

Public Assessment Report

Scientific discussion

**Volutsa 6 mg/0.4 mg modified-release tablets
(solifenacin succinate/tamsulosin HCl)**

NL/H/3131/001/MR

Date: 11 September 2014

This module reflects the scientific discussion for the approval of Volutsa 6 mg/0.4 mg modified-release tablets. The procedure was finalised on 14 May 2014. For information on changes after this date please refer to the module 'Update'.

This report includes a summary, on pages 19-21.

List of abbreviations

AR	Adrenoceptor
ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
BPH	Benign Prostatic Hyperplasia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C _{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
ECHA	European Chemicals Agency
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
EURD	European Union Reference Date
FAS	Full Analysis Set
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HRQoL	Health-related Quality of Life
ICH	International Conference of Harmonisation
IPSS	International Prostate Symptom Score
LUTS	Lower Urinary Tract Symptoms
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OAB	Overactive Bladder
OCAS	Oral Controlled Absorption System
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
PBT	Persistent, Bioaccumulative and Toxic
PDCO	Paediatric Committee
PEC	Predicted Environmental Concentration
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PPIUS	Patient Perception of the Intensity of Urgency Scale
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SmPC	Summary of Product Characteristics
STP	Sewage-Treatment Plant
t _½	Half-life
t _{max}	Time for maximum concentration
TOCAS	Tamsulosin Oral Controlled Absorption System
TSE	Transmissible Spongiform Encephalopathy
TUS	Total Urgency Score
USP	Pharmacopoeia in the United States
vPvB	very Persistent and very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Volutsa 6 mg/0.4 mg modified-release tablets from Astellas Pharma Europe B.V.

The product is indicated for 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.

A comprehensive description of the indications and posology is given in the SmPC.

Volutsa is a fixed dose combination tablet containing two active substances, solifenacin and tamsulosin. These drugs have independent and complementary mechanisms of action in the treatment of lower urinary tract symptoms (LUTS) associated with BPH, with storage symptoms.

Solifenacin is a competitive and selective antagonist of muscarinic receptors and has no relevant affinity for various other receptors, enzymes and ion channels tested. Solifenacin has the highest affinity for muscarinic M3-receptors, followed by muscarinic M1- and M2-receptors.

Tamsulosin is an alpha1-adrenoceptor (AR) antagonist. It binds selectively and competitively to postsynaptic alpha1-ARs, in particular to subtypes alpha1A and alpha1D and is a potent antagonist in lower urinary tract tissues.

This mutual recognition procedure concerns a fixed dose application. Fixed dose combinations contain active substances from medicinal products already authorised in the EEA but not hitherto used in combination for therapeutic purposes. In these kinds of applications the results of new clinical trials relating to that combination are provided. However, it is not necessary to provide pre-clinical and clinical data relating to each individual active substance.

The marketing authorisation is granted based on article 10b of Directive 2001/83/EC. The concerned member states (CMS) involved in this procedure were Italy, Portugal and Spain.

Solifenacin was first approved in the Netherlands on 16 December 2003 under the trade name of Vesicare 5 mg and 10 mg film-coated tablets (NL License RVG 29151-29152). Subsequently it was registered throughout the EU with mutual recognition procedure NL/H/0487/001-002. The recommended dose of solifenacin for the treatment of urinary frequency, urinary incontinence or urgency associated with overactive bladder (OAB) in Europe is 5 mg once daily, which can be increased to 10 mg once daily.

The innovator product containing tamsulosin, Omnic 0.4 mg modified-release capsules (NL License RVG 17931), was first approved on 11 April 1995 in the Netherlands. It is available for the treatment of patients with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) at a recommended dose of 0.4 mg once daily.

The monoproducts Vesicare and Omnic have the same MAH as the combination product Volutsa: Astellas Pharma Europe B.V. A combination product, Vesomni 6 mg/0.4 mg has been registered by this MAH in the Netherlands since 6 May 2013 and was part of MRP NL/H/2968/001. The Volutsa and Vesomni dossiers are the same.

The combination of solifenacin and tamsulosin is - among other treatment options - currently advised in "Lower urinary tract symptoms/benign prostate hyperplasia (LUTS/BPH)"¹ and in "The pharmacological treatment of urinary incontinence"². In the guidance from the European Association of Urology and the American Urological Association the combination therapy is mentioned as a possible treatment option, although not in first line.

The combination of the individual products can be considered clinically relevant and generally accepted.

¹ Lower urinary tract symptoms/benign prostate hyperplasia (LUTS/BPH) (ed. JPM Kill), 2010

² Andersson K-E, Appell R, Cardozo L et al. Pharmacological treatment of urinary incontinence, in Abrams P, Khoury S, Wein A (Eds), Incontinence, 3rd International Consultation on Incontinence. Plymouth, Plymbridge Distributors Ltd, UK, Plymouth, 2005, p 811.

National scientific advice meetings took place with the MEB in August 2008, and with AEMPS (Spain), MPA (Sweden) and MHRA (UK) in 2012. This concerned the clinical development plan.

The combination of solifenacin/tamsulosin has not been tested in children. A class waiver on the condition is listed and confirmed by the Paediatric Committee (PDCO, EMA/973755/2011 EMA Decision CW/1/2011 of 19 December 2011). A paediatric investigational plan has been approved by the PDCO for solifenacin; the investigation of tamsulosin in children was discontinued due to lack of efficacy. No paediatric indication for the FDC solifenacin/tamsulosin 6 mg/0.4 mg is anticipated and no paediatric off-label use of the fixed dose combination is expected.

II. QUALITY ASPECTS

II.1 Introduction

Volutsa 6 mg/0.4 mg is a modified-release tablet composed of one layer containing 6 mg solifenacin succinate (immediate release) and a second layer containing 0.4 mg tamsulosin hydrochloride (Oral Controlled Absorption System/modified release). It is a round, red film-coated tablet debossed with "6/0.4".

The modified-release tablets are packed in aluminium blister packs.

The excipients are: mannitol (E421), maltose, macrogol 7.000.000, macrogol 8000, magnesium stearate (E470b), butylhydroxytoluene (E321), colloidal silica anhydrous (E551), hypromellose (E464), iron oxide red (E172).

II.2 Drug Substances

Tamsulosin hydrochloride

The first active substance is tamsulosin hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is slightly soluble in water, is not hygroscopic and has no known polymorphism. Tamsulosin hydrochloride contains one chiral centre and is manufactured as the pure levorotary form.

