

## LMMG New Medicine Recommendation

### Vesomni<sup>®</sup>▼ for the treatment of Storage Symptoms associated with Benign Prostatic Hyperplasia

#### Recommendation:

Solifenacin 6mg & tamsulosin 400mcg MR (Vesomni<sup>®</sup>) one tablet daily is recommended for the treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia in men who are not adequately responding to treatment with tamsulosin monotherapy.

#### Summary of supporting evidence:

- One Phase 3 trial in patients with substantial storage component LUTS has demonstrated the short-term efficacy of Vesomni<sup>®</sup> over placebo and non-inferiority to tamsulosin in reducing the total International Prostate Symptom Score. This effect was not seen in a separate study of patients with a limited level of storage symptoms.
- The same Phase 3 trial demonstrated the short-term efficacy of Vesomni<sup>®</sup> over both placebo and tamsulosin at reducing the Total Urgency and Frequency Score (TUFS). The improvement in TUFS was also accompanied by greater improvements in disease specific quality of life markers.
- In men the risk of urinary retention and AUR (urinary retention requiring catheterization) on Vesomni<sup>®</sup> is low (0.5% and 0.3% respectively), particularly when taking into account that urinary retention is one of the complications of the underlying disease.
- There is extensive experience with the single-entity products, solifenacin and tamsulosin. Vesomni<sup>®</sup> has the same adverse reactions as the 2 individual active substances without synergism on the level of adverse events.
- With flat pricing of Vesomni<sup>®</sup> and solifenacin 5mg there would be savings on the costs of tamsulosin with the combination product. These savings would be continued through to 2018 when the patent expires on solifenacin (Vesicare<sup>®</sup>)

## Details of Review

<b>Name of medicine</b> (generic & brand name): Solifenacin & tamsulosin (Vesomni®)
<b>Strength(s) and form(s):</b> Dual layered tablet containing solifenacin 6mg and tamsulosin 400mcg MR <sup>1,2</sup>
<b>Dose and administration:</b> One tablet daily, with or without food. Do not crush or chew tablet.
<b>BNF therapeutic class / mode of action</b>  Combination product:  BNF Chapter 7.4.1 – Alpha-blocker (tamsulosin) Tamsulosin binds selectively <sup>3</sup> and competitively to postsynaptic alpha1-receptors, in particular to the subtype alpha1A, which bring about relaxation of the smooth muscle of the prostate, resulting in an increase in urinary flow-rate and an improvement in obstructive symptoms.  BNF Chapter 7.4.2 – Anti-muscarinic (solifenacin) Solifenacin is a competitive, specific cholinergic-receptor antagonist <sup>4</sup> . The urinary bladder is innervated by parasympathetic cholinergic nerves. Acetylcholine contracts the detrusor smooth muscle through muscarinic receptors of which the M3 subtype is predominantly involved. The action of solifenacin results in reduced symptoms of urgency and urge incontinence and increases bladder capacity.
<b>Licensed indication(s):</b>  Treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men who are not adequately responding to treatment with monotherapy <sup>1</sup> .
<b>Proposed use</b> (if different from, or in addition to, licensed indication above): N/A
<b>Course and cost:</b>  Pack of 30 tablets = £27.62p <sup>5</sup> , annual costs £336.04 p*
<b>Current standard of care/comparator therapies:</b>  Tamsulosin 400mcg MR tablets plus solifenacin 5mg or 10mg tablets
<b>Relevant NICE guidance:</b>  NICE Clinical Guideline 97 -The management of lower urinary tract symptoms in men

\*calculated by cost per tablet x 365

## Background and context

Vesomni<sup>®</sup> is a combination of solifenacin & tamsulosin licensed for the treatment of moderate to severe storage symptoms (urgency, increased micturition frequency) and voiding symptoms associated with benign prostatic hyperplasia (BPH) in men who are not adequately responding to treatment with monotherapy. This was identified for review via a request from a CCG and horizon scanning. No NICE Technology Appraisal is scheduled for completion at the time of writing the evidence review.

