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TRANSPARENCY COMMITTEE

Opinion
26 June 2013

VESICARE 5 mg, film-coated tablet

B/30 (CIP: 34009 365 515-0 3)

VESICARE 10 mg, film-coated tablet

B/30 (CIP: 34009 365 516-7 1)

Applicant: ASTELLAS PHARMA SAS

INN	solifenacin succinate
ATC code (2013)	G04BD08 (urinary antispasmodic)

Reason for the review	Re-assessment of the actual benefit, the improvement in actual benefit and the target population for all anticholinergic drugs indicated for the treatment of urinary incontinence following the submission to the CEPS pursuant to Article R-163-19 of the French Social Security Code.
Lists concerned	National Health Insurance (French Social Security Code L.162-17) Hospital use (French Public Health Code L.5123-2)
Indication concerned	"Symptomatic treatment of urge incontinence and/or increased urinary frequency and urge as may occur in patients with overactive bladder syndrome."¹

¹ Definitions:

Overactive bladder: clinical syndrome characterised by urge, with or without incontinence, most often associated with increased urinary frequency and nocturia with no obvious urinary tract infection or local organic pathology likely to cause these symptoms.

Increased urinary frequency: increase in the frequency of urination (generally urinating ≥ 8 times over a 24-hour period).

Urge incontinence (formerly urge): sudden, urgent and frequently irrepressible desire to urinate.

Urinary incontinence: sudden and involuntary loss of urine.

Actual Benefit	The actual benefit remains moderate in the symptomatic treatment of urge incontinence and/or urinary frequency and urinary urge in adult patients with overactive bladder.
Improvement Actual Benefit	in IAB IV in terms of safety compared to DITROPAN in the symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge in adult patients with overactive bladder.
Therapeutic use	Treatment option for the management of increased urinary frequency and/or urinary urge and/or urge incontinence in patients suffering from overactive bladder (see section 10: Therapeutic use).
Recommendations	-

ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	<u>Date of Marketing Authorisation:</u> 16 August 2004 (mutual recognition procedure)
Prescribing and dispensing conditions/ special status	List II

TRANSPARENCY COMMITTEE

Assessment report
26 June 2013

01 BACKGROUND AND PURPOSE OF THE RE-ASSESSMENT

The Transparency Committee (TC) of HAS assesses medicinal products that have obtained a Marketing Authorisation when the company marketing them wishes them to be included on the list of medicines refundable by National Health Insurance (articles L.162-17 of the French Social Security Code and L.5123-2 of the French Public Health Code) or on request.

The TC is a scientific body comprised of medical practitioners, pharmacists and specialists in methodology and epidemiology.

Its objectives are:

- to provide an opinion to ministers responsible for health and social security on the justification for reimbursement of medicinal products by social security and/or for their use in hospitals, with particular regard to their actual benefit (AB) and to the improvement in actual benefit (IAB) they are likely to offer over treatments that are already available;
- to contribute to the proper use of medicinal products by publishing relevant, independent scientific information on the products.

These objectives are defined in the French Social Security Code, in particular in articles R.163-2 to R.163-21, L.161-37, L.161-39 and L.161-41.

According to articles L. 162-17, L. 161-37, L.161-39, L. 161-41, L. 161-44, R. 163-2 to R. 163-21, R. 161-71, R. 161-76, R. 161-85 of the French Social Security Code and articles L. 5123-2 and L. 5123-3 of the French Public Health Code, the opinions of the TC specify the actual benefit and improvement in actual benefit provided by the medicinal products.

This assessment is performed on the basis of a critical analysis of available scientific data on the basis of evidence-based medicine and the opinion of experts, in accordance with indications and dosages from the Marketing Authorisation.

01.1 Background and reason for request

The CEPS, giving "special attention to the elements that can justify a price differentiation (daily cost of treatment)," in a letter dated 12 November 2012, called upon the Transparency Committee (TC) to carry out a new assessment of all the anticholinergic drugs pursuant to article R. 163-19 of the French Social Security Code.

This re-assessment only relates to the proprietary medicinal products indicated in the symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge in adult patients with overactive bladder.

A letter requesting submission of the re-assessment file by the companies was sent on 30 November 2012. These files were received at the beginning of February 2013 by the HAS Medicinal Product Assessment Department (SEM).

01.2 The proprietary medicinal products involved

In France, four anticholinergic (or antimuscarinic) proprietary medicinal products indicated in *"the symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge observed in patients suffering from overactive bladder"* are marketed. They are proprietary medicinal products DITROPAN, CERIS, VESICARE and DETRUSITOL (the only proprietary medicinal product not refundable).

Below is a table summarising the conclusions of assessments carried out by the Transparency Committee (TC) and the current conditions of reimbursement by health insurance.

01.3 Background for assessment by the TC

In 2006, when the proprietary medicinal product VESICARE was first examined by the TC (when this proprietary medicinal product had been marketed but not refundable since October 2004), an IAB level V was granted in the management of patients with overactive bladder. In 2009, based on new data submitted by the company, the TC granted VESICARE an IAB level IV in terms of safety compared to DITROPAN in patients with overactive bladder. A Good Use Guide was published.

This IAB for VESICARE having been granted, ROTTAPHARM submitted an IAB re-assessment file in April 2010 for their proprietary medicinal product CERIS (when CERIS was included on the list in 1999, the TC had granted an IAB level V compared to DITROPAN - see TC opinion of 20 October 1999).

The effect size of all anticholinergic drugs in the treatment of urinary incontinence is modest (reduction of about one urination per day compared to a placebo).

In its assessment, the Committee did not have any study directly comparing solifenacin (VESICARE), trospium chloride (CERIS) or fesoterodine (TOVIAZ) with another medical treatment. It was not able to recommend any one over another.

A meta-analysis, which compared the safety of antimuscarinic treatments in overactive bladder,^{2,3} suggests better safety of solifenacin compared to oxybutynin. This is not the case for trospium chloride or for fesoterodine, for which no difference was observed concerning discontinuation of treatment due to adverse effects during randomised placebo-controlled studies.

It should be noted that oxybutynin has a poor safety profile (mainly dry mouth, constipation, cognitive disorders etc.).

However, based on clinical experience, the proprietary medicinal products CERIS and VESICARE seem to have a better safety profile than DITROPAN.

² Chapple C, et al. The Effects of Antimuscarinic Treatments in Overactive Bladder: A Systematic Review and Meta-Analysis. European Urology 2005; 48: 873-4

³ 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

Table 1:

INN	Name (Company)	Date of opinion	AB	IAB (Wording)	Target population	Reimbursement
oxybutynin	DITROPAN (SANOFI AVENTIS)	18 March 2009 Renewal of inclusion	moderate			Included on the lists since 15/09/1985 Reimbursement rate: 30% Price B/60 for 1 month of treatment: 4.90 € Daily cost of treatment = 0.16 to 0.24 €
solifenacin	VESICARE (ASTELLAS)	15 February 2006 Inclusion on list of products refundable by National Health Insurance and approved for hospital use	moderate	Additional therapeutic means, IAB V in the management of patients with overactive bladder	556,000 patients	
solifenacin	VESICARE (ASTELLAS)	07 October 2009 Inclusion on list of products refundable by National Health Insurance and approved for hospital use	moderate	The Committee does not have any study comparing solifenacin with treatments which are available and currently refundable in France. However, based on the data in the literature and clinical experience, solifenacin seems to have a better safety profile than oxybutynin (DITROPAN). As a result, the TC considers that VESICARE provides a minor improvement in actual benefit (IAB IV) compared to DITROPAN as far as safety is concerned in patients with overactive bladder.	617,000 patients	Included on the lists since 24/07/2010 Reimbursement rate: 30% Price B/30 for 1 month of treatment: 35.40 € Daily cost of treatment = 1.18 €
tropium	CERIS (ROTTAPHARM)	05 January 2011 Re-assessment of the IAB at the company's request	moderate	Since the Transparency Committee's last re-assessment, there have been no data to conclude that tropium chloride (CERIS) has superior efficacy and/or better safety compared to solifenacin (VESICARE). As a result, the Transparency Committee considers that CERIS does not provide any improvement in actual benefit (IAB V) compared to VESICARE in patients with overactive bladder.	625,000 patients	Included on the lists since 21/05/2003 Reimbursement rate: 30% Price for 1 month of treatment: 9.80 € Daily cost of treatment = 0.32 € <i>NB: despite the opinion of the TC, the price of CERIS has remained more or less the same since its inclusion</i>
fesoterodine	TOVIAZ (PFIZER)	15 February 2012 Inclusion on list of products refundable by National Health Insurance and approved for hospital use	moderate	In the absence of any study comparing fesoterodine with medicinal products which are available and refundable and therefore any data allowing the conclusion to be made that fesoterodine (TOVIAZ) has superior efficacy and/or better safety, the Transparency Committee considers that TOVIAZ does not provide any improvement in actual benefit (IAB V) compared to the treatments available (CERIS and VESICARE) in the management of symptomatic treatment for overactive bladder.	640,000 patients	Not yet included on the list
tolterodine	DETRUSITOL (PFIZER)	Not applicable				Marketed at free price, not refundable

The list of proprietary medicinal products involved in the re-assessment appears in Table 2 below. The indications, the results of the studies available at inclusion or the last assessment by the TC and the AB and IAB levels attributed by the TC are specified there.

See table in Appendix 1 for the dosages and the main warnings and precautions for use

Table 2: assessment of efficacy by the Committee

Proprietary medicinal product	INN	Indication in Marketing Authorisation (Date of Marketing Authorisation)	Results of the studies supplied by the Committee on <u>the primary efficacy endpoint for a mutual decision on the 3 proprietary medicinal products</u> : variation in the average number of urinations over a 24-hour period	Conclusions of the Committee (AB, IAB, Date of the opinion)
VESICARE	solifenacin	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge as may occur in patients with overactive bladder syndrome. (Date of Marketing Authorisation by mutual recognition: 16 August 2004)	Four phase III trials with a similar methodology, including a total of 3,098 patients, compared doses of 5 mg and 10 mg of solifenacin versus placebo over a period of 12 weeks. The reduction in the number of daily urinations was significantly higher in the solifenacin group with dosages of 5 mg (difference of -0.9, p<0.001) and 10 mg (difference of -1.3, p<0.001) than in the placebo group (average number of daily urinations at baseline = 12). In the sub-group of patients ≥ 65 years of age: mean difference in the solifenacin 5 mg group compared to the placebo one: -1.00 [-1.4; -0.6], p<0.001 mean difference in the solifenacin 10 mg group compared to the placebo one: -1.42 [-1.7; -1.1], p<0.001.	<u>Opinion of the TC of 07 October 2009:</u> (Inclusion on list of products refundable by National Health Insurance and approved for hospital use) Modest efficacy/adverse effects ratio <u>moderate AB</u> The Committee does not have any study comparing solifenacin with treatments which are available and currently refundable in France. However, based on the data in the literature and clinical experience, solifenacin seems to have a better safety profile than oxybutynin (DITROPAN). As a result, the Transparency Committee considers that VESICARE provides a minor improvement in actual benefit (<u>IAB IV</u>) in terms of safety compared to <u>DITROPAN</u> in patients with overactive bladder.
CERIS	tropium chloride	Symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge as may occur in patients with overactive bladder syndrome (for example idiopathic or neurogenic detrusor overactivity). (Date of National Marketing Authorisation: 28 June 1999)	Randomised, double-blind Halaska study comparing the efficacy and safety of trospium chloride to that of oxybutynin administered in dosages of 5 mg twice daily over a period of 52 weeks in 357 patients.	<u>Opinion of the TC of 05 January 2011:</u> (re-assessment of the IAB) Modest efficacy/adverse effects ratio <u>moderate AB</u>