The CEP procedure is used for the active substance tamsulosin. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance

The drug substance specification is in line with the Ph.Eur. with no additional requirements. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches.

Stability of drug substance

The active substance is stable for 3 years if stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

Solifenacin succinate

The second active substance is solifenacin succinate, an established active substance that is not described in any pharmacopoeia. The active substance is freely soluble in water, is not hygroscopic and has no known polymorphism. Different isomers of solifenacin succinate exist, but the drug substance is manufactured as a single-isomer form. Full documentation on the active substance has been included in the dossier.

Manufacturing process

The manufacturing process consists of three steps. No class 1 organic solvents or heavy metal catalysts are used in the process. The active substance has been adequately characterized and acceptable specifications have been adopted for the starting materials, solvents and reagents.

Quality control of drug substance

The drug substance specification has been established in-house. The specification is acceptable in view of the route of synthesis and the various European guidelines. Batch analytical data demonstrating compliance with the drug substance specification have been provided for 25 batches of drug substance.

Stability of drug substance

Stability data on the active substance have been provided for three pilot-scale batches from the first manufacturer and six production-scale batches (three from each sites) that were stored at 25°C/60% RH (60 months) and 40°C/75% RH (6 months). No changes or trends were seen in any of the tested parameters. These data support the authorised retest period of 3 years without any special storage condition.

II.3 Medicinal Product

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The aim of the development was to make a fixed dose combination (FDC) tablet consisting of two layers to result in drug release patterns similar to those of the already authorised single-entity drug products. The formulation and manufacturing method for the tamsulosin layer for the FDC core tablets are the same as those for the TOCAS tablets. The OCAS (Oral Controlled Absorption System) technology is used in the registered product of tamsulosin prolonged-release tablets (abbreviated as TOCAS tablet). The OCAS is a prolonged release gel matrix system that is composed of a gel-forming agent and a gel-enhancing agent as its major components. During development several aspects of the formulation were evaluated that could have an effect on the dissolution characteristics of the drug product. Comparative dissolution studies at different pH levels were performed to demonstrate similarity between the finalized FDC tablet and the authorised single-entity products. The batches of drug product used in the pivotal clinical trials were manufactured according to the finalized formulation and manufacturing process. Overall, extensive studies were conducted during development of the manufacturing process. On the basis of the provided data, the manufacturing process is considered to be robust and the pharmaceutical development has been described in sufficient detail.

Manufacturing process

The granulates for the solifenacin layer and the tamsulosin layer are manufactured separately by means of wet granulation. The bi-layered tablet is then compressed in stages on a bi-layered tablet press and the bi-layered cores are film-coated. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for four full-scale batches.

Control of excipients

The excipients comply with relevant Ph.Eur. or in-house requirements. These specifications are acceptable.

Quality control of drug product

The product specification includes tests for appearance, identity, related substances, uniformity of dosage units, dissolution, assay, loss on drying and microbial quality. Except for related substances and assay, the release and shelf-life requirements are identical. The specification is acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on five production-scale batches of drug product, demonstrating compliance with the release specification.

Stability of drug product

Stability data on the product has been provided on three full-scale batches that were stored at 25°C/60%RH (30 months), 30°C/65%RH (30 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in Al-

AI blisters. A slight increase of impurities is seen at all three storage conditions as well as a decrease in tamsulosin assay. The levels of impurities and assay remained well within the acceptance criteria. No trends or changes were seen in any of the other tested parameters. The drug product was demonstrated to be photostable and no light protection is required. The proposed shelf-life of 36 months without any special storage conditions is justified.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Volutsa 6 mg/0.4 mg modified-release tablets has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitment was made:

- The MAH committed to continue the on-going stability studies.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

For this fixed dose application, no new data regarding pharmacology or pharmacokinetics have been provided. No new studies have been performed and none are considered necessary. This is acceptable, as both active substances are well known.

Solifenacin and tamsulosin are antagonists for different receptors and there is no cross reactivity of these drugs at the receptor level. It is therefore expected that the individual components of the FDC will work in a complementary manner. Based on the mode of action and the target organs of the single entity products and the large exposure margins for the adverse effects observed with tamsulosin, there are no indications that the FDC would potentiate the adverse effects of the individual compounds.

The MAH provided sufficient information to substantiate that specific solifenacin impurities showed negative results in the genotoxicity and carcinogenicity studies in its comprehensive toxicology program. These impurities are considered non-genotoxic and qualified by testing of the parent. This is considered appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Environmental Risk Assessment has been performed for the individual compounds solifenacin succinate and tamsulosin hydrochloride.

Based on the submitted studies and the environmental risk assessment performed, it can be concluded that the use of solifenacin succinate does not lead to an environmental risk for the STP, nor the surface water, groundwater and sediment compartment.

The PBT assessment is finished based on the same guidance (ECHA, 2008, Chapter R7a). Solifenacin is considered neither Persistent, Bioaccumulative and Toxic (PBT), nor very Persistent and very Bioaccumulative (vPvB).

The PBT assessment for tamsulosin is complete. Log K_{ow} of tamsulosin has been determined. The PBT assessment has been concluded. Tamsulosin is not PBT, nor vPvB. The PEC_{surfacewater} for tamsulosin is below the action limit of 0.01 µg/L. The ERA does not proceed to Phase IIA as the action limit is not exceeded and further assessment is not deemed necessary.

Considering these observations, solifenacin and tamsulosin are not expected to pose a risk to the environment.

III.3 Discussion on the non-clinical aspects

The non-clinical overview on the pharmacology, pharmacokinetics and toxicology is based on up-to-date and adequate scientific literature. Both active substances are well known. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

For the clinical development of the fixed dose combination (FDC) of solifenacin and tamsulosin, 6 studies in healthy subjects were performed (see table 1). In study 905-CL-048 separate tablets of solifenacin at a dose of 10 mg, and tamsulosin at a dose of 0.4 mg, were used. In the other studies, the FDC was used at doses of 3 mg/0.4 mg (solifenacin/tamsulosin), 6 mg/0.4 mg and/or 9 mg/0.4 mg. In study 905-CL-071, both single-entity products and FDC tablets were used.

