacy of Vesicare® as a function of patient age or sex.

Results for the secondary endpoints

The secondary endpoints were significantly improved compared with placebo, except for night-time voiding.
For the secondary endpoint *"Reduction in number of incontinence episodes per 24 hours"*, 50% of patients receiving solifenacin 5 mg and 10 mg and 34% of patients receiving a placebo were continent at the end of the trial (p < 0.001).

Assessment of impact on quality of life

Quality of life was studied as a secondary endpoint in several clinical trials, using two validated and specific quality of life scales, **Contilife™** and the **King's Health Questionnaire**. These questionnaires are specific tools for urinary incontinence.

*Results for the **Contilife™questionnaire***

The Contilife questionnaire was used to assess quality of life during a phase II clinical trial. It assesses the impact of all types of urinary incontinence on quality of life according to 28 items divided into five domains (daily activities, effort, self-image, emotional consequences, and sexuality).

The results were:

Quality of life according to the 5 Contilife™ questionnaire domains

		Placebo	Vesicare®	
			5 mg	10 mg
Daily activities	**N**	35	35	30
	mean Δ %	**- 10**	**- 27**	**- 32**
	p*	-	S.	S.
Effort	**N**	35	35	30
	mean Δ %	**- 5**	**- 17**	**- 6**
	p*	-	N.S.	N.S.
Self image	**N**	35	35	30
	mean Δ %	**- 9**	**- 19**	**- 23**
	p*	-	N.S.	S.
Emotional consequences	**N**	36	35	30
	mean Δ %	**- 5**	**- 18**	**- 27**
	p*	-	S.	S.
Sexuality	**N**	36	35	30
	mean Δ %	**+ 4**	**- 6**	**- 8**
	p*	-	N.S.	S.

S.: significant, N.S.: not significant

Solifenacin 10 mg significantly improved daily activities, self image, emotional consequences and sexuality, compared with the placebo. At 5 mg, a significant improvement over placebo was only observed with respect to daily activities and emotional consequences.

*Results of the **King's Health Questionnaire**.*

Quality of life was assessed in 2 of the 4 preceding trials using a validated and specific quality of life scale, the KHQ (King's Health Questionnaire).

Ten domains were analysed. Weighted scores for each domain 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 regarded as the minimum relevant difference for the patient. The results were as follows:

Quality of life according to the 10 domains of the King's Health Questionnaire

King's Health Questionnaire Domain	**Results at 12 weeks**	
	Mean change (%) /baseline	**p** *(Solifenacin versus placebo)*
General health perceptions	-11	S.
Incontinence impact	-32	S.
Role limitations	-33	S.
Physical limitations	-29	S.
Social limitations	-31	S.
Personal relationship	-28	N. S.
Emotions	-33	S.
Sleep/energy	-25	S.
Severity of incontinence	-26	S.
Severity of urinary symptoms []	-28	S.

An improvement on the KHQ quality of life scale was observed in 9 out of 10 domains. Only the "Personal relationships" domain showed no improvement.

Maintaining efficacy

Two of the four placebo-controlled trials were extended (open-label trials) and showed that the effect was sustained for up to 40 weeks.

3.1.2. Active comparator-controlled trial (tolterodine)

A 12-week randomised double-blind active comparator-controlled trial (STAR trial) compared solifenacin with tolterodine. The aim was to compare the efficacy and safety of solifenacin under treatment with a flexible dose of 5 mg or 10 mg (2x5), with that of tolterodine 4 mg LP once daily.

However, tolterodine LP is not marketed in France at present.

The populations studied in each arm were comparable. The main characteristics were: higher proportion of females (approx. 87%), adult (mean age: 56 years) including elderly patients (on average, 6% of patients were aged 75 years or over), with a mean of 12 voids a day at inclusion.

Results of the STAR trial

1200 patients were treated and randomised (593 patients in the solifenacin arm, 607 in the tolterodine arm).
The ITT analysis included 1177 patients.
The per-protocol analysis included 1049 patients.

With respect to efficacy, the statistical analysis plan included an analysis of non-inferiority in the per-protocol population regarding the primary endpoint "number of voids per 24 hours". If non-inferiority were proven, a superiority analysis covering the ITT population was planned for all secondary criteria. The table below shows the results of these analyses.