Proprietary medicinal product	INN	Indication in Marketing Authorisation (Date of Marketing Authorisation)	Results of the studies supplied by the Committee on <u>the primary efficacy endpoint for a mutual decision on the 3 proprietary medicinal products: variation in the average number of urinations over a 24-hour period</u>	Conclusions of the Committee (AB, IAB, Date of the opinion)
			No hypothesis formed. No endpoint defined. Descriptive analysis of efficacy and safety. <u>Result for information:</u> reduction of 3.5 urinations over a 24-hour period for trospium chloride and 4.2 for oxybutynin (number of urinations over a 24 hour period at baseline: 11.4 in the trospium group and 12.5 in the oxybutynin group.)	Since the Transparency Committee's last re-assessment, there have been no data to conclude that trospium chloride (CERIS) has superior efficacy and/or better safety compared to solifenacin (VESICARE). As a result, the Transparency Committee considers that CERIS does not provide any improvement in actual benefit (IAB V) compared to VESICARE in patients with overactive bladder.
TOVIAZ	fesoterodine	Treatment of the symptoms (increased urinary frequency and/or urinary urge and/or urge incontinence) that may occur in patients with overactive bladder syndrome. (Date of Centralised Marketing Authorisation: 20 April 2007)	Two phase III, randomised, double blind studies compared fesoterodine (4 mg/day and 8 mg/day) with a placebo and tolterodine in 1,964 patients over a period of 12 weeks. difference in the fesoterodine 4 mg/d group compared to the placebo: <u>-0.81 95% CI [-1.26; -0.36] p<0.001</u> in the SP583 study, <u>-0.53 95% CI [-1.02; -0.04] p=0.032</u> in the SP584 study. difference in the fesoterodine 8 mg/d group compared to the placebo: <u>-0.93 95% CI [-1.38; -0.49] p<0.001</u> in the SP583 study, <u>-1.01 95% CI [-1.50; -0.52] p<0.001</u> in the SP584 study. average number of daily urinations = 12	<u>Opinion of the TC of 15 February 2012:</u> (Inclusion on list of products refundable by National Health Insurance and approved for hospital use) Modest efficacy/adverse effects ratio <u>moderate AB</u> In the absence of any study comparing fesoterodine with available and refundable medicinal products and therefore any data to conclude that fesoterodine (TOVIAZ) has superior efficacy and/or better safety, the Transparency Committee considers that TOVIAZ does not provide any improvement in actual benefit (IAB V) compared to the available treatments (CERIS and VESICARE) in the management of symptomatic treatment for overactive bladder.

The proprietary medicinal product DITROPAN does not appear in this table as its initial assessment is very old. The last opinion concerning renewal of inclusion dated 18 March 2009 does not support any clinical data. The Committee maintained the inclusion of this proprietary medicinal product with a moderate AB.

Reminder of the main results of the meta-analysis by Chapple **Erreur ! Signet non défini.**, evaluating the safety of anticholinergic drugs based on previous assessments performed by the TC:

Table 3: tolerability of adverse effects, discontinuation of anticholinergic treatment compared to a placebo

	tropium 40 mg/d vs placebo	solifenacin 5 mg/d vs placebo	solifenacin 10 mg/d vs placebo	fesoterodine 4 mg/d vs placebo	fesoterodine 8 mg/d vs placebo	oxybutynin 7.5-10 mg/d vs placebo	oxybutynin 15 mg/d vs placebo
Any adverse effect	RR=1.30	RR=1.23	RR=1.32	RR=1.31	RR=1.54	RR=1.72	RR=1.29
	[1.15;1.45]	[1.10;1.37]	[1.06;1.66]	[1.08;1.59]	[1.29;1.84]	[1.38;2.14]	[1.19;1.40]
	p<0.01	p<0.01	p=0.02	p=0.01	p<0.01	p<0.01	p<0.01
	N=1409	N=1230	N=488	N=555	N=570	N=289	N=748
Dry mouth (any severity)	RR=3.17	RR=3.32	RR=5.90	RR=3.01	RR=3.95	RR=2.96	RR=4.42
	[2.37;4.24]	[2.55;4.32]	[4.59;7.59]	[2.17;4.20]	[2.87;5.44]	[2.46;3.55]	[3.53;5.53]
	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01	p<0.01
	N=1389	N=3691	N=2951	N=1010	N=1016	N=923	N=1006
Discontinua- tion of treatment because of adverse effect	RR=1.27	RR=1.16	RR=1.53	RR=1.4	RR=1.33	RR=1.91	RR=1.89
	[0.86;1.88]	[0.79;1.72]	[1.02;2.3]	[0.69;2.82]	[0.65;2.71]	[1.18;3.1]	[1.23;2.9]
	p NS	p NS	p=0.04	p NS	p NS	p=0.01	p<0.01
	N=1490	N=3575	N=2689	N=926	N=929	N=488	N=743

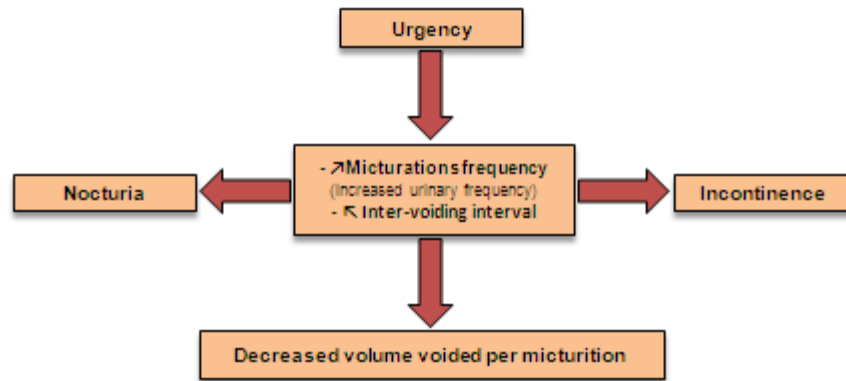
1st line: effect size (RR); 2nd line: 95% CI; 3rd line: p-value (vs null hypothesis; RR=1); 4th line: number of patients included in the meta-analysis.

The TC's conclusion was the following: "The meta-analysis by Chapple, which compared the safety of antimuscarinic treatments in overactive bladder, suggests better safety of solifenacin compared to oxybutynin. This is not the case for tropium chloride or for fesoterodine, for which no difference was observed concerning discontinuation of treatment due to adverse effects during randomised placebo-controlled studies. It should be noted that oxybutynin has a poor safety profile (mainly dry mouth, constipation, cognitive disorders etc.) for all its efficacy."

02 THERAPEUTIC NEED

Overactive bladder is a clinical syndrome characterised by an irrepressible need to urinate (urge) with or without incontinence, most often associated with increased urinary frequency and nocturia with no obvious urinary tract infection or local organic pathology likely to cause these symptoms. Among the symptoms of overactive bladder, urge is the pivotal symptom as it constitutes the trigger for any other associated symptoms:

Figure 1: Schematic diagram of overactive bladder syndrome (Chapple 2005)



The risk factors for overactive bladder include age, a history of one or more pregnancies, a history of vaginal birth and gynaeco-obstetric traumas, a history of pelvic or abdominal surgery, obesity, intensive physical activity and bed-wetting in childhood.

Several therapeutic means are available to treat urge incontinence.^{4, 5}

Behavioural treatments (adjustment of fluid intake, reprogramming of voiding, keeping a voiding calendar) and pelvic floor rehabilitation are recommended (grade C). These different methods can be combined to achieve rehabilitation to inhibit bladder contractions. They can be offered as first line treatment.

Behavioural treatments, pelvic floor rehabilitation and functional electrostimulation, surgery (sacral nerve stimulation in the event of resistance to drug treatment) and palliative treatments (protectors, urine collection devices, urinary catheter, penile sheaths etc.) can also be considered as alternatives to drug treatments for urinary incontinence.

Anticholinergic drug treatment can also be offered as first line treatment or after the failure of behavioural and/or rehabilitation treatment (grade B). In a recent meta-analysis,⁶ an improvement in urinary incontinence symptoms was observed when the anticholinergic drugs were combined with rehabilitation compared to rehabilitation alone (RR of symptom improvement=0.55 95% CI [0.32; 0.93]).

Anticholinergic treatment is only prescribed:

- after ruling out a diagnosis of urinary tract infection or urinary retention;
- if there are no contraindications for the use of anticholinergic drugs and if there is no anticholinesterase treatment already underway.

Oxybutynin or tolterodine or trospium chloride are recommended (grade B). They showed moderate efficacy, but were significantly superior to a placebo in removing or relieving urge incontinence (average reduction of approximately 1 urinary incontinence episode every 48 hours).

⁴ Agence Nationale d'Accréditation et d'Evaluation en Santé. Prise en charge de l'incontinence urinaire de la femme en médecine générale. Services des recommandations professionnelles May 2003; 136 p.

⁵ 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). April 2007

⁶ A.A. Alhasso et al. Anticholinergic drugs versus non-drug active therapies for overactive bladder syndrome in adults. Cochrane Review 2009.

It is likely that tolterodine and trospium chloride are better tolerated than oxybutynin but this likelihood is not supported by sufficiently robust data in methodology.

Taking into account the risk of urinary retention associated with anticholinergic drugs (oxybutynin, tolterodine and trospium chloride), monitoring the occurrence of a distended bladder, particularly in vulnerable elderly patients, is recommended. If anticholinergic treatment is considered, the patients must be warned of the side effects (dry mouth, constipation, cognitive disorders), how long it takes for maximum effectiveness to occur (which may be up to 5 to 8 weeks) and the need for consultation if there is no effectiveness after this period (particularly if it is "trial" anticholinergic treatment prescribed without any prior urodynamic testing) or in the event of a urinary tract infection or difficulties in urinating.

These guidelines prior to the Marketing Authorisation of TOVIAZ and VESICARE do not therefore cite fesoterodine and solifenacin as treatment for overactive bladder.

The Committee considered that the proprietary medicinal products VESICARE, CERIS and TOVIAZ constituted a therapeutic option in the treatment of increased urinary frequency and/or urinary urge and/or urge incontinence in patients suffering from overactive bladder.

The latest guidelines from Canada⁷ and the US⁸ support the previous guidelines: all the anticholinergic drugs have similar efficacy and immediate-release oxybutynin generates more adverse effects than the other anticholinergic drugs.

According to the authors of a recent meta-analysis,⁹ the main disadvantage of anticholinergic drugs is their safety profile, dry mouth being the effect most commonly observed (in approximately 30% of patients receiving anticholinergic drugs). The most recent anticholinergic drugs (trospium, solifenacin, fesoterodine) have fewer adverse effects in comparison to the old ones (i.e. oxybutynin).

Around the world there are nine anticholinergic drugs (in the form of immediate- or extended-release, administered orally or transdermally), but only three immediate-release drugs and one extended-release drug are available and refundable in France.

According to the authors of a meta-analysis,¹⁰ the extended-release formulations should be preferred over immediate-release formulations given their better safety profile (reduction in adverse effects).

According to the latest guidelines from the European Association of Urology,¹¹ there are no data proving that one anticholinergic drug is superior to another in terms of improvement in the symptoms of urinary incontinence and quality of life, nor is it certain that they are superior to a behavioural treatment. However, the combination of therapy and anticholinergic drugs may be beneficial.

⁷ Traitements visant la vessie hyperactive : accent sur la pharmacothérapie. Directive clinique de la société des obstétriciens et gynécologues du Canada. J Obstet Gynaecol Can 2012; 34: S1-S12

⁸ E.A. Gormley et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: American Urological Association Guideline. 2012

⁹ C. Roxburgh et al. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. Cochrane Review 2009.

¹⁰ Novara G, Galfano A, Secco S et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol. 2008; 54: 740-63. Epub 2008 Jul 9.