Table 1 Individual Clinical Pharmacology Studies

905-CL-048	An open label three-way crossover multiple dose study to evaluate the pharmacokinetic interaction between solifenacin succinate and tamsulosin HCl
905-CL-053	An open-label, randomized, two-way crossover multiple dose study to evaluate the steady state pharmacokinetics of the two final combination tablet formulations (EC905; tamsulosin HCl/solifenacin succinate; 6 mg/0.4 mg and 9 mg/0.4 mg) in healthy male volunteers over 45 years of age
905-CL-054	An open-label, single-dose, randomized, three-way crossover study to evaluate the effect of food on the pharmacokinetics of solifenacin and tamsulosin administered as combination tablet in young, healthy male subjects
905-CL-071	An open-label, parallel group, randomized, two-way crossover, multiple dose study to compare the pharmacokinetic profiles of solifenacin succinate and tamsulosin HCl following co-administration of single entity tablets and administration of three different dose strengths of the FDC tablet
905-CL-072	An open-label, randomized, three-period crossover, single-dose study to compare the pharmacokinetics of the final FDC formulation to marketed solifenacin and tamsulosin OCAS
905-CL-078	A phase 1, open-label, one-sequence study to assess the effect of verapamil on the steady state pharmacokinetics of solifenacin and tamsulosin administered as combination tablet in healthy male subjects

IV.2 Pharmacokinetics

Fully validated analytical methods have been applied showing that the methods were selective, sensitive, accurate and precise.

The interaction study 905-CL-048 evaluating the interaction between solifenacin and tamsulosin showed only an effect of solifenacin on the pharmacokinetics of tamsulosin, resulting in a increase in AUC values by about 24%. In this 3-way crossover interaction study, 24 healthy male volunteers received Omnic OCAS 0.4 mg (tamsulosin prolonged-release tablet) once daily for 12 days, Vesicare (10 mg solifenacin tablet) once daily for 12 days and the combination of Omnic OCAS and Vesicare once daily for 12 days, in one of the treatment periods. As both drugs are substrate for CYP3A4 but do not inhibit this enzyme, an interaction was not expected. A possible explanation could be that solifenacin due to its antimuscarinic effect may prolong the transit time and as such may increase the bioavailability of tamsulosin. As solifenacin and tamsulosin are co-administered in clinical practise, this observation is considered to be clinically not relevant.

Comparing the pharmacokinetics of the 0.4 mg/9 mg FDC with the marketed 0.4 mg Omnic OCAS and the 10 mg Vesicare tablet (study 905-CL-072), solifenacin exposure is about 10% lower after administration of the 0.4 mg/9 mg FDC tablet vs. the 10 mg Vesicare tablet. The observed difference can be likely explained to the difference in the administered dose, taking into account the known linear pharmacokinetics for solifenacin (SmPC Vesicare). For tamsulosin, the AUC and C_{max} was about 27 and 24% higher after administration of the 0.4 mg/9 mg FDC compared to Omnic OCAS 0.4 mg tablet. This was already observed in the interaction study -048.

As in clinical studies separate tablets have been used, a bioavailability study is carried out to evaluate the pharmacokinetics of solifenacin and tamsulosin after administration of the FDC and the single clinical trial formulations (study 905-CL-071). The statistical analysis showed that the single formulations were bioequivalent to the fixed dose combinations and that the data obtained for the single formulations can be combined and/or extrapolated to the fixed dose combinations.

The effect of food on the pharmacokinetics of both single entity compounds has previously been investigated (solifenacin in studies 905-CL-003 and 905-CL-030, tamsulosin OCAS in study 617-CL-302 and G580G06A11). For solifenacin no food effect was observed. For tamsulosin the rate and extent of absorption of tamsulosin administered as Omnic OCAS prolonged release tablet are not affected by a food low-fat meal, while the extent of absorption increased by 64% and 149% (AUC and C_{max} respectively) by a high-fat meal compared to fasted.

The results obtained for the FDC in the current submitted study 905-CL-054 are in line with the results obtained previously. For solifenacin no clinical significant food effect is observed after intake of a low-fat or a high-fat meal. For tamsulosin no clinical significant food effect is observed after intake of a low-fat meal. AUC and C_{max} increased 33 and 54%, respectively after intake of a high-fat meal. This is considered not clinically relevant and the FDC can be taken with or without food, as recommended in the SmPC.

After once daily administration of the FDC no unexpected accumulation occurred (905-CL-053). Dose normalised AUC_{tau} and C_{max} indicated a dose linear increase for solifenacin after administration of the 0.4 mg/6 mg and the 0.4 mg/9 mg FDC.

Solifenacin and tamsulosin are both substrates for CYP3A4. Verapamil, a moderate CYP3A4 inhibitor, increased the steady state AUC_{tau} and C_{max} values of solifenacin (a CYP3A4 substrate) by 63 and 60%, respectively (study 905-CL-078). This effect was smaller than observed with ketoconazole (200mg/day) resulting a 2-fold increase in AUC (SmPC Vesicare). In the same study it was shown that verapamil increased the steady state AUC_{tau} and C_{max} values of tamsulosin (a CYP3A4 substrate) by 122 and 115%, respectively. This effect was smaller than observed with ketoconazole (400 mg/day) resulting in a 180% increase in AUC and 120% increase in C_{max} (SmPC Omnic OCAS).

Population pharmacokinetic analysis identified alpha1-acidglycoprotein as the strongest covariate with the most relevant impact on AUC of solifenacin and tamsulosin (data from studies 905-CL-052 and 905-CL-055). This is not unexpected as tamsulosin and solifenacin are strongly bound to alpha1-acidglycoproteins. In study 905-CL-052, food intake, co-administration with tamsulosin OCAS and concomitant intake of CYP3A4 inhibitors were not identified as significant covariates for solifenacin. The lack of a clear signal of the covariate CYP3A4 can be explained by the fact that the data base only included a limited number of subjects treated with CYP3A4 inhibitors which were also mostly mild inhibitors. For tamsulosin, food intake, co-administration with solifenacin (6 and 9 mg) and concomitant intake of either CYP3A4 or CYP2D6 inhibitors were not identified as significant covariates. The lack of food effect may be because most patients who took their medication after a meal, probably had a light meal which does not affect the PK of tamsulosin. The number of subjects using a CYP3A4 or CYP2D6 inhibitor was too small to detect an effect.

Additional *in vitro* inhibition studies have been submitted to evaluate the potential of solifenacin and its metabolites and tamsulosin to inhibit CYP enzymes. The results showed that solifenacin, its N-oxide metabolite, its 4R-hydroxy metabolite, its 4R-hydroxide-N-oxide metabolite and its N-glucuronide metabolite do not inhibit CYP2B6, 2C8 and 2E1. Furthermore, tamsulosin does not inhibit CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4.

