CBG MEB

Public Assessment Report

Scientific discussion

Vesicare 1 mg/ml, oral suspension

(solifenacin succinate)

NL/H/0487/003/DC

Date: 31 October 2016

This module reflects the scientific discussion for the approval of Vesicare 1 mg/ml, oral suspension. The procedure was finalised on 10 August 2015. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AGP	Alpha-1-acid glycoprotein
AUC_{tau}	Area under the plasma concentration-time curve for a dosing interval
CHMP	Committee for Medicinal Products for Human Use
CL/F	Apparent total clearance of the drug from plasma after oral administration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMR	Carcinogenic, Mutagenic and Reprotoxic
CMS	Concerned Member State
DT50	Degradation Time for 50% of a substance to be degraded under laboratory conditions
EC	Effect concentration
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
FAS	Full Analysis Set
FFM	Fat-free mass
F_{pen}	Penetration factor
FSH	Follicle-stimulating hormone (FSH)
ICH	International Conference of Harmonisation
K_a	Absorption rate constant
K_{ow}	Octanol-Water partition coefficient
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board of the Netherlands
MVV	Mean Volume Voided
NDO	Neurogenic Detrusor Overactivity
NOEC	No Observed Effect Concentration
OAB	Overactive Bladder
OECD	Organisation for Economic Co-operation and Development
PBT	Persistent, Bioaccumulative and Toxic
PD	Pharmacodynamics
PEC	Predicted Environmental Concentration
PED	Paediatric equivalent dose
Ph.Eur.	European Pharmacopoeia
PK	Pharmacokinetics
PL	Package Leaflet
popPK	Population Pharmacokinetic
RH	Relative Humidity
RMP	Risk Management Plan
SAF	Safety Analysis Set
SD	Standard Deviation
SmPC	Summary of Product Characteristics
TEAE	Treatment-emergent adverse event
TSE	Transmissible Spongiform Encephalopathy
USP-NF	United States Pharmacopoeia National Formulary
V/F	Apparent volume of distribution after non-intravenous administration
vPvB	very Persistent very Bioaccumulative

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Vesicare 1 mg/ml, oral suspension, from Astellas Pharma Europe B.V.

The product is indicated for symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome.
A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a line extension to existing marketing authorisations of Vesicare 5 mg and 10 mg film-coated tablets (NL licence RVG 29151-29152), which were approved for marketing in The Netherlands on 16 December 2003 and subsequently approved throughout Europe via mutual recognition procedures (NL/H/0487/001-002).

The current application adds a new pharmaceutical form, an oral suspension, to the marketing authorisation of Vesicare. Adult patients having an OAB who are treated with solifenacin succinate might benefit from using the oral suspension if they experience difficulties taking tablets. The oral suspension formulation has the same dosing recommendation as the film-coated tablets.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Bulgaria, Cyprus, the Czech Republic, Germany, Denmark, Estonia, Greece, Finland, France, Croatia, Hungary, Ireland, Iceland, Italia, Liechtenstein, Lithuania, Luxembourg, Latvia, Malta, Norway, Poland, Portugal, Romania, Sweden, Slovenia, Slovakia and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 8(3) of Directive 2001/83/EC. The dossier includes complete modules on quality. Regarding the non-clinical and clinical modules, only the data relevant for the extension are included. For the non-clinical and clinical data of solifenacin, reference is made to the existing marketing authorizations of solifenacin succinate 5 mg and 10 mg film-coated tablets.

Scientific advice
Regulatory/pre-submission advice was given by the MEB regarding this application, first in 2012 and again in 2014. Questions were raised regarding the legal basis for the extension application, the choice of regulatory procedure, the necessity of submission of the Paediatric Investigation Plan (PIP) results in the extension application and the need for a PIP compliance check at the time of submission of the extension application. The advice was followed by the MAH.

Partial compliance check
The MAH submitted a letter of compliance with the Paediatric Investigation Plan (PIP) issued by the Paediatric Committee (PDCO) of the European Medicines Agency (EMA), to fulfil the requirements of the Paediatric Regulation. The procedure is a partially completed compliance check, because there are studies in the agreed paediatric investigation plan that are not subject to this application procedure.