¹¹ M.G. Lucas et al. EAU European Association of Urology Guidelines on assessment and nonsurgical management of urinary incontinence. Eur Urol 2012; 4179: 1-13

03 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCTS

Proprietary medicinal products	Country	REIMBURSEMENT	
		YES/NO If no, why not	Population(s) That of the Marketing Authorisation or restricted
DITROPAN	15 countries in the European Union (including Spain, Germany and Italy)	Yes	That of the MA
CERIS	Germany, Great Britain, Austria, Spain, Denmark, United States	Yes	That of the MA
	Canada	Yes (100% in all the provinces except Ontario where it is not refundable)	after the failure of oxybutynin
VESICARE	Netherlands	Yes 10 mg: 100% 5 mg: 76%	That of the MA
	UK	Yes	As second line treatment after oxybutynin
	Scotland	Yes	Recommended after the failure of cheaper anticholinergic drugs
	Italy	No	
	Spain, Germany, Belgium, Sweden	Yes	That of the MA
TOVIAZ	Italy	No	
	Germany, Great Britain, Spain	Yes	That of the MA

04 LITERATURE SEARCH

04.1 Bibliographical research by HAS: strategy and results of the literature search

A systematic literature search was conducted from January 1984 (date of the Marketing Authorisation of DITROPAN) to November 2012 using a medical bibliographical database query:

- Medline (National Library of Medicine, United States);
- The Cochrane Library (Wiley Interscience, United States);
- BDSP (Banque de Données en Santé Publique - Public Health Database);
- Internet sites publishing guidelines and technological or economic assessment reports;
- Internet sites of learned societies relevant to the field being studied;
- Specialised sources in particular epidemiology and economy.

The search was limited to publications in English and French. Observation was carried out until May 2013.

Technological assessments, guidelines, consensus conferences, meta-analyses, systematic reviews, randomised controlled trials (or non-randomised non-controlled trials) and comparative studies were sought out.

The research strategy and the list of sources queried are detailed in Appendix 2.

The quantitative results of this research were:

Number of unique references identified: 1,332
Number of references used and analysed: 40

04.2 Criteria for selecting studies - Comments

The majority of data retrieved in the literature concerned studies already assessed by the Committee (these studies having been the subject of numerous publications with sub-group analyses or *post-hoc* analyses), observational studies conducted on very small populations, studies with active substances not available in France. Among the studies, the systematic reviews and the meta-analyses found in the literature, those performed in accordance with the Marketing Authorisation and of a good level of evidence are presented in this document as well as new data from records filed by the companies.

A critical reading of these studies was undertaken so as to retain only those data which appeared after the last opinion issued by the Committee, along with meta-analyses, systematic reviews of good-quality methodology and studies with a high level of evidence (phase III, randomised, comparative studies evaluating clinical endpoints) conducted within the indications and at the dosages recommended by the Marketing Authorisation for the various proprietary medicinal products and depending on the context of re-assessment.

The results of the studies and the meta-analysis by Chapple previously assessed by the TC are summarised in Tables 2 and 3.

Thus, the pooled or *post-hoc* analyses previously submitted and assessed by the TC were not used. The same applies to the studies:

- evaluating pharmaceutical forms, dosages, proprietary medicinal products not existing in France and not refundable (*example*: tolterodine, oxybutynin as a extended release tablet or as a patch, etc.)
- evaluating dosing schedules which are different from those from the Marketing Authorisations granted in France for the various anticholinergic drugs
- off-label (evaluation of associations)
- in hyperactivity of neurological origin
- which are pharmacological
- which are observational and performed in other countries (problem of extrapolating the data)
- with methodological weaknesses (small population <100 patients, open study, *post-hoc* analysis, pooled analyses etc.).

An audit of the exhaustive account of all the individual studies, both provided by the companies and from the bibliographical research by HAS, was performed in the available and used meta-analyses.

04.3 Data submitted by the pharmaceutical companies

The licence holding companies were called upon to provide HAS with all the clinical evidence to re-assess the AB, the IAB and the target population of all the anticholinergic drugs refundable by health insurance and approved for hospital use.

In the case of DITROPAN, the company has not provided a new clinical study but two meta-analyses [were] found in the bibliographical research by HAS.

In the case of CERIS, the company has provided:

- Six clinical studies (one¹² already examined by the TC, one¹³ off-label dosage, four^{14,15,16,17} included in the meta-analyses used and described in this document)
- Five meta-analyses described below including that of Chapple already known by the TC.

In the case of VESICARE, the company has provided:

- Three studies which cannot be used: the SENIOR¹⁸ safety study including only 24 patients; the SONIC unpublished study evaluating the detrusor overactivity of neurogenic origin (off label); a study¹⁹ analysing the prescribing data from a British database (not used because non-transposable);
- Three observational studies, VESTALE, VEGA and E-CARE (this last one being a post-inclusion study requested by the CEPS, the protocol of which was not validated in advance by HAS)
- Four meta-analyses identical to those identified by HAS.

In the case of TOVIAZ, the (unpublished) studies filed by the company cannot be used. They are two randomised, double blind placebo-controlled clinical studies (1049 study and Weiss study) that evaluated the efficacy and safety of variable doses of fesoterodine according to the dosage schedule which is different from that of the Marketing Authorisation; a phase I study (1086 study) that pharmacologically evaluated the effects of fesoterodine on the cognitive function of healthy elderly people; and an open study (SAFINA) that evaluated the efficacy and safety of variable doses of fesoterodine in British patients (problem of extrapolating data).

¹² Halaska M, et al. Controlled, double-blind, multicentre clinical trial to investigate long-term tolerability and efficacy of trospium chloride in patients with detrusor instability. *World J Urol* 2003; 20: 392-399.

¹³ Zellner M, Madersbacher H, Palmtag H, Stohrer M, Bodeker R-H, and the P195 Study Group. Trospium Chloride and Oxybutynin Hydrochloride in a German Study of Adults With Urinary Urge Incontinence: Results of a 12-Week, Multicenter, Randomized, Double-Blind, Parallel-Group, Flexible-Dose Noninferiority Trial. *Clinical Therapeutics*/Volume 31, Number 11, 2009.

¹⁴ Zinner N, Gittelman M, Harris R, Susset J, Kanelos A, Auerbach S; Trospium Study Group. Trospium chloride improves overactive bladder symptoms: a multicenter phase III trial. *J Urol* 2004; 171(6 Pt 1): 2311-2315.

¹⁵ Cardozo L, Chapple C. R., Toozs-Hobson M., Bulitta M., Lehmacher W., Strösser W., Ballering-Brühl B. and Schäfer M. Efficacy of trospium chloride in patients with detrusor instability: a placebo-controlled, randomized, double-blind, multicentre clinical trial. *BJU International* 2000; 85: 659-664.

¹⁶ Alloussi S. et al. (1999) Trospium chloride (Spasmo-lyt) in patients with motor urge syndrome (detrusor instability): a double-blind, randomized, multimember, placebo controlled study. *J. of Drug Assessment* 1999; 2: 1-9.

¹⁷ Rudy D et al. Multicenter phase III trial studying trospium chloride in patients with overactive bladder. *Urology* 2006; 67: 275-280.

¹⁸ Wagg D et al. Randomised, multicenter, placebo-controlled, double-blind crossover study investigating the effect of solifenacin and oxybutynin in elderly people with mild cognitive impairment: the SENIOR study. *European Urology* 2013; 64(1): 74-81

¹⁹ A. Wagg et al. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. *BJU Int* 2012; 110: 1767-74

05 CLINICAL DATA ON EFFICACY

05.1 Clinical studies

All the clinical studies, provided by the companies and from the bibliographical research by HAS, meeting the selection criteria used, were included in the meta-analyses available and used and described below.

As a reminder, the data previously provided to the TC are summarised in Table 2.

05.2 Meta-analyses and systematic reviews

05.2.1. Meta-analysis by Novara²⁰ (2008)

The objective of this meta-analysis was to evaluate the efficacy and safety of seven anticholinergic treatments used in the treatment of overactive bladder: oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin and fesoterodine.

The meta-analysis comprised two parts: one comparing the different dosages and forms of release for the same anticholinergic drug and the other comparing the anticholinergic drugs between themselves. The first part will not be described as the data are, for the most part, from studies which led to the granting of Marketing Authorisation or are known by the TC.

An exhaustive search of the data was performed. Among the 1,657 references identified, 53 articles were included in this meta-analysis (50 randomised, controlled trials, 3 pooled analyses).

After the analysis and taking into account the treatments authorised and refundable in France, the only comparison that can be used is that of oxybutynin with trospium chloride in a single study, the Halaska study, already evaluated by the TC (see Table 2).

05.2.2. Meta-analysis by Nabi²¹ (2009)

The objective of this meta-analysis was to evaluate the efficacy and safety of nine anticholinergic treatments used in the treatment of overactive bladder: oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin, emepronium bromide, emepronium carrageenan and propantheline versus a placebo.

It included 61 trials of a total of 11,956 patients: 7,888 in the active treatment group, 4,134 in the placebo group. An exhaustive search was performed. The average duration of treatment was 3 to 12 weeks.

The evaluation criteria were multiple. There are no individual results per drug relating to efficacy.

A cure for or improvement in symptoms was observed in 56% of patients receiving active treatment and 41% receiving the placebo, RR versus placebo = 1.39 95% CI [1.28; 1.51] p<0.05 (heterogeneity test NS, N=2,742 patients, involving 8 studies).

The difference observed in patients receiving anticholinergic drugs versus the placebo:

- in terms of urinary leakages/24 hours was -0.54 95% CI [-0.67; 0.41] p<0.05 (heterogeneity test NS, N=4,582 patients, 12 studies)
- in terms of incontinence episodes/24 hours was -0.69 95% CI [0.84; -0.54] p<0.05 (heterogeneity test NS, N=5,977 patients, 12 studies).

The authors conclude an improvement in the symptoms of urinary incontinence compared to the placebo, but this efficacy must be compared with the safety profile (see Section 06. Adverse effects). They underline the existence of a non-negligible placebo effect and a modest improvement in quality of life.

²⁰ Novara G, Galfano A, Secco S et al. A systematic review and meta-analysis of randomized controlled trials with antimuscarinic drugs for overactive bladder. Eur Urol 2008; 54: 740-63. Epub 2008 Jul 9.

²¹ Nabi G et al. Anticholinergic drugs versus placebo for overactive bladder syndrome in adults. Cochrane Review 2009

05.2.3. Meta-analysis by Madhuvrata²² (2012)

The objective of this meta-analysis was to compare the therapeutic effect and the safety profile of different anticholinergic drugs (including oxybutynin, tolterodine, propiverine, trospium and solifenacin) indicated in the treatment of overactive bladder symptoms.

Among the studies selected, only the randomised studies either comparing different dosages or different formulations of the same drug, or different anticholinergic drugs compared to each other, were used, that is 86 trials including a total of 31,249 patients.

The primary efficacy endpoint was specific quality of life, measured by the incontinence impact questionnaire, the overall quality of life measured by the SF36 questionnaire and the psychosocial evaluations.

The main secondary endpoints were:

- a score based on the assessment of the patient (symptom score, perception of improvement or cure, and satisfaction vis-à-vis the treatment),
- quantification of symptoms (number of incontinence episodes, frequency of urination, number of episodes of urinary urge, void volume).
- adverse events, measurement of adherence to treatment, long-term follow up.

Only the results comparing the efficacy of immediate-release oxybutynin with those of the drugs approved and refundable in France (trospium chloride and solifenacin) are presented.

- Comparison of the efficacy data between oxybutynin and trospium chloride

Four studies were used.

As regards the primary efficacy endpoint, quality of life, no difference was observed between oxybutynin and trospium.

As regards the secondary endpoints, no difference was observed regarding the score based on the assessment of the patient and the evaluation of symptoms of urinary incontinence.

- Comparison of the efficacy data between oxybutynin and solifenacin

Only a trial comparing an oral treatment of 5 mg solifenacin with an oral treatment of 15 mg oxybutynin was included in the meta analysis. As a reminder, this study was not used by the Committee in 2009 when solifenacin was evaluated because it was performed in Canada according to the dosage as defined by the Marketing Authorisation granted by the local authorities (1 tablet of 5 mg 2 to 3 times daily, that is 10 to 15 mg daily) and different from that of France. The French SPC recommends an initial dose of 2.5 mg oxybutynin 3 times/d, a standard dose of 5 mg 2 or 3 times daily, with a maximum dose of 20 mg/d).