IV.3 Pharmacodynamics

Only one study including pharmacodynamic data was submitted (study 905-CL-052). This study evaluated the optimum solifenacin dose, for the tamsulosin dose of 0.4 mg day was considered as optimal a priori. Efficacy and safety data were used to identify the optimal dose supported by modelling data. The fixed tamsulosin dose limited the conclusions on this active substance.

The effect on micturition frequency of the FDC was proportional with the AUC of solifenacin. The effect was independent of the AUC of tamsulosin. The decrease in micturition frequency was most pronounced patients with 2 or 3 urgencies and more than 8 micturitions a day (as compared to patients with 0 to 1 urgencies and more that 8 micturitions a day).

Urgency decreased with an increase in AUC of solifenacin in the presence of tamsulosin. The drug and placebo effect are more pronounced in subjects with 2 or 3 urgencies and more than 8 micturitions a day (as compared to patients with 0 to 1 urgencies and more than 8 micturitions a day).

Mean volume voided increased with an increase in solifenacin AUC and this effect was independent of the baseline value.

The model predicts an increase in IPSS (International Prostate Symptom Score) voiding score with increasing AUC of solifenacin indicating that solifenacin alone has a negative effect on the IPSS voiding score. In the presence of tamsulosin, an improvement of the IPSS voiding score is observed for the combination.

In conclusion, the placebo and drug effect are proportional to the baseline value and simulations have shown that the decrease in total urgency score is most pronounced in patients with LUTS associated with BPH, 8 or more micturitions per day and 3 or more urgencies of grade 3 or 4.

IV.4 Clinical efficacy

In the clinical development program of the fixed dose combination, efficacy was evaluated in 2 double-blind, randomized, placebo-controlled studies, i.e. the phase 2 dose-ranging study 905-CL-052 and the phase 3 study 905-CL-055.

Efficacy was also evaluated, as a secondary objective, in the phase 2 urodynamic safety study 905-CL-058 and the long-term safety follow-up phase 3 study 905-CL-057. Studies 905-CL-058 and 905-CL-052 used combination therapy of single-entity tablets, while studies 905-CL-055 and 905-CL-057 used the FDC tablets.

Study 905-CL-052 (SATURN) was a randomized, double-blind, parallel group, placebo controlled, multi-centre dose ranging study of solifenacin succinate (3 mg, 6 mg and 9 mg) in combination with tamsulosin OCAS 0.4 mg compared with solifenacin succinate monotherapy (3 mg, 6 mg and 9 mg) and tamsulosin OCAS 0.4 mg monotherapy in males with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). The total IPSS should be of ≥ 13 .

The efficacy parameters (total IPSS, number of micturitions/24 h, the number of urgency episodes/24 h and voided volume/micturition, as assessed by means of a patient micturition diary) included in this study are well-known and generally used in the assessment of incontinence and storage problems. Quality of life is measured by IPSS (well validated and generally used). This is important to assess the clinical relevance of the found effect. The Primary Efficacy Variable is the change from baseline to endpoint in total IPSS.

Following the run-in period, at visit 2, eligible patients were randomized to one of the 8 treatment groups. The patients took double-blind treatment for a period of 12 weeks. A total of 937 subjects were randomized, of whom 930 (99.3%) took at least 1 dose of the double-blind study drug.

In this study no statistically significant effect was observed for total IPSS obtained with placebo compared with the score obtained with tamsulosin alone, or with any of the FDCs. Further there was no statistically significant effect between tamsulosin alone and the various FDCs. This might be a result of the less severe population included in this study. With this outcome the objective of this study was not met, as none of the active treatments appeared superior over tamsulosin in this trial on the primary endpoint IPSS.

Further it was shown that both FDC 6 mg/0.4 mg and the FDC 9 mg/0.4 mg were on the plateau of the dose-response relationship. There is therefore no additional benefit with the FDC 9 mg/0.4 mg compared to the FDC 6 mg/0.4 mg. In the SmPC it is mentioned that the FDC 6 mg/0.4 mg is the maximal dose.

Post-hoc analyses showed opposite trends in the limited storage symptoms subgroup versus the storage symptoms subgroups in most of the parameters. The treatment effect was related to the severity of storage symptoms at baseline. Subjects with LUTS associated with BPH with storage symptoms (micturition frequency ≥ 8 and ≥ 1 urgency episodes grade 3 or 4) received additional benefit from combination treatment of solifenacin – tamsulosin OCAS in comparison with tamsulosin OCAS alone. This beneficial effect was even more pronounced in subjects with a micturition frequency ≥ 8

and ≥ 2 or ≥ 3 urgency episodes grade 3 or 4 (storage symptoms subgroups 2 and 3 respectively). Subjects with limited storage symptoms (<1 urgency/day or <8 micturitions/day) showed a deterioration compared to treatment with tamsulosin alone. The results of the post-hoc analysis are considered only supportive. As this study was designed for finding the optimal dose, a post-hoc analysis is acceptable for identifying the most optimal dose. The results of the post-hoc analysis however do not contribute to the assessment of the efficacy of the FDC.

In conclusion, the results of study 905-CL-052 indicated 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.

Study 905-CL-055 (Neptune) was a randomized, double-blind, parallel group, placebo controlled, multi-centre study of fixed dose combinations of solifenacin succinate (6 mg and 9 mg) with tamsulosin hydrochloride OCAS 0.4 mg and tamsulosin hydrochloride OCAS 0.4 mg monotherapy, in male subjects with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH) with a substantial storage component. Therefore this pivotal study included patients with a micturition frequency of ≥ 8 and at least 2 episodes of urgency with a patient perception of the intensity of urgency scale [PPIUS] grade 3 or 4 per day. The patient criteria for inclusion are clearly based on the results of the dose-finding study (CL-052). The population is comparable with the population intended to be treated

The study comprised a single-blind, 2-week placebo run-in period followed by a randomized, double-blind, placebo-controlled, 12-week treatment period. Patients visited the clinic at screening (visit 1), at the end of the placebo run-in period (visit 2, *i.e.* baseline visit), and after 4, 8 and 12 weeks of double-blind treatment (visits 3, 4, and 5).