The Committee noted that from the methodological point of view, the superiority analysis for secondary endpoints should be regarded as exploratory only.

STAR trial – Comparative analysis of primary efficacy endpoints.

	Solifenacin	***Tolterodine LP 4mg***	***p****	***Type of analysis***
Primary endpoint (per-protocol population)				
Number of patients	525	524		
Number of voids /24h at baseline Δ baseline/end of treatment	11.78 - 2.45	11.66 - 2.24	≤ 0.004	non-inf.
Secondary endpoints (ITT population)				
Number of patients	578	599		
Episodes of urgency/24 hours at baseline Δ baseline/end of treatment	6.01 - 2.85	5.84 - 2.42	0.035	Sup.
Episodes of incontinence/24 hours at baseline Δ baseline/end of treatment	2.77 - 1.60	2.55 - 1.11	0.006	Sup.
Urge incontinence/24 hours at baseline Δ baseline/end of treatment	2.31 - 1.42	2.12 - 0.83	0.001	Sup.
Night voids/24 hours at baseline Δ baseline/end of treatment	2.02 - 0.71	2.93 - 0.63	0.730	Sup.
No. of pads used/24 hours at baseline Δ baseline/end of treatment	3.25 - 1.72	2.93 - 1.19	0.002	Sup.
Volume voided/void at baseline Δ baseline/end of treatment	146.71 mL + 38 mL	145.13 mL + 31 mL	0.01	Sup.

** value of p for comparison with tolterodine 4 mg*

With respect to the primary endpoint, solifenacin was not shown to be inferior to tolterodine ($p \leq 0.004$).
The secondary endpoints were significantly improved by comparison with tolterodine, with the exception of night voiding.

3.2. Undesirable effects

Given its pharmacological effect, the undesirable effects of solifenacin are those of the class of anticholinergics.

The following table shows the safety results from the four phase III trials:

Safety results during the four controlled phase III trials: 12 weeks of treatment

	Placebo	**Vesicare®**	
		5 mg	**10 mg**
Number of patients	1216	578	1233
Adverse events (AE)	634 (52.1%)	265 (45.8%)	773 (62.7%)
Early withdrawal because of AEs	66 (5.4%)	21 (3.6%)	85 (6.9%)
AEs 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%)

Adverse events recorded during the 905-CL-015 trial including a tolterodine arm were:

	Placebo	**Vesicare®**		**Tolterodine**
		5 mg	**10 mg**	**2 x 2 mg**
N	267	279	268	263
Dry mouth (%)	13 (4.9%)	39 (14.0%)	57 (21.3%)	49 (18.6%)
Constipation (%)	5 (1.9%)	20 (7.2%)	21 (7.8%)	7 (2.6%)
Blurred vision (%)	7 (2.6%)	10 (3.6%)	15 (5.6%)	4 (1.5%)

The incidence of adverse events was shown to be dose-dependent. It was higher in the solifenacin 10 mg group.

Analysis by subgroup (< 65, ≥ 65 and ≥ 75 years) showed a greater incidence of adverse events (dry mouth, constipation, urinary infection, weakness) in patients aged over 65 and over 75 than in patients under 65.
No safety data are available for cognitive function.

Other available data

One study, combining published data on anticholinergics, compared the safety and efficacy of solifenacin, oxybutynin, tolterodine and trospium (unpublished study). It could not be used as a reference because of its insufficiently rigorous methodology. There was considerable heterogeneity regarding some of the endpoints (volume of urine voided, dry mouth, constipation, etc.), requiring the use of a random effects model to estimate the total effect with its confidence interval, but this was not performed.

A meta-analysis compared the undesirable effects of antimuscarinic treatments in overactive bladder[5]. This meta-analysis did not enable a conclusion that solifenacin caused fewer undesirable effects than other antimuscarinics.

The Committee regrets the fact that no direct comparison with oxybutynin or trospium is available.

No studies are available which compare solifenacin with other therapies for urge urinary incontinence (particularly behavioural therapies).

3.3. Conclusion

The reduction in number of voids per day was significantly greater in the solifenacin arm at dosages of 5 mg (Δ= -0.9, p<0.001) and 10 mg (Δ= -1.3, p<0.001) than in the placebo arm. The effect was modest, and similar to that of other drugs in the same class.
A positive impact on patients' quality of life was observed in the majority of domains assessed.