The main conclusion the authors reach is the inadequacy of the data to draw definite conclusions as regards the improvement in quality of life between the different anticholinergic drugs.

05.2.4. Meta-analysis by Shamliyan²³ (2012)

Its objective was to analyse the efficacy and safety of different antimuscarinic drugs in women.

It grouped together 94 randomised controlled clinical trials including more than 80% women but an exhaustive search of the data is not guaranteed.

The primary efficacy endpoint was improvement in continence. The RR for improvement in continence versus the placebo was:

- 1.3 95% CI [1.1; 1.5] for fesoterodine (n=2,465)
- 1.7 95% CI [1.3; 2.1] for oxybutynin (n=992)
- 1.5 95% CI [1.4; 1.6] for solifenacin (n=6,304)
- 1.7 95% CI [1.5; 2.0] for trospium (n=2,677)

²² Madhuvrata P, Cody JD, Ellis G, Herbison GP, Hay-Smith EJC. Which anticholinergic drug for overactive bladder symptoms in adults. Cochrane Database of Systematic Reviews 2012, Issue 1. Art. No.: CD005429.

²³ Shamliyan T, Wyman Jean F, Ramakrishnan R, Sainfort F and Kane Robert L. Benefits and Harms of Pharmacologic Treatment for Urinary Incontinence in Women: A Systematic Review FREE. Ann Intern Med 2012; 156: 861 874.

For 1,000 women treated, continence was restored in 114 women receiving oxybutynin 95% CI [64; 163], 107 receiving solifenacin 95 CI % [58; 156], 114 receiving trospium 95% CI [83; 144]. We do not have the data for fesoterodine.

The adverse effect most commonly observed was dry mouth. The low level of evidence of the data does not allow any conclusion to be made in inter-treatment evaluation.

For 1,000 women treated, discontinuation of treatment due to adverse effects concerned 63 [12; 127] women receiving oxybutynin, 18 [4; 33] taking trospium, 13 [1; 26] receiving solifenacin.

According to the authors, the anticholinergic drugs are more effective than the placebo in symptomatic improvement of urinary incontinence but the effect is slight. There is no evidence of improvement in the quality of life.

05.2.5. Meta-analysis by Buser²⁴ (2012)

This network meta-analysis proposed a comparative evaluation of the efficacy and safety profile of the anticholinergic drugs indicated in the treatment of symptoms of overactive bladder.

An exhaustive search of the data was performed. All the comparative randomised trials including at least one anticholinergic group versus a placebo group or other anticholinergic drugs were included, with the exception of crossover trials and abstracts. Seventy-six clinical trials were therefore included with a total of 38,662 patients.

As regards efficacy, the six criteria analysed were ranked in the following order by five neuro-urologist experts: number of episodes of urge/24 hours, number of episodes of urinary incontinence/24 hours, number of urinary leakages a day, number of urinations a day, perception of improvement, number of episodes of nocturia/24 hours.

The results on the anticholinergic drugs subject to re-assessment are as follows (*see Appendix 3 for detailed results and relative risks*).

There was a statistically significant decrease versus placebo in the episodes of:

- urge for all the anticholinergic drugs, with the exception of oxybutynin (N=19,479)
- urge incontinence for all of them, with the exception of trospium and oxybutynin in dosages of 10 mg/d (N=17,251).

A statistically significant release in the urinary leakages versus placebo was only observed for solifenacin (N=14,807).

There was a statistically significant decrease in the number of urinations/24 hours for fesoterodine, solifenacin, trospium and oxybutynin in all the Marketing Authorisation dosages compared to a placebo (N=32,021 patients evaluated).

A cure/improvement in symptoms versus placebo was observed for fesoterodine, trospium and oxybutynin at 10 mg/d. There is no evaluation of solifenacin for this endpoint.

Episodes of nocturia statistically decreased versus placebo for trospium, fesoterodine at 8 mg/d and solifenacin at 10 mg/d (N=13,247).

The authors conclude that the anticholinergic drugs have modest efficacy at best without formally distinguishing one anticholinergic drug from another, with the exception of strong doses of oxybutynin considered less effective given their safety profile.

²⁴ N. Buser et al. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analysis. European urology 2012; 62: 1040-1060

06 CLINICAL SAFETY DATA

06.1 Data from meta-analyses

As a reminder, the data previously provided to the TC (meta-analysis by Chapple) are summarised in Table 3.

06.1.1. Meta-analysis by Nabi²¹

Oxybutynin (evaluated in 19 studies), trospium (8 studies) and solifenacin (3 studies) are the anticholinergic drugs used in our analysis and for which there are data in this meta-analysis.

Overall, the relative risk of dry mouth occurring due to the anticholinergic drugs (31% of patients, 1,907/6,165) versus a placebo (9.8% of patients, 350/3,567) was 3.00 95% CI [2.70; 3.34] $p < 0.05$.

This risk compared to placebo was:

- 3.23 95% CI [2.48; 4.20] in patients receiving oxybutynin with no heterogeneity between the studies
- 3.62 95% CI [2.29; 5.74] in patients receiving solifenacin with heterogeneity between the studies
- 2.66 95% CI [1.98; 3.55] in patients receiving trospium with no heterogeneity between the studies.

There was no difference in terms of discontinuation of treatment due to adverse effects between the anticholinergic drugs and the placebo, but heterogeneity in the studies was revealed.

06.1.2. Meta-analysis by Madhuvrata²²

Three studies reported data on the number of patients who had stopped their treatment because of the occurrence of adverse events. The meta-analysis showed a smaller number of discontinuations of treatment in patients treated with trospium chloride than in those treated with oxybutynin (RR of discontinuation of trospium/oxybutynin treatment = 0.66; 95% CI [0.48; 0.91], $p = 0.012$).

Moreover, a significant reduction in the risk of dry mouth in patients treated with trospium chloride compared to patients treated with oxybutynin was reported (RR=0.64; 95% CI [0.52; 0.77], $p < 0.00001$).

06.1.3. Meta-analysis by Paquette²⁵ (2011)

This meta-analysis aimed to evaluate the central nervous system adverse effects associated with anticholinergic drugs.

All the randomised versus placebo studies including at least one anticholinergic drug were sought out, provided that the incidence of neurosensory effects is reported in the trial. Thirty-three studies were used for this meta-analysis including 15,273 patients.

The authors note that among the patients receiving anticholinergic drugs, those receiving oxybutynin (in particular 15 mg/d) reported more central nervous system effects (dizziness, drowsiness, insomnia, confusion) than when receiving placebo.

The conclusions of this meta-analysis are difficult to use given the:

- heterogeneity of the studies, which were not all designed to evaluate safety, or did not have the necessary power to detect central nervous system adverse effects.
- the low number of studies to be evaluated; indeed 77% of the studies used according to the search criteria neither measured nor reported neurological adverse events.
- the evaluation bias for adverse effects on the central nervous system (carryover problem, inhomogeneous definitions of disorders etc.).

²⁵ A. Paquette et al. Systematic Review and Meta-Analysis: Do clinical trials testing antimuscarinic agents for overactive bladder adequately measure central nervous system adverse events? JAGS 2011.

06.1.4. Meta-analysis by Kessler²⁶ (2011)

This network meta-analysis was designed to analyse and compare the safety of the anticholinergic drugs available compared to a placebo (seven in total: oxybutynin, propiverine, tolterodine, solifenacin, trospium, darifenacin and fesoterodine).

It made an exhaustive selection of all the randomised controlled trials comparing the anticholinergic drugs between themselves or with a placebo where the adverse events were evaluated endpoints. These trials were evaluated by two independent investigators.

Sixty-nine trials including in total 26,229 patients were used; 83% of the studies were versus placebo and the average duration of treatment was 8 weeks.

The adverse events were grouped together into seven disease categories, each one graded with an overall score defined according to a VAS²⁷ (from 0 to 10) weighting the effects depending on the severity (according to expert interviews - See Appendix 4 for the grading of adverse events according to the VAS)

The mean age of the patients was 59 years and 76% of patients were women. The mean duration of treatment was 1 to 52 weeks (on average 8 weeks).

The adverse events most frequently reported were gastrointestinal, mainly dry mouth. The authors did not find any difference between the different anticholinergic drugs with regards to cutaneous, urinary, neurosensory, cardiac adverse events.

According to the authors, the overall safety score, the detailed results of which are not available, showed that fesoterodine 4 mg/d, solifenacin 5 mg/d and trospium in doses of 40 mg/d seem to be "equivalent", while the doses of oxybutynin which were higher than 10 mg/d are associated with a less favourable safety profile.

06.1.5. Meta-analysis by Buser (2012)

This meta-analysis is an updated version of the one by Kessler described above.

Safety has thus been evaluated in 90 studies (21 more than Kessler) including 39,919 patients.

Overall, the following have been reported:

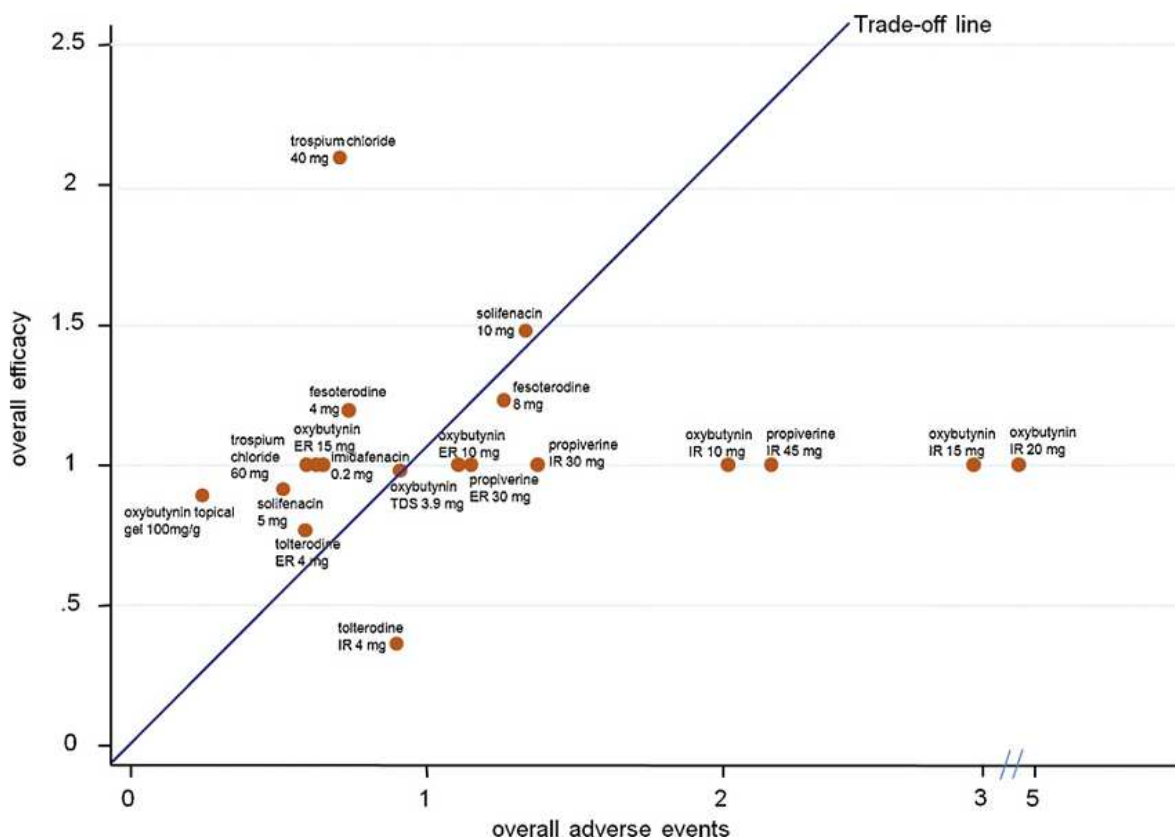
- gastrointestinal effects in 22 patients receiving oxybutynin (16 taking 15 mg/d), 17 receiving solifenacin, 12 receiving fesoterodine, 7 receiving trospium.
- neurological effects in 16 patients receiving oxybutynin (11 taking 15 mg/d), 7 receiving fesoterodine, 6 receiving solifenacin, 5 receiving trospium
- ocular effects in 16 patients receiving solifenacin, 14 receiving oxybutynin (11 taking 15 mg/d), 7 receiving fesoterodine, 1 receiving trospium.