The efficacy parameters (total IPSS, number of micturitions/24 h, the number of urgency episodes/24 h and voided volume/micturition, as assessed by means of a patient micturition diary) included in the various studies are well-known and generally used in the assessment of incontinence and storage problems. There were two primary efficacy variables: change from baseline to endpoint in total IPSS, and change from baseline to endpoint in TUS (from micturition diary). Quality of life is measured by IPSS and OAB-questionnaire (both well validated and generally used) this is important to assess the clinical relevance of the found effect. Some importance is given to the urodynamic parameters (Qmax and flow rate). Safety analysis is more or less standard.

A total of 1334 patients were randomized of whom 1329 (99.6%) took at least one dose of the double-blind study medication.

Superiority over placebo is clearly shown for the patient group intended for treatment. The reduction in total IPSS with the FDC tamsulosin/solifenacin 0.4 mg/6 mg was proven non-inferior to the decrease with TOCAS 0.4 mg (-6.2); superiority versus TOCAS 0.4 mg was not shown. Although the improvement with the FDC tamsulosin/solifenacin 0.4 mg/9 mg was numerically better than with TOCAS 0.4 mg, the reduction in total IPSS with the FDC 0.4 mg/9 mg was not proven non-inferior to the reduction with TOCAS 0.4 mg. In all treatment groups, a reduction in total IPSS was observed by week 4, with a small additional improvement observed at week 12.

Table 2 Change from Baseline to Endpoint in Total IPSS (FAS)

	Placebo (n = 318)	TOCAS 0.4 mg (n = 298)	FDC 0.4/6 (n = 313)	FDC 0.4/9 (n = 301)
Baseline				
n	318	297	311	299
Mean (SD)	19.0 (4.48)	18.7 (4.63)	18.3 (4.31)	18.6 (4.31)
Endpoint				
n	316	297	312	297
Mean (SD)	12.8 (6.51)	11.7 (6.07)	10.7 (5.82)	11.4 (6.15)
Mean change from baseline (SE)	-5.4 (0.41)	-6.2 (0.42)	-7.0 (0.41)	-6.5 (0.42)
Mean change vs. placebo (SE)		-0.8 (0.41)	-1.6 (0.40)	-1.1 (0.41)
95% CI		(-1.6, -0.0)	(-2.4, -0.9)	(-1.9, -0.3)
P value vs. placebo		0.039‡	< 0.001§	0.006§
Mean change vs. TOCAS 0.4 mg (SE)			-0.8 (0.41)	-0.3 (0.41)
95% CI			(-1.61, -0.01)	(-1.10, 0.52)

97.5% CI			(-1.73, 0.11)§	(-1.22, 0.64)
P value vs. TOCAS 0.4 mg non-inferiority testing			0.001§	0.028
P value vs. TOCAS 0.4 mg superiority testing			0.048	0.483

‡ Statistically significant not multiplicity adjusted

§ Statistically significant with multiplicity adjustments

On the basis of the results of the general LUTS/BPH parameter total IPSS, it can be concluded that in patients with LUTS associated with BPH, with storage symptoms, the FDC 6 mg/0.4 mg provides a greater improvement in LUTS than placebo and is non-inferior with tamsulosin alone.

The higher dose of FDC 9 mg/0.4 mg is, surprisingly, worse than the lower FDC 6 mg/0.4 mg. This observation further strengthens the observation that both FDC 6 mg/0.4 mg and the FDC 9 mg/0.4 mg were on the plateau of the dose-response relationship.

The FDC 6 mg/0.4 mg improves the total urgency score per 24 hours (TUS/24 h) to a statistically significantly greater extent than both placebo and TOCAS 0.4 mg alone. Again the FDC 9 mg/0.4 mg appeared worse than the FDC 6 mg/0.4 mg.

Table 3 Change from Baseline to Endpoint in TUS (FAS)

	Placebo (n = 320)	TOCAS 0.4 mg (n = 299)	FDC 0.4/6 (n = 314)	FDC 0.4/9 (n = 302)
Baseline				
n	318	299	314	302
Mean (SD)	27.1 (8.80)	27.8 (9.02)	27.0 (8.66)	26.4 (8.34)
Endpoint†				
n	315	295	313	302
Mean (SD)	22.3 (11.39)	20.4 (9.54)	18.5 (9.13)	18.7 (9.51)
Mean change from baseline (SE)	-4.4 (0.68)	-6.7 (0.69)	-8.1 (0.67)	-7.6 (0.69)
Mean change vs. placebo (SE)		-2.3 (0.64)	-3.7 (0.62)	-3.2 (0.63)
95% CI		(-3.5, -1.0)	(-4.9, -2.5)	(-4.4, -1.9)
P value vs. placebo		< 0.001‡	< 0.001‡	< 0.001‡
Mean change vs. TOCAS 0.4 mg (SE)			-1.4 (0.64)	-0.9 (0.64)
95% CI			(-2.7, -0.2)	(-2.2, 0.4)
97.5% CI			(-2.9, 0.0)	(-2.3, 0.5)
P value vs. TOCAS 0.4 mg			0.025§	0.162

‡ Statistically significant not multiplicity adjusted

§ Statistically significant with multiplicity adjustments

Quality of life related to LUTS/BPH was also improved by the FDC tamsulosin 0.4 mg/6 mg as shown by a statistically significantly greater reduction in IPSS QoL score compared to both placebo and TOCAS 0.4 mg.

In addition, bother due to storage symptoms was improved by the FDC tamsulosin/solifenacin 0.4 mg/6 mg. The Overactive Bladder questionnaire (OAB-q) symptom bother score was improved by the FDC tamsulosin/solifenacin 0.4 mg/6 mg to a statistically significantly greater extent than placebo; the greater improvement compared to TOCAS 0.4 mg did not reach statistical significance (P=0.068). The health-related quality of life (HRQoL) total score and the HRQoL coping, concern, sleep and social subscale scores were improved to a statistically significantly greater extent than with both placebo and TOCAS 0.4 mg.

Significantly more patients treated with the FDCs tamsulosin/solifenacin 0.4 mg/6 mg and 0.4 mg/9 mg reported an improvement in overall bladder symptoms since the start of the study compared to patients treated with placebo and TOCAS 0.4 mg. Consistent with the improvement reported by patients, the clinicians also reported a significant improvement in patient's overall bladder symptoms with both FDCs as compared to placebo. In addition, significantly more patients treated with both FDCs reported an improvement in general health since the start of the study compared to patients

treated with placebo.