Undesirable effects were similar to those for antimuscarinics, without showing that Vesicare is better tolerated. The Committee regrets that the proportion of older patients in the studies presented was not more representative of the population with overactive bladder. No safety data are available on cognitive function.

Solifenacin was not shown to be inferior to tolterodine LP 4 mg ($p \leq 0.004$) in terms of reducing the number of voids per day. However, tolterodine LP is not marketed in France at present.
The Committee does not have access to any studies directly comparing solifenacin to any compound available in France, or to other forms of treatment for urge urinary incontinence (particularly behavioural therapies).

4 TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Overactive bladder is a condition leading to marked deterioration in quality of life, and may develop into a social handicap.
This is a symptomatic therapy.
The efficacy/ safety ratio is moderate.
These medicinal products are to be used in first-line therapy.
Other drug and non-drug therapies are available.

Overactive bladder constitutes a low public health burden.
The therapeutic need is only partially met, particularly in view of:
- the modest efficacy of anticholinergic drugs and their undesirable effects, which can lead to the discontinuation of treatment;
- the fact that non-drug alternatives cannot be envisaged in certain patients.

Vesicare constitutes a supplementary therapeutic method to manage overactive bladder. However, because it is also an anticholinergic drug, Vesicare does not in principle offer an additional response to the requirement for therapy.

[5] Chapple C, *et al*, The Effects of Antimuscarinic Treatments in Overactive Bladder: A Systematic Review and Meta-Analysis, European Urology 48 (2005) 5–26

On the basis of the data available, no additional impact on morbidity or quality of life at population level is anticipated for Vesicare compared with other anticholinergic therapies.
Consequently, in the current state of knowledge and in view of the other therapies currently available, it is not expected that Vesicare will benefit public health.

The actual benefit of these medicinal products is moderate.

4.2. Improvement in actual benefit

The Committee considers that Vesicare is an additional form of treatment but does not offer any improvement in actual benefit (IAB V) in the management of patients with overactive bladder.

4.3. Therapeutic use [6]

Urge urinary incontinence is characterised by an involuntary loss of urine preceded by an urgent and irresistible need to void, resulting in voiding that cannot be delayed. It is very often (but not always) associated with involuntary detrusor contraction, detrusor instability or bladder instability, revealed by urodynamic investigations.

Several forms of treatment are available for urge urinary incontinence.

Behavioural therapies (adjustment of liquid intake, bladder retraining, keeping a voiding diary) and pelvic floor exercises are recommended (grade C). These different methods can be combined in a retraining programme to inhibit bladder contractions. They can be proposed first-line in healthy, motivated patients with no cognitive problems.

Drug therapy with an anticholinergic agent can also be used as first-line therapy or following the failure of behavioural treatment or retraining (grade B) It is prescribed:

- after urinary infection and urinary retention have been ruled out;
- if there are no contraindications to the use of anticholinergics and provided that the patient is not already being treated with a cholinesterase inhibitor.

It may be combined with keeping a voiding diary and with retraining measures (spacing of drinks during the day, changing the times at which diuretic drugs are taken).

4.4. Target population

The target population is all adult patients with overactive bladder.
According to a European study[7] (in Germany, France, UK, Italy, Sweden and Spain), the mean prevalence of overactive bladder is 16.6% of the population over the age of 40. In France, prevalence in this population is thought to be 12%, i.e. around 3.4 million people affected.
60% of affected patients see their doctor for this reason, i.e. around 2 million patients.
At the time of the European cross-section study, only 27% of patients who had been treated were being treated with drug therapy.
Applying these results to the population in France, the population likely to be given drug therapy for overactive bladder would be around 556,000 patients.

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[6] Agence Nationale d'Accréditation et d'Evaluation en Santé. *Prise en charge de l'incontinence urinaire de la femme en médecine générale* (Management of female urinary incontinence in general practice), Professional Guidelines Department, May 2003; 136 p.

[7] 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.

4.5. Transparency Committee recommendations

The Committee recommends inclusion on the list of medicinal products reimbursed by National Insurance and approved for use by institutions and various public services in the indication and at the dosages specified in the Marketing Authorisation.

Packaging: Appropriate for the conditions under which it is prescribed
Reimbursement rate: 35%