The conclusions of the authors are identical to those of the meta-analysis by Kessler.

Oxybutynin at dosages of 15 mg/d and 20 mg/d were considered as the treatment with the worst safety profile. In contrast, treatments considered as the best tolerated are trospium, fesoterodine (4 mg) and solifenacin (5 mg and 10 mg). *See diagram below.*

²⁶ T.M. Kessler et al. Adverse event assessment of antimuscarinics for treating overactive bladder: A network meta-analytic approach. February 2011, volume 6, Issue 2, e16728.

²⁷ The score for each adverse event was calculated for each arm of each trial taking into account, for each trial, the total number of patients, the incidence and a grading according to the nature of the adverse event. A linear regression model taking into account the dose and the route of administration allowed study of the relation between treatment and the occurrence of the adverse events compared to the placebo group.



06.2 SPC data

The ANSM [French National Medicines and Health Products Safety Agency] was asked to communicate to the TC any assessment report, any new pharmacovigilance data or any new signals subsequent to the latest assessments by the TC. For the ANSM, the safety profile of different proprietary medicinal products reported in the SPCs is consistent with the available data. No re-assessment of the benefit/risk ratio is planned.

06.2.1. DITROPAN

The SPC states that "since oxybutynin may cause drowsiness or blurred vision, patients' attention is drawn to this potential risk, particularly when driving, or using machines.

The adverse effects most frequently reported are atropine-like: dry mouth, constipation, blurred vision, mydriasis, tachycardia, nausea, facial reddening, agitation and disorders of micturition. Reduction in dosage diminishes the incidence of these adverse effects. "

06.2.2. CERIS

According to the SPC, "the ability to drive or use machines may be impaired because of blurred vision. However, investigations into other parameters measuring the ability to drive a motor vehicle (visual orientation, general ability to react, reaction under stress, concentration and motor coordination) have not revealed any negative effects of trospium chloride.

During treatment with trospium chloride, anticholinergic side effects may occur such as dry mouth, dyspepsia and constipation.

Very common effects ($\geq 1/10$) are gastrointestinal: dry mouth.

Common effects ($\geq 1/100$, $< 1/10$) are dyspepsia, constipation, abdominal pain, nausea. "

Compared to the date of the previous opinion of the TC (5 January 2011), the following section was added to section 4.8. Undesirable effects from the SPC:

"Central nervous system: hallucinations, confusion, agitation (indefinite frequency, cannot be estimated from the available data).

Although the blood-brain barrier is practically impermeable to trospium chloride by virtue of its chemical properties (low lipophilicity as a quaternary amine), sporadic cases of hallucinations, confusion and agitation were reported during post-marketing surveillance mainly in elderly patients suffering from neurological diseases and/or because of interaction with other anticholinergic medicines."

06.2.3. VESICARE

According to the SPC: "the treatment may impair the ability to drive and use machines, since solifenacin, like other anticholinergics, may cause blurred vision and, uncommonly, somnolence and fatigue.

Due to the pharmacological effect of solifenacin, VESICARE may cause anticholinergic undesirable effects, of mild to moderate severity where the frequency is dose related.

The most commonly reported adverse reaction with VESICARE is dry mouth. It occurred in 11% of patients treated with 5 mg once daily, in 22% of patients treated with 10 mg once daily and in 4% of placebo-treated patients. The severity of dry mouth was generally mild and did only occasionally lead to discontinuation of treatment. The other most common effects are blurred vision and gastrointestinal disorders (constipation, nausea, dyspepsia, abdominal pain)."

Since the date of the last assessment by the TC (7 October 2009), the following adverse effects have been added to the SPC:

- confusional states, erythema multiforme of very rare occurrence (<1/10,000)
- angioedema of very rare occurrence (<1/10,000)
- decreased appetite, hyperkalaemia, delirium, glaucoma, Torsade de Pointes, prolongation of the QT interval on the electrocardiogram, dysphonia, ileus, abdominal discomfort, liver disorders, abnormal liver function tests, exfoliative dermatitis, muscular weakness, renal impairment (observed post-marketing and of indefinite frequency which cannot be estimated from the available data)
- dizziness, headache, vomiting, pruritus and erythema the frequency of which has progressed from "very rare" to "rare".

06.2.4. TOVIAZ

The SPC states that "TOVIAZ has minor influence on the ability to drive and use machines. Caution should be exercised when driving or using machines due to possible occurrence of side effects such as blurred vision, dizziness, and somnolence.

The safety of fesoterodine was evaluated in placebo-controlled clinical trials in a total of 2,859 patients with overactive bladder, of which 780 received placebo. Due to the pharmacological properties of fesoterodine, treatment may cause mild to moderate antimuscarinic effects like dry mouth, dry eye, dyspepsia and constipation. Urinary retention may occur uncommonly.

Dry mouth, the only very common adverse reaction, occurred with a frequency of 28.8% in the fesoterodine group compared to 8.5% in the placebo group. The majority of adverse effects occurred during the first month of treatment, with the exception of cases classified as urinary retention or post void residual urine greater than 200 ml, which could occur after long-term treatment and were more common in male than female subjects.

Among the common adverse events, the following occur in particular: insomnia, nervous system disorders (dizziness, headache), dry eye, gastrointestinal disorders (abdominal pain, diarrhoea, dyspepsia, constipation, nausea)."

06.3 Pharmacovigilance data from the PSURs:

06.3.1. DITROPAN

The analysis of the PSURs covering the period from 18/07/2006 until 17/07/2009 and from 18/07/2009 until 17/07/2012 did not reveal any new signal.

06.3.2. CERIS

No new specific safety signal was revealed during the period from 27 December 2007 until 30 September 2012 (53 cases of adverse events in total are known to have been reported).

03.3.3. VESICARE

Between June 2008 and June 2011, a total of 1,902 medically confirmed cases was compiled.

There is no evidence to date of an increase in the incidence of adverse effects identified or a change in their characteristics (in terms of severity, target population or prognosis).

However, because of increased exposure to treatment, the following updates to the SPC have been necessary since the previous assessment by the TC:

- Section 4.4. Special warnings and precautions for use:
 - o *"QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia."*
 - o *"Angioedema with airway obstruction has been reported in some patients on solifenacin succinate. If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken."*
 - o *"Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken."*

- Section 4.8. Adverse events:
 - o *"Very rare (<1/ 10,000): erythema multiforme, angioedema."*
 - o *"Indefinite frequency (cannot be estimated from the available data): anaphylactic reaction, decreased appetite, hyperkalaemia, delirium, glaucoma, Torsade de Pointes, prolongation of the QT interval on the electrocardiogram, dysphonia, ileus, abdominal discomfort, liver disorders, abnormal liver function tests, exfoliative dermatitis, muscular weakness, renal impairment. "*
 - o *"confusional states of very rare occurrence (<1/10,000)"*
 - o *"dizziness, headache, vomiting, pruritus and erythema the frequency of which has progressed from "very rare" to "rare".*

06.3.4. TOVIAZ

The first PSUR covering the period from 20/4/2011 until 19/4/2012 led to the addition of the following paragraph in Section 4.4 "Special warnings and precautions for use" of the SPC: *"Angioedema has been reported with fesoterodine and has occurred after the first dose in some cases. If angioedema occurs, fesoterodine should be discontinued and appropriate therapy should be promptly provided."* Added in 4.8: *addition of urticaria and pruritus as adverse effects in the organ system "Skin and subcutaneous tissue disorders."*

Over the course of this monitoring, the following was reported: 13 cases of blurred vision, 7 cases of gastrointestinal disorders, mainly vomiting, 13 cases of oedema, 10 cases of hallucinations, 22 nervous system disorders, mainly impaired memory and loss of consciousness.

TOVIAZ must be used with caution in patients with a risk of QT prolongation (e.g.: hypokalaemia, bradycardia and concomitant administration of medicines known to prolong the QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure).

Because of its centralised Marketing Authorisation, TOVIAZ is subject to an RMP which includes monitoring the risks identified in the phase III studies, namely elevated liver enzymes, and urinary retention. It also includes monitoring the main potential risks: prolongation of the QT interval, and consequences on cognitive function. It also allows the study of populations not included in the phase III studies: women who are pregnant or breastfeeding; children and adolescents; men aged 65 and over.

07 OTHER DATA

07.1 Prescribing data

07.1.1. Data from the IMS Health panel

According to the IMS data (November 2012 moving annual total), the following was observed:

- 107,000 prescriptions of DITROPAN 5 mg in 75% of cases in the Marketing Authorisation indication and at the average daily dosage of 1.5 tablets in accordance with the SPC
- 341,000 prescriptions of CERIS 20 mg in 71% of cases in the Marketing Authorisation indication and at the average daily dosage of 1.7 tablets in accordance with the SPC
- 413,000 prescriptions of VESICARE (86,000 for the 10 mg dosage, 327,000 for the 5 mg dosage) in more than 70% of cases in the Marketing Authorisation indication and at the average daily dosage of 1 tablet in accordance with the SPC.

In about 63% of cases, these proprietary medicinal products were prescribed in patients aged over 65 years.

To date, the TOVIAZ proprietary medicinal products for which the TC issued a favourable opinion for inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use are neither included in the lists, nor marketed.

07.1.2. Prescription data from the EGB [échantillon généraliste de bénéficiaires database]

According to EGB data extrapolated to the French population²⁸, 573,358 (95% CI 557,773 to 588,943) people received at least one reimbursement for an anticholinergic drug between 1 January and 31 December 2012.

The distribution by proprietary medicinal product is as follows:

Proprietary medicinal product (INN)	n	n extrapolated	95% CI Lower limit	95% CI Upper limit
CERIS (trospium)	1,644	182,887	174,059	191,716
DITROPAN and generics (oxybutynin)	1,937	215,482	205,902	225,063
VESICARE (solifenacin)	2,070	230,278	220,375	240,180
Total number*	5,154	573,358	557,773	588,943

* the same person may have had several proprietary medicinal products refundable in 2012

These data are consistent with the target population estimated at a maximum of 640,000 patients.

With regard to the age distribution of patients with at least one anticholinergic reimbursement, 61% of patients are 65 years or older.

²⁸ The EGB is a representative sample (1/97) from all French health insurance beneficiaries. It contains anonymous information about the demographic characteristics of those persons, the benefits paid and chronic (long-term) conditions since 2003. The extrapolation of EGB data to the French population was done by calculating an extrapolation coefficient. This extrapolation coefficient was obtained from the number of beneficiaries in the EGB on 01/01/2012 (n = 589,561) in relation to the French population on 01/01/2013 (n = 65,585,857). The extrapolation coefficient obtained is 1/111.24.

07.2 Usage data

07.2.1. The VEGA study

The VEGA study is a multicentre prospective cohort study conducted in Germany in patients aged 70 years or older treated with VESICARE and monitored over 12 weeks. The main objective of this study was to describe the safety and potential impact on cognition of solifenacin in the geriatric population.

As the Committee does not have the necessary information to assess the methodology of the VEGA study (study protocol and clinical report not provided), the results of this study cannot be taken into consideration in this re-assessment.

07.2.2. VESTALE study

The VESTALE study is a multicentre prospective cohort study conducted in France by 186 urologists, which included 1,629 adult patients presenting with symptoms of overactive bladder and who started anticholinergic treatment between December 2010 and July 2012.

The main objective was to describe the adherence reported directly by the patients (GIRERD self-assessment questionnaire) presenting with idiopathic overactive bladder 6 months after starting anticholinergic treatment prescribed by the urologist.