The NICE Clinical Guideline 97 covers the treatment of Lower Urinary Tract Symptoms (LUTS) in men, LUTS comprises storage symptoms (e.g. frequency, nocturia, urgency, urinary incontinence), voiding symptoms (e.g. weak or intermittent stream, hesitancy, straining, terminal dribbling and incomplete emptying) and post-micturition symptoms (e.g. post micturition dribbling) affecting the lower urinary tract.<sup>6</sup>

Age is an important risk factor for LUTS and the prevalence of LUTS increases as men get older. Bothersome LUTS can occur in up to 30% of men older than 65 years.<sup>6</sup>

There are many possible causes of LUTS such as abnormalities or abnormal function of the prostate, urethra, bladder or sphincters. In men, the most common cause is benign prostatic enlargement (BPE), which obstructs the bladder outlet. BPE happens when the number of cells in the prostate increases, a condition called benign prostatic hyperplasia (BPH).<sup>6</sup>

Treatment of LUTS is only recommended to men with bothersome LUTS when conservative management options have been unsuccessful or are not appropriate. An alpha blocker (alfuzosin, doxazosin, tamsulosin or terazosin) should be offered to men with moderate to severe LUTS (taking into account comorbidities and current treatment). An anticholinergic should be considered as well as an alpha blocker to men who still have storage symptoms after treatment with an alpha blocker alone.<sup>6</sup>

## Summary of evidence

### Summary of efficacy data in proposed use:

The key evidence in support of Vesomni<sup>®</sup> is a 12-week double-blind trial which aimed to demonstrate superiority compared with placebo and noninferiority compared with tamsulosin alone for total International Prostate Symptom Score (IPSS), as well as superiority compared with tamsulosin for Total Urgency and Frequency Score (TUFS). It comprised a once-daily fixed dose combination tablet containing solifenacin and an oral controlled absorption system formulation of tamsulosin.<sup>9</sup>

1334 male patients aged 45 years and over with substantial storage<sup>14</sup> and voiding component LUTS for three or more months, not adequately treated by  $\alpha$ -blocker monotherapy were included. They had a total International Prostate Symptom Score (IPSS)  $\geq 13$ , maximum urinary flow rate ( $Q_{max}$ ) 4.0-12.0ml/s, two or more urgency episodes per 24h of Patient Perception of Intensity of Urgency Scale 3 or 4, and eight or more micturitions per 24h.

Patients were randomised to treatment with placebo, tamsulosin oral controlled absorption system (TOCAS) 0.4mg, solifenacin 6mg and tamsulosin 0.4mg OCAS, and solifenacin 9mg and tamsulosin 0.4mg OCAS.

Solifenacin 9mg plus tamsulosin 0.4mg did not meet the success criteria against tamsulosin and is not licensed in the UK, for this reason this is not discussed further.<sup>1,14</sup>

Solifenacin 6mg plus tamsulosin 0.4mg was statistically significantly superior to placebo and non-inferior to tamsulosin in reducing total IPSS. It was statistically significantly superior to both placebo and tamsulosin alone in reducing TUFS. The mean improvement in TUFS from a baseline of 27 points was 8.1 points, this was 3.7 and 1.4 points greater than that achieved with placebo and tamsulosin respectively.<sup>14</sup>

The statistically significant greater improvement in TUFS compared with tamsulosin was supported by effects on some (but not all) secondary storage parameters, micturition frequency, mean voided volume per micturition and IPSS storage score. This was also accompanied by significant improvements in the disease specific quality of life markers IPSS QoL and OAB-QHRQoL total score<sup>1</sup>.

### Other efficacy data:

A further study reviewing the efficacy of Vesomni<sup>®</sup> is a randomised double-blind, parallel-group, placebo-controlled, multicentre, dose-ranging study.<sup>10</sup> In this study 937 male patients aged 45 years and over with storage and voiding LUTS were investigated. They had a total International Prostate Symptom Score (IPSS)  $>13$ , maximum urinary flow rate ( $Q_{max}$ ) 4.0-15.0ml/s, with a volume voided during free flow  $\geq 120$ ml.

Patients were randomised to treatment with placebo, tamsulosin OCAS 0.4mg monotherapy, solifenacin 3, 6 or 9mg plus tamsulosin 0.4mg OCAS, or dose-matched solifenacin monotherapy. The primary endpoint was change from baseline to end of treatment of IPSS.