Conclusion on clinical efficacy

In 1328 patients with LUTS associated with BPH, with a micturition frequency of ≥ 8 and at least 2 episodes of urgency with a patient perception of the intensity of urgency scale (PPIUS) grade 3 or 4 per day, the FDC had to be statistically significantly superior to placebo and non-inferior to TOCAS 0.4 mg alone in terms of improvement of the total IPSS and statistically significantly superior to TOCAS 0.4 mg alone in terms of improvement of the storage parameter TUS/24 h (which captures both frequency and urgency in a single parameter) in the pivotal, confirmatory phase 3 study 905-CL-055.

The above mentioned predefined success criteria for the study were met for the FDC 6 mg/0.4 mg, but not for the FDC 9 mg/0.4 mg. There was no further improvement with the FDC 9 mg/0.4 mg for either primary efficacy variable. The higher dose FDC appeared less effective. This observation is inline with the observation that both FDC 6 mg/0.4 mg and the FDC 9 mg/0.4 mg were on the plateau of the dose-response relationship.

In men with LUTS associated with BPH, with a micturition frequency of ≥ 8 and at least 2 episodes of urgency with a PPIUS grade 3 or 4 per day, the FDC 6 mg/0.4 mg over a 12-week period was:

- Statistically significantly superior to placebo in reducing total IPSS. The mean improvement in total IPSS from a baseline of 18.3 points is 7.0 points reaching a mean total IPSS of 10.7 points. This mean improvement in total IPSS is 1.6 points greater than that achieved with placebo.
- Non inferior to TOCAS 0.4 mg alone in reducing total IPSS (upper limit of 97.5% CI 0.11 in FAS, 0.17 in PPS, non inferiority margin 0.5).
- Statistically significantly superior to both placebo and TOCAS 0.4 mg alone in reducing the TUS/24 h. The mean improvement in TUS/24 h from a baseline of 27 points is at least 8 points, reaching a mean TUS/24 h of 18.5 points.

The FDC 6 mg/0.4 mg was also tested for superiority vs. TOCAS 0.4 mg alone on total IPSS as a secondary comparison after showing non-inferiority. The mean improvement in total IPSS was numerically greater than with TOCAS 0.4 mg alone, however superiority was not reached ($p = 0.048$, significance level to be reached 0.025 due to multiplicity correction).

The greater improvement (statistically significant) with the FDC 6 mg/0.4 mg compared with TOCAS 0.4 mg alone on the primary storage parameter TUS/24 h was supported by effects demonstrated on some - but not all - secondary storage parameters in study 905-CL-055:

- the micturition frequency,
- the mean voided volume/micturition and
- the IPSS storage score.

In addition, the greater improvements in storage parameters with the FDC 6 mg/0.4 mg than with TOCAS 0.4 mg alone were accompanied by greater improvements in disease-specific "urinary" QoL as measured by:

- the IPSS QoL and
- the OAB-q HRQoL total score and coping, concern, sleep and social subscale scores.

Furthermore, the improvements in the storage parameter TUS/24 h correlated with improvements in disease-specific QoL, *i.e.* with the IPSS QoL and OAB-q symptom bother score.

The above described effects were already apparent at the first assessment in the phase 3 study (*i.e.* after 4 weeks of treatment) with continued improvements up to 12 weeks.

For the secondary storage efficacy variables, there were also no further improvements on the FDC 9 mg/0.4 mg.

The results in the phase 3 study were in line with those in storage symptoms subgroup 2 of the phase 2 dose-ranging study 905-CL-052.

It can therefore be concluded that the FDC 6 mg/0.4 mg is non-inferior on total IPSS and superior on the primary storage parameter TUS/24 h and most secondary efficacy parameters compared to TOCAS 0.4 mg alone, and superior to placebo for both total IPSS, TUS/24 h and most secondary parameters.

Indication

The indication for Volutsa is restricted to '*... in men who are not adequately responding to treatment with monotherapy*', rather than '*men who are not adequately responding to treatment with tamsulosin*'. The reason for the wider indication is the expected use of this product in clinical practice. Besides tamsulosin, there are other alpha1-adrenoceptor antagonists on the market for the same indication (doxazosin, silodosin, alfuzosin, terazosin). As physicians are not expected to switch a patient on one of these other alpha1-adrenoceptor antagonists to tamsulosin before prescribing the combination, pre-treatment with tamsulosin alone is not the preferred wording for the indication.

Furthermore, to expect a patient that is already on solifenacin for previous complaints to stop using solifenacin and to try tamsulosin alone before switching to the combination product when additional complaints arise, is not the preferred treatment option from a clinical perspective either. Thus, the wording '*men who are not adequately responding to treatment with monotherapy*' is considered appropriate.

IV.5 Clinical safety

A total of 12 studies are included in the analysis of the safety of combination therapy with solifenacin and tamsulosin:

- 6 phase 1 studies in healthy volunteers. These studies used combination therapy of the single-entity products solifenacin and tamsulosin OCAS 0.4 mg and/or the FDC.
- 2 phase 2 studies in men with lower urinary tract symptoms (LUTS) associated with benign prostatic hyperplasia (BPH). These studies used combination therapy of the single-entity products solifenacin and tamsulosin OCAS 0.4 mg.
- 1 phase 3 study in men with LUTS associated with BPH, with storage symptoms: 905-CL-055 (12 weeks, double-blind, randomized: NEPTUNE), followed by its long-term, open-label, safety follow-up study 905-CL-057 (NEPTUNE II) with an additional 40 weeks of treatment. These studies used the FDC tablets.
- 2 phase 4 solifenacin post-marketing studies in men with LUTS with residual overactive bladder (OAB) symptoms after \geq 4-6 weeks of treatment with tamsulosin MR capsule or WOWTAB. These studies used combination therapy of the single-entity products solifenacin and tamsulosin and different dosages.

Given the vast experience with tamsulosin and solifenacin as separate medicines and the cumulating experience in the combination treatment, the submitted studies will be sufficient for an adequate analysis of the safety of the product.

The most frequently reported treatment-related TEAEs with the FDC are, dry mouth (9.5%), constipation (3.2%), dyspepsia including abdominal pain (2.4 %), dizziness including vertigo (1.4%), vision blurred (1.2%), fatigue (1.2%) and ejaculation disorders 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.

In men the risk of urinary retention and AUR (urinary retention requiring catheterization) on the FDC 6 mg/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 are no clinically relevant effects on laboratory parameters, vital signs or the ECG (including QTc abnormalities).

There is extensive experience with the single-entity products, solifenacin and tamsulosin. The FDC has the same adverse reactions as the 2 individual active substances without synergism on the level of AEs.