Given the low methodological quality of this study and the fact that almost 70% of patients do not have data available at 6 months, the results of this study cannot be taken into consideration and are therefore not presented.

07.3 Results of the E-CARE follow-up study requested by the CEPS

The E-CARE study is a multicentre prospective cohort study to evaluate the impact of the simplified support programme designed for generalist physicians in the context of the management of overactive bladder in their patients with an anticholinergic treatment.

The study doctors were randomised in 2 groups:

- one intervention group: receiving self-training on the management of overactive bladder.
- a control group: does not have training prior to the study.

Each doctor had to include the first four consecutive patients seen in consultation and recently being treated with an anticholinergic drug. There were two collection times: on inclusion (when the anticholinergic drug was prescribed), then about 3 months after inclusion (monitoring after treatment). For each of the two times, the study doctor completed a medical questionnaire and had his patient fill in a self-assessment questionnaire. If the patient did not come to the doctor's surgery within around 3 months after being started on the treatment, a telephone call by the doctor allowed him to collect follow-up data which did not require the patient to be physically examined.

The primary efficacy endpoint is based on the score from the B-SAQ questionnaire (self-assessment questionnaire on bladder control: symptoms and discomfort).

The centres were recruited and set up from January until July 2012. The end of the study was scheduled for the end of December 2012. On 12/11/12 (the date of the analysis), 733 (57.6%) doctors were active (= inclusion of at least one patient) among the 1,272 doctors put in place (364 in the intervention group and 369 in the control group).

On 12/11/12, 3,101 patients were included in the study, including 1,520 (49.0%) by the GPs of the intervention group and 1,581 (51.0%) by the GPs of the control group. Among the patients included over 3 months ago, 81.7% (n=2,318) had a follow-up at 3 months. Two hundred and eighty five patients displaying major protocol violations (inclusion outside the study period, time between visits, failure to comply with the inclusion criteria) and 31 patients displaying major inconsistencies in the data completed were excluded from the interim analysis (13.6%).

In the end, 1,936 patients were included in the analysis, 90% of whom were treated with VESICARE®. Only half of the patients (50.2%) had follow-up data at 3 months on the primary endpoint and only the follow-up questionnaires processed in data management have been included in this interim analysis.

Given the low percentage of available data, the results of this study cannot be taken into consideration in this re-assessment and are therefore not detailed.

08 SUMMARY & DISCUSSION

Since the last assessments by the TC and in particular the meta-analysis by Chapple, who concluded a modest effect size for all anticholinergic drugs in the treatment of urinary incontinence²⁹ and a poor safety profile for oxybutynin, new data (mainly meta-analyses) are available.

In terms of efficacy, the authors of five meta-analyses of good methodological quality conclude that the efficacy of the anticholinergic drugs (oxybutynin, trospium, solifenacin, fesoterodine) is superior to that of a placebo for the symptomatic improvement of urinary incontinence, but the effect is modest (reduction of approximately one urination episode daily compared with a placebo).

No distinction in terms of efficacy can be made between the different anticholinergic drugs. There is only a small amount of data comparing anticholinergic drugs between themselves. The main studies were performed versus placebo. The placebo effect on the criteria of urinary incontinence is not negligible.

The latest European and international guidelines estimate that all the anticholinergic drugs are of similar efficacy.

Few data are available with a sufficient level of evidence to demonstrate any impact of anticholinergic drugs on improving quality of life compared with placebo.

The following should be noted:

- the short-term evaluation of anticholinergic drugs in the studies (on average 12 weeks),
- the lack of evaluation as primary efficacy endpoint in studies of the change in urge incontinence episodes despite the fact that it is a pivotal symptom of overactive bladder.³⁰

The adverse effects most commonly reported are atropine-like: dry mouth, gastrointestinal disorders (constipation, nausea, dyspepsia, abdominal pain), eye disorders (blurred vision) – see *section 06. Clinical safety data*.

There are no robust safety data concerning the central nervous system. The available data concerning cognitive disorders in particular have contradictory results. The meta-analyses are faced with the problem of heterogeneity in populations studied or an inadequate duration in the follow-up treatment.

The adverse effect most commonly observed in the studies and reported in the meta-analyses is dry mouth, the relative risk of occurrence of this effect being greater when taking oxybutynin than when taking other anticholinergic drugs.

Since the date of the last assessment by the TC, the following adverse effects have been added to the SPC of the different drugs: confusional states, angioedema, prolongation of the QT interval and Torsade de Pointes, as well as cases of anaphylactic reactions (angioedema).

According to the authors of two new network meta-analyses, fesoterodine (4 mg/d), solifenacin (5 mg/d and 10 mg/d) and trospium (in doses of 40 mg/d) seem to be equivalent in terms of safety

²⁹ Reduction of approximately one urination episode daily compared with a placebo.

³⁰ With the exception of a study with solifenacin performed and assessed in 2009 by the TC

whilst doses of oxybutynin higher than 10 mg/d are associated with a less favourable safety profile. The latest Canadian and US guidelines support these data: immediate-release oxybutynin generates more adverse effects than the other anticholinergic drugs.

There are no studies or guidelines for the use of anticholinergic drugs in the elderly with comorbidities (mobility disorders, muscle weakness, cognitive disorders etc.).³¹

The Committee regrets the lack of data in the more representative elderly patients of the population suffering from overactive bladder, especially as differences exist for the prescription of anticholinergic drugs in this population. Indeed, no dosage adjustment is required when CERIS, VESICARE and TOVIAZ are administered, whilst DITROPAN must be used with caution in elderly patients given its deleterious effect observed in practice on the central nervous system (cognitive disorders, memory disorders, dizziness etc.).³²

09 THERAPEUTIC USE

The latest guidelines from Canada⁷ and the US⁸ support the previous guidelines: all the anticholinergic drugs have similar efficacy, but immediate-release oxybutynin (DITROPAN) generates more adverse effects than the other anticholinergic drugs.

According to the latest guidelines from the European Association of Urology,¹¹ there are no data proving that one anticholinergic drug is superior to another in terms of improvement in the symptoms of urinary incontinence and quality of life, nor is it certain that they are superior to a behavioural treatment. However, the combination of therapy and anticholinergic drugs may be beneficial.

The anticholinergic drugs remain the drug treatment for urinary incontinence as they improve symptoms compared with a placebo, but the benefits are of limited clinical relevance.³²

In practice, the experts underline the action of anticholinergic drugs on urge incontinence, the trigger of all the symptoms of overactive bladder, but their effect on urge incontinence has not been studied in the trials.

The limits in using anticholinergic drugs lie indeed in their moderate efficacy and their poor safety in terms of common adverse effects, either in terms of the discomfort experienced (dry mouth, severe constipation, blurred vision) or in terms of their morbidity, particularly concerning the resulting cognitive disorders, more particularly in the elderly. Particular attention is devoted in practice to the prescription of DITROPAN which, more than the other anticholinergic drugs, crosses the blood-brain barrier, which leads to a significant risk of confusion, particularly in the elderly, those suffering from Parkinson's disease or multiple sclerosis.

The Committee does not have any data directly comparing the anticholinergic drugs between themselves. None can be recommended in preference over the other. The Committee regrets the lack of comparison with other therapeutic means, particularly the behavioural treatments, especially as they represent 1st line treatments.

The proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ constitute a therapeutic option in the treatment of increased urinary frequency and/or urinary urge and/or urge incontinence in patients suffering from overactive bladder.

As discontinuation of treatment over the course of the first 3 months of treatment was observed in more than 50% of patients receiving anticholinergic drugs, because of a lack of clinical benefit and/or adverse effects, the anticholinergic treatment should be subject to a regular re-assessment:

³¹ C.E. Dubeau et al. Incontinence in the frail elderly: report from the 4th International Consultation on Incontinence. *Neuro urol. Urodynam*, 2010; 29: 165-178.

³² K.E. Andersson et al. Pharmacological treatment of overactive bladder: report from the International Consultation on Incontinence. *Current Opinion in Urology* 2009; 19: 380-394

- DITROPAN treatment should be assessed after 4 to 6 weeks since normal bladder function can be re-established in some patients
- the need to continue CERIS treatment should be re-assessed every 3 to 6 months
- the optimum effect of VESICARE can be assessed at the earliest after 4 weeks of treatment
- an individual re-assessment of the efficacy of TOVIAZ in patients after 8 weeks of treatment is recommended.

Please remember that safety and efficacy have not been established in the case of detrusor overactivity of neurogenic origin.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

010.1 Re-assessment of actual benefit

Urge incontinence is characterised by the involuntary loss of urine preceded by an urgent and irrepressible need to urinate resulting in urination that cannot be delayed.

Overactive bladder is a condition that causes marked deterioration in quality of life and possible development of a social handicap.

The proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ fall within the framework of symptomatic treatment.

Given all the available data, the effect on the symptoms of overactive bladder is not different between the four anticholinergic drugs, but the scale of effect observed is modest. In terms of safety, the adverse effects observed and known are atropine-like. They are more common when taking DITROPAN administered in doses higher than 10 mg/d than when taking the other three proprietary medicinal products.

The efficacy/adverse effect ratio for CERIS, VESICARE and TOVIAZ is modest. That of DITROPAN is low.

There are treatment alternatives. Anticholinergic drug treatment can be offered as first line therapy or after the failure of behavioural and/or rehabilitation therapy.

Public health benefit:

In terms of public health, the burden induced by urinary incontinence, urge incontinence and increased urinary frequency in adult patients suffering from overactive bladder is low.

The symptomatic management of urinary incontinence, urge incontinence and/or increased urinary frequency in adult patients suffering from overactive bladder does not constitute a public health need.

Given the available data, the proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ have not shown any impact in terms of reduced morbidity or improved quality of life.

In addition, the discontinuation rate is higher with DITROPAN due to the poor safety of this treatment compared with the other anticholinergic treatments. DITROPAN could therefore have a negative impact on public health in the symptomatic management of urinary incontinence, urge incontinence and/or increased urinary frequency in adult patients suffering from overactive bladder.

As a result, in the current state of knowledge and in view of the fact that therapies are already available, the proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ do not present any public health benefit.

As a result, the actual benefit of the proprietary medicinal products DITROPAN, CERIS, VESICARE and TOVIAZ remains moderate in the symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge in adult patients with overactive bladder.

010.2 Re-assessment of the improvement in actual benefit

In previous assessments by the Transparency Committee, VESICARE was considered to be associated with a better safety profile compared to DITROPAN in terms of discontinuation of treatment due to adverse effects, particularly on the basis of the results of the meta-analysis by Chapple. This advantage was not found in the case of CERIS or TOVIAZ. However, based on clinical experience, the proprietary medicinal products CERIS and VESICARE seem to have a better safety profile than DITROPAN.

New data found in the literature (rigorous methodology meta-analyses) confirm the superiority of VESICARE compared to DITROPAN in terms of safety, and provide data for CERIS and TOVIAZ confirming previous assessments.

Thus, given:

- the comparable efficacy between the four anticholinergic drugs,
- a better safety profile for CERIS, VESICARE and TOVIAZ compared with DITROPAN supported by recent international guidelines and meta-analyses of good methodological quality,
- the lack of data distinguishing CERIS, VESICARE and TOVIAZ in terms of clinical performance,
- the poor safety profile of DITROPAN, particularly in elderly patients, which raises concerns,

the Transparency Committee considers that the proprietary medicinal products CERIS, VESICARE and TOVIAZ provide a minor improvement in actual benefit (IAB IV), in terms of safety compared with DITROPAN, in the symptomatic treatment of urge incontinence and/or increased urinary frequency and urinary urge in adult patients with overactive bladder.

010.3 Re-assessment of the target population

The target population corresponds to all the adult patients with overactive bladder.

According to a European study³³ (Germany, France, United Kingdom, Italy, Sweden, Spain), the average prevalence of overactive bladder is 16.6% in the population aged over 40 years. In France, the prevalence in this population³⁴ is 12%, i.e. about 3.9 million people affected.