In this study there was no statistically significant decrease in total IPSS obtained with tamsulosin alone, or with any of the solifenacin / tamsulosin preparations compared with the decrease associated with placebo. Further, there was no statistically significant effect between tamsulosin alone and the combination products.<sup>10</sup> The Medicines Evaluation Board concluded that patients with a limited level of storage symptoms do not benefit from additional treatment with solifenacin and should therefore not be part of the target population of the combination treatment.<sup>14</sup>

### Summary of safety data:

In the NEPTUNE trial<sup>9</sup>, the safety assessments included adverse events (AE), PVR volume,  $Q_{max}$ , vital signs, electrocardiogram parameters, physical examination and standard laboratory measurements. 13% of patients reported adverse events that were considered to be related to the study medication, and 2% of patients discontinued treatment. The most common reported drug related adverse events were dry mouth and constipation for the combination product. Small increases in PVR volume were observed but were not considered to be clinically relevant and all other safety assessments were within expected ranges.

There have been historical concerns that men with bladder outlet obstruction (BOO) may experience urinary retention (UR) and a trial<sup>11</sup> intending to investigate the safety of a combination of solifenacin and tamsulosin in men with LUTS and BOO was undertaken. This was a randomised, double-blind, parallel-group, placebo-controlled multicentre (36 sites across Europe and USA) study in men aged 45 years or over, with LUTS and BOO for  $\geq 3$  months, total IPSS  $\geq 8$ , maximum urinary flow rate ( $Q_{max}$ )  $\leq 12$  mL/s, BOO index  $\geq 20$  and voided volume  $\geq 120$  mL during free flow at baseline. The primary objective was to evaluate the non-inferiority of tamsulosin 0.4mg plus solifenacin 6mg and 9mg versus placebo on urodynamic variables as safety measures. Secondary objectives were to evaluate safety and tolerability. Of 222 patients enrolled in the study 192 (87%) completed. Both active treatment groups were non-inferior to placebo at week 12 indicating that the combination has no negative effect on bladder function during voiding in an obstructed population. There was no statistical evidence of an increased risk of acute urinary retention.

The Medicines Evaluation Board concluded that in men the risk of urinary retention and AUR (urinary retention requiring catheterization) on Vesomni<sup>®</sup> is low (0.5% and 0.3% respectively), particularly when taking into account that urinary retention is one of the complications of the underlying disease.<sup>14</sup>

VICTOR trial<sup>12</sup> was a 12-week, double-blind, placebo controlled trial assessing the safety and tolerability of solifenacin 5mg and tamsulosin 0.4mg dual therapy against tamsulosin 0.4mg monotherapy. Efficacy primary endpoint was the mean change from baseline to week 12 or end of treatment in micturitions per 24 hours, measured by 3-day bladder diary. All adverse events were monitored throughout the study.

203 patients were randomised and of these 82% of the combination therapy and 89% of the monotherapy completed the study. The most common reason for discontinuation was adverse events, resulting in a withdrawal of 22 patients, 15 (7%) in the combination therapy and 7 (4%) in

the monotherapy. 91 (45%) of the combination therapy and 77 (39%) of the monotherapy had treatment emergent adverse events reported but only 18% and 19% respectively were treatment related. Frequently reported adverse events were dry mouth (7% and 3%), dizziness (3% and 2%) and urinary retention (3% and 0%), percentages reported respectively in brackets. Overall the solifenacin and tamsulosin combination was well tolerated compared with placebo and tamsulosin. However it recommended further studies to include larger patient populations and longer durations of therapy.

The most frequently reported adverse reactions during the clinical studies performed for the development of Vesomni<sup>®</sup> were dry mouth (9.5%), followed by constipation (3.2%) and dyspepsia (including abdominal pain; 2.4%). Other common undesirable effects are dizziness (including vertigo; 1.4%), vision blurred (1.2%), fatigue (1.2%), and ejaculation disorder (including retrograde ejaculation; 1.5%). This is in line with the well-known AE profile of the individual substances; no new AEs specific for the combination were detected.<sup>14</sup>

### Strengths and limitations of the evidence:

- Efficacy data is limited to a single Phase 3 trial of 12 weeks duration.
- The trial demonstrated the short-term efficacy of Vesomni over both placebo and tamsulosin at reducing the Total Urgency and Frequency Score (TUFS). The improvement in TUFS were also accompanied by greater improvements in disease specific quality of life markers.
- In men the risk of urinary retention and AUR (urinary retention requiring catheterization) on the FDC 6mg/0.4 mg is low (0.5% and 0.3% respectively), particularly when taking into account that urinary retention is one of the complications of the underlying disease.
- There is extensive experience with the single-entity products, solifenacin and tamsulosin. Vesomni has the same adverse reactions as the 2 individual active substances without synergism on the level of adverse events.