IV.6 Risk Management Plan

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations. Neither additional pharmacovigilance activities, nor additional risk minimisation beyond routine measures and SmPC labelling were proposed. Considering the well-known safety profile of the separate active substances solifenacin and tamsulosin, routine pharmacovigilance and risk minimisation are deemed sufficient, provided that the

MAH will monitor the on-going safety concerns as listed in the Risk Management Plan (RMP). During postmarketing follow-up adverse event reports related to the fixed dose combination will be clearly distinguished from the reports of the monoproducts and any potential effects of the combination should be taken into account.

The summary table of proposed pharmacovigilance activities and proposed risk minimisation activities by safety concern is presented below.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risks		
Urinary retention	<p>This risk can be adequately managed through appropriate wording in the SmPC for Volutsa as described below: <u>Section 4.4 (Warnings and precautions)</u> Volutsa should be used with caution in patients at risk of urinary retention. <u>Section 4.8 (Undesirable effects, ADR frequency observed during development of Volutsa)</u> Renal and urinary disorders: urinary retention (uncommon). <u>Section 4.8 (Undesirable effects, ADR frequency observed with solifenacin)</u> Renal and urinary disorders: urinary retention (rare).</p>	None.
Hypersensitivity	<p>This identified risk for solifenacin is an identified risk for Volutsa and is well characterized based on clinical and postmarketing experience and can be adequately managed through appropriate wording in the SmPC for Volutsa as described below: <u>Section 4.3 (Contraindications)</u> Volutsa is contraindicated in patients with hypersensitivity to the active substance(s) or to any of the excipients. <u>Section 4.4 (Warnings and precautions)</u> Angioedema with airway obstruction has been reported in some patients on solifenacin succinate and tamsulosin. If angioedema occurs, Volutsa should be discontinued and not restarted. 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, Volutsa should be discontinued and appropriate therapy and/or measures should be taken. <u>Section 4.8 (Undesirable effects, frequency observed during development of Volutsa)</u> Skin and subcutaneous tissue disorders: pruritus (uncommon) <u>Section 4.8 (Undesirable effects, ADR frequency observed with solifenacin or tamsulosin)</u> Skin and subcutaneous tissue disorders: rash (rare/uncommon); angioedema (very rare/rare); erythema multiforme (very rare); urticaria (very rare/uncommon).</p>	None.
QT prolongation/ Torsade de Pointes	<p>This important identified risk for solifenacin and identified risk for Volutsa is well characterized based on nonclinical, clinical and postmarketing experience with the solifenacin monotherapy product and can be adequately managed through appropriate wording in the SmPC for Volutsa as described below: <u>Section 4.4 (Warnings and precautions)</u> 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.</p>	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	<p><u>Section 4.8 (Undesirable effects, ADR frequency observed with solifenacin)</u> Cardiac disorders: QT prolongation and Torsade de Pointes (not known).</p> <p><u>Section 4.8 (Undesirable effects, ADR frequency observed with tamsulosin)</u> Palpitations (uncommon), atrial fibrillation, arrhythmia and tachycardia (not known).</p>	
Glaucoma	<p>This identified risk for solifenacin and identified risk for Volutsa is well characterized based on nonclinical, clinical and postmarketing experience with the solifenacin monotherapy product and can be adequately managed through appropriate wording in the SmPC for Volutsa as described below:</p> <p><u>Section 4.3 (Contraindications)</u> Contraindicated in patients with narrow-angle glaucoma and in patients at risk for this condition.</p> <p><u>Section 4.8 (Undesirable effects, ADR frequency observed with solifenacin)</u> Eye disorder: glaucoma (not known).</p>	None.
Ileus	<p>This identified risk for solifenacin and identified risk for Volutsa is well characterized based on nonclinical, clinical and postmarketing experience with solifenacin and can be adequately managed through appropriate wording in the SmPC for Volutsa as described below:</p> <p><u>Section 4.3 (Contraindications)</u> Contraindicated in patients with severe gastrointestinal condition (including toxic megacolon) and patients at risk for this condition.</p> <p><u>Section 4.4 (Warnings)</u> Volutsa should be used with caution in patients with gastrointestinal obstructive disorders and risk of decreased gastrointestinal motility.</p> <p><u>Section 4.8 (Undesirable effects, ADR frequency observed with solifenacin)</u> Gastrointestinal disorders: colonic obstruction (rare), fecal impaction (rare), ileus (not known).</p>	None.
IFIS	<p>This identified risk for tamsulosin and identified risk for Volutsa is well-characterized based on observational studies in patients needing cataract surgery. The risk can be adequately managed through appropriate wording in the SmPC as described below:</p> <p><u>Section 4.4 (Warnings)</u> The 'Intraoperative Floppy Iris Syndrome' (IFIS, a variant of small pupil syndrome) has been observed during cataract and glaucoma surgery in some patients on or previously treated with tamsulosin hydrochloride. IFIS may increase the risk of eye complications during and after the operation. Therefore, the initiation of therapy with Volutsa in patients for whom cataract or glaucoma surgery is scheduled is not recommended. Discontinuing treatment with Volutsa 1-2 weeks prior to cataract or glaucoma surgery is anecdotally considered helpful, but the benefit of treatment discontinuation has not been established. During pre-operative assessment, surgeons and ophthalmic teams should consider whether patients scheduled for cataract or glaucoma surgery are being or have been treated with Volutsa in order to ensure that appropriate measures will be in place to manage IFIS during surgery.</p> <p><u>Section 4.8 (Undesirable effects, ADR frequency observed</u></p>	None.

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	with tamsulosin) Eye disorders: IFIS (not known).	
Orthostatic hypertension	This identified risk for tamsulosin can be adequately managed through appropriate wording in Volutsa SmPC as described below: <u>Section 4.3 (Contraindications)</u> Contraindicated in patients with a history of orthostatic hypotension. <u>Section 4.4 (Warnings and precautions)</u> 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 Volutsa should be cautioned to sit or lie down at the first signs of orthostatic hypotension (dizziness, weakness) until the symptoms have disappeared. <u>Section 4.8 (Undesirable effects, ADR frequency observed with tamsulosin)</u> Vascular disorders: Orthostatic hypotension (uncommon).	None.
Important potential risks		
None		
Important missing information		
None		

IV.7 Discussion on the clinical aspects

For this authorisation sufficient clinical studies have been performed. The results show efficacy and an acceptable level of safety. This fixed dose combination can be used in case men are not adequately responding to treatment with monotherapy. Risk management is adequately addressed.