The proportion of patients consulting doctors for this reason is 60%, i.e. about 2.4 million patients. Of these, at the time of the European cross-sectional survey, the only relevant data available in the literature, only 27% were on medication.

Applying these results to the French population, the population likely to be treated with medication for overactive bladder is around **640,000 patients**.

³³ 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.

³⁴ Population aged 40 years and over on 1st January 2012: 32,920,200. INSEE age pyramid 2012.

APPENDIX 1: Summary table of dosages and warnings from the SPC for anticholinergic drugs

Proprietary medicinal products	Dosage	Special warnings and precautions for use
DITROPAN	<u>"Adult</u> The initial dose is 2.5 mg three times a day; it will be increased, if necessary, until the minimum effective dose for a satisfactory clinical response is achieved. The usual dose is 5 mg two or three times a day and the maximum dose is 5 mg four times a day. <u>Elderly patients</u> In elderly patients, the elimination half-life may be increased; as a result, the initial dose is 2.5 mg twice a day; it will be increased, if necessary, until the minimum effective dose for a satisfactory clinical response is achieved. A standard dose of 10 mg in two doses is generally adequate, particularly in patients with low body mass."	"Oxybutynin treatment should be assessed after 4 to 6 weeks, since normal bladder function can be re-established in some patients. Oxybutynin hydrochloride should not be used in the treatment of urinary incontinence due to stress. Oxybutynin hydrochloride should be used with caution in elderly patients who may be more sensitive to the effects of oxybutynin, as well as in patients with autonomic neuropathy, hiatus hernia, or any other severe gastrointestinal disorder, hepatic or renal impairment, tachyarrhythmia, cerebrovascular insufficiency. Oxybutynin hydrochloride may aggravate the, symptoms of hyperthyroidism, coronary heart disease, congestive heart disease, prostatic hypertrophy, cardiac arrhythmias, tachycardia. Prolonged administration of oxybutynin may cause discomfort by reducing salivary flow and thus promoting the development of caries, parodontosis and oral candidiasis.
CERIS	"One coated tablet twice a day (corresponding to 40 mg of trospium chloride daily). The coated tablet should be taken whole on an empty stomach with a large glass of water before meals. In patients with severe renal dysfunction (creatinine clearance between 10 and 30 ml/min/1.73 m²), the recommended dose is one 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 re-assessed at regular intervals of 3 to 6 months. As no corresponding data are available, the use of this product is contraindicated in children under 12 years of age."	"Trospium chloride should be used with caution in patients with: - obstructions to the gastrointestinal tract (for example pyloric stenosis), - urinary obstructions, with the risk of formation of residual urine, - autonomic neuropathy, - hiatus hernia associated with reflux oesophagitis, - as well as in patients for whom an accelerated pulse rate is undesirable (e.g. patients with hyperthyroidism, coronary diseases or congestive heart failure). As no results of clinical trials are available with respect to patients with severe liver dysfunction, the treatment of these patients with trospium chloride is discouraged. In patients with slight to moderate liver insufficiency, trospium chloride should be used with caution. Trospium chloride is mainly excreted via the kidney. A considerable rise in plasma levels has been observed in patients with severe impairment to kidney function. Trospium chloride should therefore be used with caution in this type of patient, as well as in patients with mild to moderate renal failure."

VESICARE	<u>"Adults, including the elderly</u> The recommended dose is 5 mg solifenacin succinate once daily. If needed, the dose may be increased to 10 mg solifenacin succinate once daily. <u>Children and adolescents</u> As the safety of use and efficacy of solifenacin in children have not yet been established, VESICARE 5 mg should not be used in children."	"VESICARE should be used with caution in the following situations: - clinically significant and decompensated bladder outflow obstruction at risk of urinary retention. - gastrointestinal obstructive disorders. - risk of decreased gastrointestinal motility. - severe renal impairment (creatinine clearance $\leq$ 30 ml/min; see sections 4.2 and 5.2); doses should not exceed 5 mg daily for these patients. - moderate hepatic impairment (Child-Pugh score of 7 to 9; see sections 4.2 and 5.2); doses should not exceed 5 mg daily for these patients. - concomitant use of a potent CYP3A4 inhibitor such as ketoconazole (see sections 4.2 and 4.5). - hiatus hernia/gastro-oesophageal reflux and/or patients who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis - autonomic neuropathy. Safety and efficacy of VESICARE have not yet been established in patients with a neurogenic cause for detrusor overactivity. This medicine is contraindicated in patients with hereditary galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption syndrome. QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia. Angioedema with airway obstruction has been reported in some patients on solifenacin succinate. If angioedema occurs, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken. Anaphylactic reaction has been reported in some patients treated with solifenacin succinate. In patients who develop anaphylactic reactions, solifenacin succinate should be discontinued and appropriate therapy and/or measures should be taken. The maximum effect of VESICARE can be determined after 4 weeks of treatment at the earliest."
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TOVIAZ	<i>"In adults (including elderly patients)</i> The recommended starting dose is 4 mg once daily. Based on individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg. Full treatment effect was observed between 2 and 8 weeks. Hence, it is recommended to re-evaluate the efficacy for the individual patient after 8 weeks of treatment. In subjects with normal renal and hepatic function and receiving concomitant administration of potent CYP3A4 inhibitors, the maximum daily dose of TOVIAZ should be 4 mg once daily."	"TOVIAZ should be used with caution in patients with: - clinically significant bladder outflow obstruction at risk of urinary retention (e.g. clinically significant prostate enlargement due to benign prostatic hyperplasia) - gastrointestinal obstructive disorders (e.g. pyloric stenosis) - gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as oral bisphosphonates) that can cause or exacerbate oesophagitis - decreased gastrointestinal motility - autonomic neuropathy - controlled narrow-angle glaucoma. Safety and efficacy have not yet been established in patients with a neurogenic cause for detrusor overactivity. Angioedema has been reported with fesoterodine and has occurred after the first dose in some cases. If angioedema occurs, fesoterodine should be discontinued and appropriate therapy should be promptly provided. TOVIAZ should be used with caution in patients with a risk for QT prolongation (e.g. hypokalaemia, bradycardia and concomitant administration of medicines known to prolong the QT interval) and relevant pre-existing cardiac diseases (e.g. myocardial ischaemia, arrhythmia, congestive heart failure). This especially holds true when taking potent CYP3A4 inhibitors.
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Appendix 2: detailed description of the strategy for literature searches by HAS

1. Medline bibliographical database

The search strategy for the Medline bibliographic database was constructed using, for each subject, either terms from the thesaurus (MESH descriptors for Medline) or free terms (from the title or abstract). These were combined with terms describing the types of studies. The search strategy was the following:

"Urinary Bladder, Overactive"[Mesh] OR "Urinary Incontinence"[Majr] OR urinary incontinence[ti] OR overactive bladder[ti] OR overactive urinary bladder[ti] AND "Muscarinic Antagonists"[Mesh] OR "Cholinergic Antagonists"[Mesh:noexp] OR "Urinary Bladder, Overactive/drug therapy"[Mesh:noexp] OR "Urinary Bladder, Overactive/therapy"[Mesh:noexp] OR "Urinary incontinence/drug therapy"[Mesh:noexp] OR "Urinary incontinence/epidemiology"[Mesh:noexp] OR "Urinary bladder, overactive/epidemiology"[Mesh:noexp] OR "Urinary incontinence/therapy"[Mesh:noexp] OR "Muscarinic Antagonists" [Pharmacological Action] OR antimuscarinic[ti] OR "muscarinic* antagonist"[ti] OR drug therapy[ti] OR drug treatment[ti] OR "cholinergic antagonist"[ti] OR "oxybutynin N-oxide" [Supplementary Concept] OR "oxybutynin" [Supplementary Concept] OR "trospium chloride" [Supplementary Concept] OR "fesoterodine" [Supplementary Concept] OR "tolterodine" [Supplementary Concept] OR "solifenacin succinate" [Supplementary Concept]

Table legend

Mesh: Descriptor; *: truncation; de: descriptor, ti: title; ab: abstract; pt: publication type; so: journal title

2. Visited sites

Last consultation: April 2013

French information:

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé [Agency for the Evaluation of Technologies and Intervention Methods in Health], Canada
- Agence Nationale de Sécurité Sanitaire (Anes) [French National Food Safety Agency], France
- Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM) [National Medicines and Health Products Security Agency], France
- Association Française d'Urologie (AFU) [French Association of Urology], France
- Bibliothèque Médicale AF Lemanissier [AF Lemanissier Medical Library], France
- Catalogue et Index des Sites Médicaux Francophones [Catalogue and Index of French-language Medical Sites], France
- Centre fédéral d'expertise des soins de santé [Federal Centre of Healthcare Expertise], Belgium
- Direction de la recherche, des études, de l'évaluation et des statistiques [Directorate for Research, Surveys, Assessment, and Statistics], France
- Expertise collective de l'INSERM [INSERM collective expertise], France
- Haute Autorité de Santé, France
- Institut national de prévention et d'éducation pour la santé (INPES) [National Prevention and Health Education Institute], France
- Institut de recherche et documentation en économie de la santé [Institute for research and information in health economics], France
- Institut National de la Statistique et des Etudes Economiques (French National Institute of Statistics and Economic Studies).
- Institut de veille sanitaire (InVS) [Health Monitoring Institute], France
- La Documentation française [French public publishing service of general documentation], France
- Portail de la statistique publique française [French public statistics portal], France
- Société Française de Médecine Générale [French General Medical Society], France

- Unions Régionales des Caisses d'Assurance Maladie [Regional Associations of Health Insurance Funds], France

English information:

- Adelaide Health Technology Assessment, Australia
- Agency for Healthcare Research and Quality, United States
- Alberta Heritage Foundation for Medical Research, Canada
- Alberta Medical Association, Canada
- American College of Cardiology, United States
- American College of Physicians, United States
- American Heart Association, United States
- Blue Cross Blue Shield Association, United States
- American Urological Association, United States
- BMJ Clinical Evidence, United Kingdom
- Canadian Agency for Drugs and Technologies in Health, Canada
- Canadian Cardiovascular Disease, Canada
- Canadian Task Force on Preventive Health Care, Canada
- Centers for Disease Control and Prevention Infection Control Guidelines, United States
- Centre for Clinical Effectiveness, Australia
- Centre for Reviews and Dissemination, United Kingdom
- CMA Infobase, Canada
- College of Physicians and Surgeons of Alberta, Canada
- European Association of Urology (EAU), Holland
- European Medicines Agency, United Kingdom
- European Society of Cardiology, France
- Guidelines and Protocols Advisory Committee, Canada
- Guidelines International Network
- Institute for Clinical Systems Improvement, United States
- Minnesota Department of Health - Health Technology Advisory Committee, United States
- National Coordinating Centre for Health Technology Assessment, United Kingdom
- National Guidelines Clearinghouse, United States
- National Health Services Scotland, United Kingdom
- National Health Service Corps (NHSC), United States
- National Institute for Health and Clinical Excellence, United Kingdom
- National Institute for Health Research - Horizon Scanning Centre, Australia
- National Institutes of Health, United States
- National Library of Guidelines Specialist Library, United Kingdom
- New Zealand Guidelines Group, New Zealand
- New Zealand Health Technology Assessment, New Zealand
- Ontario Medical Advisory Secretariat, Canada
- Regional Evaluation Panel, United Kingdom
- Scottish Intercollegiate Guidelines Network, United Kingdom
- Singapore Ministry of Health, Singapore
- U.S. Preventive Services Task Force, United States
- Veterans Affairs Technology Assessment Program, United States

3. Monitoring

Medline continued to be monitored until May 2013 based on the search terms presented in point 2. This led to four additional references being found.

The contents of the following reviews were examined throughout the project: British Medical Journal (BMJ), Journal of the American Medical Association (JAMA), The Lancet, The New England Journal of Medicine; the daily medical and paramedical press, and news from the Agence Presse Médicale (APM) [Medical Press Agency].