### Summary of evidence on cost effectiveness:

No published evidence on the cost effectiveness of Vesomni<sup>®</sup> in the UK has been identified. There are no published active-comparator trials for the use of Vesomni<sup>®</sup>

### Prescribing and risk management issues:

Vesomni<sup>®</sup> is contra-indicated in patients<sup>1</sup>

- with hypersensitivity to the active substance(s) or to any of the excipients
- undergoing haemodialysis
- with severe hepatic impairment
- with severe renal impairment who are also treated with a strong cytochrome P450 (CYP)

3A4 inhibitor, e.g., ketoconazole

- with moderate hepatic impairment who are also treated with a strong CYP3A4 inhibitor, e.g., ketoconazole
- with severe gastrointestinal conditions (including toxic megacolon), myasthenia gravis or narrow-angle glaucoma and patients at risk for these conditions
- with a history of orthostatic hypotension
- scheduled for cataract or glaucoma surgery

Caution is advised when used in severe renal impairment, risk of urinary retention, gastrointestinal obstructive disorders, risk of decreased gastrointestinal motility, hiatus hernia/gastro-oesophageal reflux and/or who are concurrently taking medicinal products (such as bisphosphonates) that can cause or exacerbate oesophagitis, autonomic neuropathy.

The patient should be examined in order to exclude the presence of other conditions, which can cause similar symptoms to benign prostatic hyperplasia. If a urinary tract infection is present, appropriate antibacterial therapy should be started.

QT prolongation and Torsade de Pointes have been observed in patients with risk factors, such as pre-existing long QT syndrome and hypokalaemia, who are treated with solifenacin succinate.

As with other alpha1-adrenoceptor antagonists, a reduction in blood pressure can occur in individual cases during treatment with tamsulosin, as a result of which, rarely, syncope can occur. Patients starting treatment with Vesomni® should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have disappeared.

## Commissioning considerations:

### Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Tamsulosin 400mcg MR capsules	One daily	£5.10	£64.48
Solifenacin 5mg tablets	One daily	£27.62	£336.04
Oxybutinin 10mg MR	One daily	£27.54	£335.07
Solifenacin 10mg tablets	One daily	£35.91	£436.90
Solifenacin 6mg + tamsulosin 400mcg MR tablets	One daily	£27.62	£336.04

Costs based on Drug Tariff prices April 2014  
This table does not imply therapeutic equivalence of drugs or doses.

**Associated additional costs or available discounts:**

No additional monitoring costs are anticipated with the use of Vesomni®

**Productivity, service delivery, implementation:**

No productivity, service delivery or implementation impacts are anticipated.

**Anticipated patient numbers and net budget impact:**

There are 126,000 men > 65 years in Lancashire, NICE estimates that bothersome LUTS can occur in 30% of men over the age of 65 years. Based on this estimation there are 37,800 men over the age of 65 years with bothersome LUTS in Lancashire.

Assuming that 50% of these patients will present for treatment this estimates that 18,900 patients would present for treatment with an alpha-blocker. This estimation is supported by prescribing data which estimates that there are 15,000 patients currently being treated with alpha-blockers in Lancashire.

Assuming that 25% of patients will not adequately respond to monotherapy and require the addition of an anticholinergic 4,725 patients will require treatment with combination therapy.

Based on savings of £64.48 per patient per year for Vesomni® versus tamsulosin and solifenacin prescribed as separate agents the annual cost saving if all patients on combination therapy received Vesomni® the savings generated from replacing the separate agents with Vesomni® would be in the order of £304,668.

**Innovation, need, equity:**

There is no evidence to suggest Vesomni® is more innovative than tamsulosin and solifenacin as individual agents, or that there is an unmet pharmaceutical need.  
No specific equity considerations are anticipated.



## References

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4. Astellas. Summary of Product Characteristics – Vesicare 5mg and 10mg film-coated tablets; December 2013. Accessed 14<sup>th</sup> April 2014 at: <http://www.medicines.org.uk/emc/medicine/14900/SPC/Vesicare+5mg+%26+10mg+film-coated+tablets/>
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6. The management of lower urinary tract symptoms in men. NICE Clinical Guideline 97. May 2010. Accessed 20<sup>th</sup> April 2014 at: <http://guidance.nice.org.uk/CG97>
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12. Steven A. Kaplan, Kurt McCammon, Roger Fincher, Allam Fakhoury and Weizhong He: “Safety and Tolerability of Solifenacin Add-on Therapy to  $\alpha$ -Blocker Treated Men With Residual Urgency and Frequency (VICTOR)”. *J Urol* 2013;189: S129-S134. DOI: <http://dx.doi.org/10.1016/j.juro.2012.11.030>
13. MIMS October 2013, p225 – 231
14. Netherlands Medicines Agency. European Public Assessment Report – Vesomni; 6 May 2013; <http://www.cbg-meb.nl/CBG/en/search/searchresult/default.htm?qry=vesomni&language=en>