V. USER CONSULTATION

The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of a pilot test with 4 participants, followed by two rounds with 10 participants each. Because this medicine is mainly intended for use in older men, the younger age groups contain less participants than the older age groups. Only males were included. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. Overall, each and every question met criterion of 81% correct answers. No weaknesses were identified. The participants were also asked to provide comments on both content and layout, but this did not result in any changes. The readability test has been sufficiently performed.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Volutsa 6 mg/0.4 mg modified-release tablets has a proven chemical-pharmaceutical quality and is considered an approvable fixed dose combination. Both solifenacin and tamsulosin are well known, established substances, which are used as a combination in clinical practice.

The chemical-pharmaceutical dossier in support of the application is considered approvable. Non-clinical testing showed that solifenacin and tamsulosin are antagonists for different receptors and there is no cross reactivity of these drugs at the receptor level. It is therefore expected that the individual components of the FDC will work in a complementary manner.

Efficacy of the FDC has been shown. In men with LUTS associated with BPH, with a micturition frequency of ≥ 8 and at least 2 episodes of urgency with a patient perception of the intensity of urgency scale grade 3 or 4 per day, the FDC 6 mg/0.4 mg over a 12-week period was statistically

significantly superior to placebo in reducing total IPSS. It was also shown to be non-inferior to TOCAS 0.4 mg alone in reducing total IPSS. Statistically it was significantly superior to both placebo and TOCAS 0.4 mg alone in reducing the TUS/24h. In addition, the greater improvements in storage parameters with the FDC 6 mg/0.4 mg than with TOCAS 0.4 mg alone were accompanied by greater improvements in disease-specific "urinary" QoL aspects.

There is extensive experience with the single-entity products, solifenacin and tamsulosin. The FDC has the same adverse reactions as the 2 individual active substances without synergism on the level of adverse events.

The content of the SmPC approved during the mutual recognition procedure is acceptable, as it contains all relevant information for each of the active substances.

The Board determined the acceptable therapeutic indication *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.*

Volutsa 6 mg/0.4 mg modified-release tablets was authorised in the Netherlands on 16 December 2013. The concerned member states mutually recognised the Dutch evaluation for the marketing authorisation. There was no discussion in the CMD(h). The mutual recognition procedure was finished on 14 May 2014.

The following post-approval commitment has been made during the procedure:

Quality - active substance

- The MAH committed to continue the on-going stability studies is noted.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached

Summary Public Assessment Report
non-generics

Volutsa 6 mg/0.4 mg modified-release tablets
(solifenacin succinate and tamsulosin hydrochloride)

NL/H/3131/001/MR

Date: 11 September 2014

Summary Public Assessment Report

non-generics

Volutsa 6 mg/0.4 mg modified-release tablets

Active substances: solifenacin succinate and tamsulosin hydrochloride

This is a summary of the public assessment report (PAR) for Volutsa 6 mg/0.4 mg. It explains how this medicine was assessed and its authorisation recommended as well as its conditions of use. It is not intended to provide practical advice on how to use Volutsa.

For practical information about using this medicine, patients should read the package leaflet or contact their doctor or pharmacist.

What is Volutsa 6 mg/0.4 mg and what is it used for?

Volutsa tablets contain two active substances: solifenacin succinate and tamsulosin hydrochloride. These substances are also available as separate tablets marketed under several trade names such as Vesicare® (solifenacin) and Omnic® (tamsulosin).

These medicines are prescribed to treat men with moderate to severe urine storage symptoms and voiding symptoms of the lower urinary tract which are caused by bladder problems and an enlarged prostate (benign prostatic hyperplasia). The combination tablet containing both solifenacin and tamsulosin is used when previous treatment with one separate product for this condition cannot relieve symptoms adequately.

How does this medicine work?

As the prostate grows, it can lead to urinary problems (voiding symptoms) such as hesitancy (difficulty to start urinating), difficulty urinating (poor stream), dribbling and feeling of incomplete bladder emptying. At the same time, the bladder is also affected and contracts spontaneously at times you do not want to void. This causes storage symptoms such as changes in bladder sensation, urgency (having a strong, sudden desire to urinate without prior warning), and having to urinate more frequently.

The active substance solifenacin belongs to a group of medicines called anticholinergics. It reduces the undesired contractions of the bladder and increases the amount of urine that the bladder can hold. Therefore the user can wait longer before going to the toilet. Tamsulosin belongs to a group of medicines called alpha-blockers and enables urine to pass more readily through the urethra and facilitates urination.

How is this medicine used?

The pharmaceutical form of Volutsa is a modified-release tablet and the route of administration is oral. The medicine can only be obtained with a prescription.

Please read section 3 of the PL for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

What benefits of this medicine have been shown in studies?

The company provided data on efficacy and safety studies. In these studies Volutsa was more effective than placebo (dummy treatment) at improving bladder and prostate symptoms in patients with a benign enlarged prostate. The effect on the total of the prostate symptoms was about the same as with use of tamsulosin alone. However, patient who received treatment with the Volutsa combination tablet experienced less symptoms of urgency compared to the use of tamsulosin alone. The results are based on the evaluation of the patients themselves.

What are the possible side effects from this medicine?

The most common side effects with this medicine (which may affect up to 1 in 10 people) are dry mouth, constipation, indigestion, dizziness, blurred vision, tiredness, feeling sick (nausea) and abdominal pain. Ejaculation disorders (abnormal ejaculation) may also occur. This means that semen does not leave the body via the urethra, but instead goes into the bladder (retrograde ejaculation) or the ejaculation volume is reduced or absent (ejaculation failure). This phenomenon is harmless.

For the full list of all side effects reported with this medicine, see section 4 of the package leaflet.

Why is this medicine approved?

The Medicines Evaluation Board of the Netherlands decided that Volutsa's benefits are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of this medicine?

A risk management plan has been developed to ensure that this medicine is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Volutsa 6 mg/0.4 mg, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously as well.

Other information about this medicine

In the Netherlands, the marketing authorisation for Volutsa 6 mg/0.4 mg modified-release tablets was granted on 17 December 2013.

The full PAR for this medicine can be found on the website <http://mri.medagencies.org/Human>. For more information about treatment with Volutsa 6 mg/0.4 mg modified-release tablets, read the package leaflet (http://mri.medagencies.org/download/NL_H_3131_001_FinalPI.pdf) or contact your doctor or pharmacist.

This summary was last updated in September 2014.