Appendix 3: results in graph form of the meta-analysis by Buser in terms of the efficacy of anticholinergic drugs

Figure 2: Meta-analysis by Buser 2012 - Reduction in the number of urge episodes per 24-hour period / placebo (N=19,479)

(■ : Medicines authorised in France and where the dosage corresponds to the French SPC)

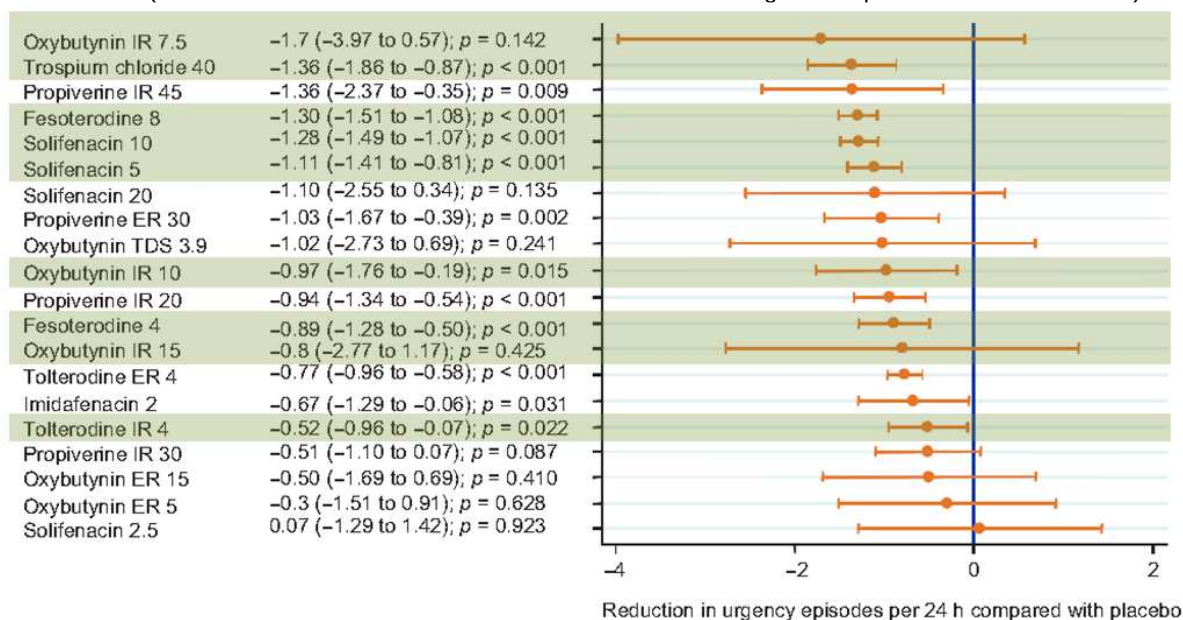


Figure 3: Meta-analysis by Buser 2012

Reduction in the number of urge incontinence episodes per 24-hour period / placebo (N=17,251)

(■ : Medicines authorised in France and where the dosage corresponds to the French SPC)

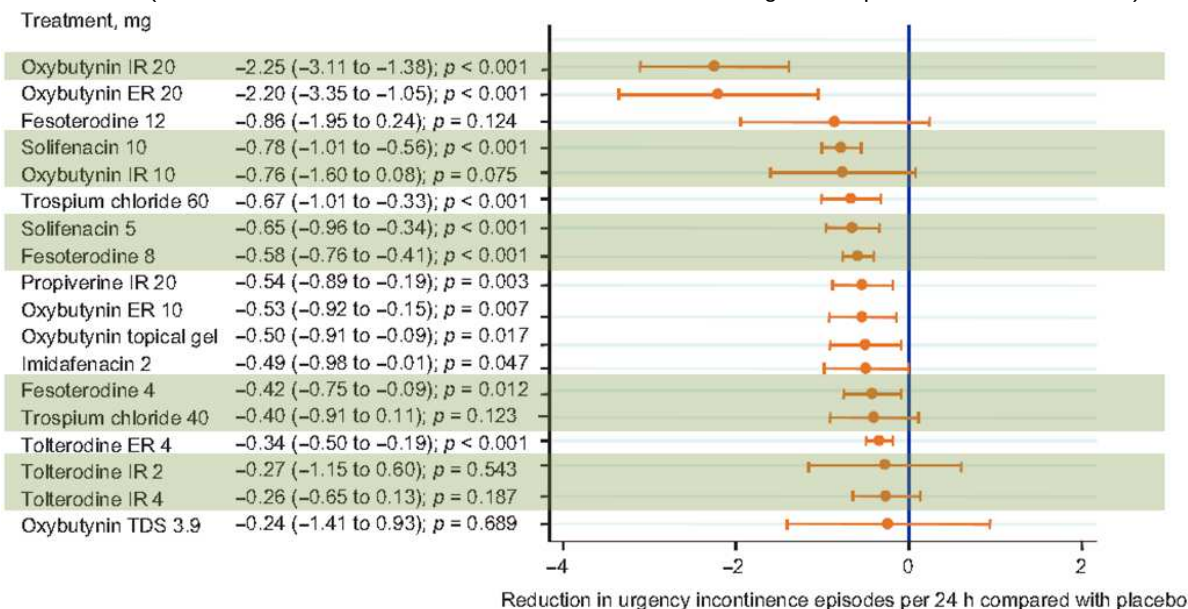


Figure 4: Meta-analysis by Buser 2012

Reduction in the number of leakage episodes per 24-hour period / placebo (N=14,807)

(■ : Products authorised in France and where the dosage corresponds to the French SPC)

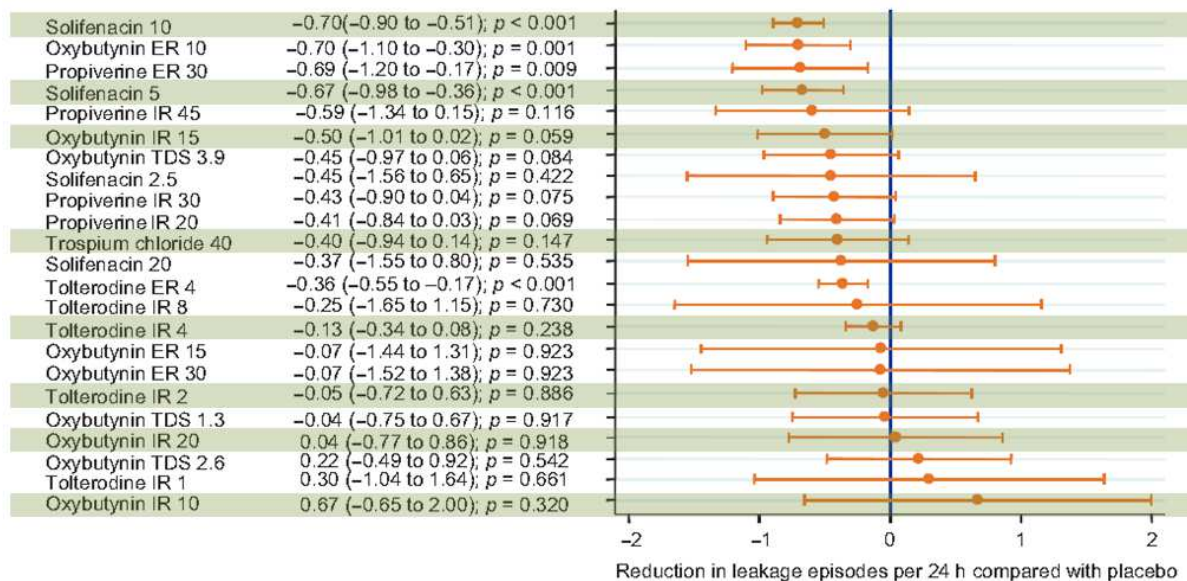
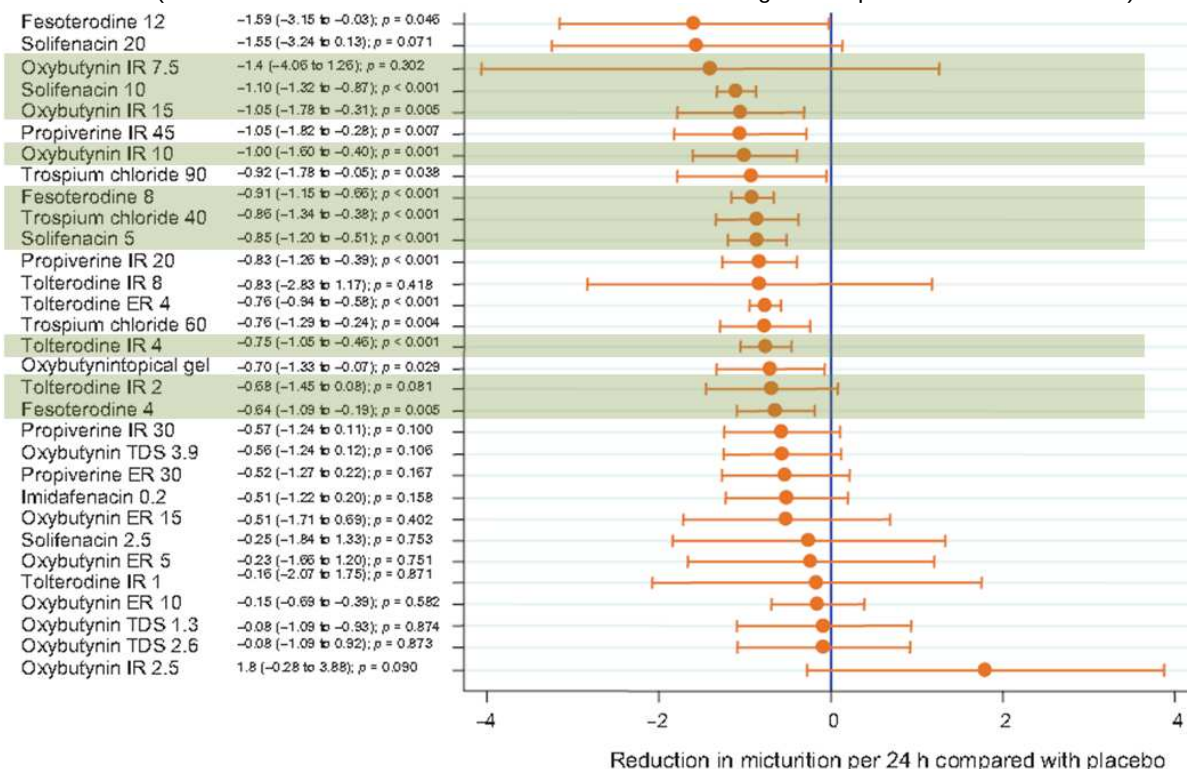


Figure 5: Meta-analysis by Buser 2012

Reduction in the number of urinations per 24 hours compared with placebo (N=32,021)

(■ : Products authorised in France and where the dosage corresponds to the French SPC)



Appendix 4: meta-analysis by Kessler, grading of adverse events

	Adverse events	Grade according to a VAS (0: minimum severity – 10: maximum)
Gastrointestinal disorders	• Dry mouth, dry throat, dysgeusia, constipation, diarrhoea, dyspepsia	4
	• Abdominal pain, gastritis, nausea, unspecified conditions	5
	• Vomiting	6
Eye disorders	• Dry eye	4
	• Blurred vision	6
Renal and urinary disorders	• Voiding difficulty, dysuria	5
	• Urinary tract infection, unspecified conditions	6
	• Urinary retention	7
Nervous and psychiatric disorders	• Fatigue, dizziness / vertigo, headache	5
	• Insomnia	6
	• Sedation, confusion, cognitive impairment, depression / lethargy	7
	• Somnolence	8
Cardiac disorders	• Palpitations/tachycardia	5
	• Hypertension, orthostatic disturbance	6
	• Fall	8
Respiratory diseases	• Dry nose	3
	• Cough, nasopharyngitis, sinusitis	4
	• Upper respiratory tract infection, influenza-like illness	6
Skin and subcutaneous tissue disorders	• Dry skin	2
	• Erythema / rash	4
	• Pruritus	5