II. QUALITY ASPECTS

II.1 Introduction

The product is a white to off-white coloured aqueous, homogenous suspension with an orange flavour and pH 5.8-6.8.

Vesicare oral suspension contains 1 mg/ml solifenacin succinate, equivalent to 0.75 mg/ml solifenacin. It is packed per 150 ml in an amber polyethylene terephthalate (PET) bottle with polyethylene (PE) screw-cap with a pulp and vinylseal liner, packed in a carton.

The excipients are: polacrilin potassium, methyl parahydroxybenzoate (E218), propyl parahydroxybenzoate (E216), propylene glycol (E1520), simethicone emulsion 30% (consisting of

simethicone, polyethylene glycol sorbitan tristearate (E436), methylcellulose (E461), polyethylene glycol stearate, glycerides, xanthan gum (E415), benzoic acid (E210), sorbic acid (E200), sulphuric acid (E513) and water), carbomer, xylitol (E967), acesulfame potassium (E950), natural orange flavour (consisting of orange essential oils, natural flavouring substances, ethanol, propylene glycol (E1520), butylated hydroxyanisol (E320) and water), sodium hydroxide and purified water.

II.2 Drug Substance

The active substance is solifenacin succinate, an established active substance. Solifenacin succinate was not described in the any Pharmacopoeia at the time of initial marketing authorisation. Solifenacin succinate is freely soluble in water, is not hygroscopic and has no known polymorphism. Solifenacin succinate molecule has two chiral centres leading to four possible diastereoisomers. The 1S,3R-isomer is produced.

Two active substance manufacturers are used. Full information on the drug substance is provided in the dossier.

Manufacturing process
There are two manufacturing processes used that each comprise three steps. Both processes are sufficiently described.
The MAH has sufficiently justified the use of the starting materials, provided an adequate discussion on the potential impurities based on the preparation routes, and the use of adequate specifications. All starting materials, reagents and solvents are clearly described.

Quality control of drug substance
The active substance specification is considered adequate to control the quality. Batch analytical data demonstrating compliance with this specification have been provided for three (manufacturer-I) and nineteen batches (manufacturer-II).
The MAH has applied a non-routine drug substance specification on limiting benzene instead of a solvent specification for ethanol. The method (or final method) still has to be developed although batch results on 9 batches have been provided. A commitment has been made to develop an analytical method being able to detect benzene in the drug substance and to include a drug substance specification on limiting benzene.

Stability of drug substance
Stability data are available of six batches, three per manufacturer, stored at 25°C/60% RH for 36 months (three batches) or 24 months (three batches), and at 40°C/75% RH for 6 months. All stability results were in accordance with the specification. Sufficient data are available as support for the claimed retest period of three years for the drug substance without specific storage condition.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. All functions of the excipients have been explained. The drug substance has an unpleasant taste (bitter and astringent). Therefore, polacrilin potassium was applied as a suitable adsorbent of solifenacin to form a complex that can mask the unpleasant taste of the drug substance. Initially, suspension Formulation A (1 mg/ml) was developed. However it was not considered optimal for outpatient use or commercialisation because of the complexity of preparing and administering this formulation. Formulation A was also associated with issues, including relatively rapid sedimentation of the suspended components, foaming after shaking the suspension and difficult redispersibility after long-term storage.

To improve the usability of the suspension formulation, the MAH developed an optimised suspension formulation (suspension Formulation B, also 1 mg/ml), which is the final suspension formulation intended for marketing. With Formulation B, issues associated with Formulation A, were eliminated. The taste-masking technology used for suspension Formulations A and B is identical. Since the modifications to the suspension formulation were limited to excipients that are not expected to impact the adsorption and/or release of solifenacin from the drug-resin complex, no differences in the

bioavailability of suspension Formulations A and B were anticipated. *In vitro* analysis of these two suspension formulations showed no differences in the dissolution profiles at 0.1M HCl, pH 4.5 and pH 6.8.
To ensure accurate dose delivery of Formulation B, three commercially available oral syringes were tested. Hence oral syringes provide a more accurate dosing for a liquid dosage form compared to the use of a spoon or cup. Both lowest volume and highest volume sampling for all three oral syringes was accurately and reproducibly performed. The data showed that the oral syringes can be used repeatedly for dispensing the solifenacin succinate oral suspension.