Table: Summary of key solifenacin/tamsulosin RCT relevant to use for LUTS in BPH

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Combination Therapy with Solifenacin and Tamsulosin Oral Controlled Absorption System in a Single Tablet for Lower Urinary Tract Symptoms in Men: Efficacy and Safety Results from the Randomised Controlled NEPTUNE Trial						
9	Randomised, double-blind, parallel group, placebo controlled, multicentre 12-week, phase 3 study. N=1334	Male $\geq$ 45 years with BPH, mean age 65yrs, 99% white, LUTS $\geq$ 3mths with total IPSS $\geq$ 13 and a Qmax of 4.0-12.0 ml/s with a voided volume $\geq$ 120mL during free flow, two or more urgency episodes per 24hr (PPIUS grade 3 or 4) and $\geq$ 8 micturitions per 24hr.  Exclusion criteria: prostate weight >75g, evidence UTI or history/diagnosis of relevant medical condition, and a PVR volume > 150mL.	1334 patients randomised 1:1:1:1  Solifenacin 6mg + tamsulosin MR 0.4mg (S6T) n=339, 88% completed  Solifenacin 9mg + tamsulosin MR 0.4mg (S9T) n=327, 90% completed  Tamsulosin MR 0.4mg (T) n=327, 90% completed  Placebo (P) n=341, 92% completed  Overall 1199 (90%) patients completed trial	Change in IPSS from baseline to end of treatment  S6T (from a mean baseline of 18.3): -7.0***,^^,¥ S9T(from a baseline of 18.6): -6.5**,^,β Tamsulosin (from a baseline of 18.7): -6.2* Placebo (from a baseline of 19): -5.4  Improvement in TUFS from baseline to end of treatment S6T (from a mean baseline of 27.0) : -8.1***,^ S9T (from a mean baseline of 26.4)): -7.6*** Tamsulosin (from a mean baseline of 27.8):-6.7*** Placebo (from a mean baseline of 27.1):-4.4	Secondary endpoints:  Change from baseline to end of treatment of IPSS sub-scores (DOO), micturition diary variables (DOO), and quality of life parameters (POO).  Significant improvement in QoL scores with combination compared with placebo and with tamsulosin.	Predominantly DOOs but POOs in both primary and secondary outcomes.  Allocation concealment stated using interactive response technology. All treatment confirmed as identical in appearance.  Power calculations presented.  Level 1 & 3 evidence
Footnotes: BPH - benign prostatic hyperplasia; LUTS – lower urinary tract symptoms; UTI – urinary tract infection; PVR – post-void residual; MR – modified release; IPSS – International Prostate Symptom Score; DOO – disease orientated outcomes; TUFS – total urgency and frequency score; POO – patient orientated score; AE – adverse effect; AUR – acute urinary retention *p<0.05 compared with placebo, **p<0.01 compared with placebo, ***p≤0.001 compared with placebo ^p<0.05 compared with tamsulosin, ^^p<0.001 compared with tamsulosin ¥Noninferiority compared with tamsulosin was demonstrated by S6T, (p=0.001 with multiplicity adjustment) βNoninferiority of S9T compared with tamsulosin was not shown to be statistically significant when evaluated by multiplicity testing.						

### Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
<b>Level 1</b>	Patient-oriented evidence from: <ul style="list-style-type: none"> <li>• high quality randomised controlled trials (RCTs) with low risk of bias</li> <li>• systematic reviews or meta-analyses of RCTs with consistent findings</li> </ul>	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
<b>Level 2</b>	Patient-oriented evidence from: <ul style="list-style-type: none"> <li>• clinical trials at moderate or high risk of bias</li> <li>• systematic reviews or meta-analyses of such clinical trials or with inconsistent findings</li> <li>• cohort studies</li> <li>• case-control studies</li> </ul>	
<b>Level 3</b>	Disease-oriented evidence, or evidence from: <ul style="list-style-type: none"> <li>• consensus guidelines</li> <li>• expert opinion</li> <li>• case series</li> </ul>	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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