The formulation development is adequately described, including the information on the taste masking measures, uniformity, sedimentation, resuspendability, viscosity, micro-biological attributes, and container closure system.

In vivo bioequivalence was demonstrated between the oral suspension and Vesicare 10 mg tablets by Astellas Pharma B.V. The study used Formulation A and B as test products. The bioequivalence study test batches were manufactured according to the finalised manufacturing process and composition.

Manufacturing process
The manufacturing process of the oral suspension is a standard process comprising mixing, filtering, pH adjusting, filling and capping. For this standard process validation data can be provided post approval. Adequate process validation schemes are presented in the dossier.

Control of excipients
The excipients comply with their respective European Pharmacopoeia (Ph.Eur.) or United States Pharmacopoeia National Formulary (USP-NF) monographs except the natural orange flavour. Regarding the natural orange flavour, the MAH confirmed that the components of the flavour are listed in the EC "Register of flavouring substances", as presented in Commission Decision 1999/217/EC and its amendments. A chromatographic method for identifying the main flavouring components in the flavour has been described. It is concluded that the use of the natural orange flavour is safe. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for identification, pH, viscosity, related substances, preservative assay, dissolution, assay, microbial limit. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Abundant batch analytical data have been provided, demonstrating compliance with the specification.

Stability of drug product
Three batches have been stored for 18 months at 25°C/60% RH and for 6 months at 40°C/75% RH. No changes in the appearance of solifenacin succinate oral suspension are observed. The suspension is slightly sensitive to the light exposure. However it was confirmed that the proposed packaging (amber PET bottle) is suitable as light protection for the commercial product. On basis of the data submitted, a shelf life was granted of 24 months without specific storage temperature.
Results of in-use stability testing confirm that the product is stable up to 28 days after first opening of the bottles and repeatedly dispensing the suspension.

Specific measures concerning the prevention of the transmission of animal spongiform encephalo-pathies
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 Vesicare oral suspension has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

One post-approval commitment was made:

- The MAH committed to develop an analytical method being able to detect benzene in the drug substance and to include a drug substance specification on limiting benzene in the drug substance. The change will be performed by means of a variation.

III. NON-CLINICAL ASPECTS

III.1 Pharmacology, pharmacokinetics and toxicology

For the non-clinical studies with solifenacin succinate, reference is made to the existing marketing authorisation of Vesicare 5 mg and 10 mg film-coated tablets. The non-clinical data set submitted for the tablet formulation is considered adequate to support the use of the oral suspension. The data set reviews relevant preclinical pharmacology and pharmacodynamic literature. It also describes the pharmacokinetics of solifenacin succinate using studies performed by the MAH and literature publications. The dose or patient population is not amended compared to the existing tablet formulation. The non-clinical data package presented in the overview shows solifenacin to be a safe and potent cholinergic receptor antagonist. Two additional studies were performed with regard to the toxicological profile of solifenacin.

Additional toxicity studies
Although no impurities were identified in the oral solution, a DEREK analysis was performed on two potential degradation products to evaluate potential genotoxicity. No alert for mutagenicity was identified.

Also an ocular irritation study was performed with the oral suspension formulation in rabbits showing no potential for eye irritation up to 72 hours after exposure.

The outcome of both studies is consistent with the known toxicological actions.

III.2 Ecotoxicity/environmental risk assessment (ERA)

No increase in use or environmental exposure is expected due to the change in formulation from tablet to oral solution. An environmental risk assessment is therefore not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Pharmacokinetics

The tablet formulation of solifenacin succinate is marketed by Astellas under the trade name Vesicare. Astellas has since developed and investigated aqueous suspension formulations of solifenacin succinate. The drug substance has an unpleasant taste (bitter and astringent). Therefore, polacrilin potassium was applied as a suitable adsorbent of solifenacin to form a complex that can mask the unpleasant taste of the drug substance. The release of solifenacin from the suspended components is dependent on environmental conditions, such as pH and ionic strength.

Initially, suspension Formulation A was developed. To improve the usability of the suspension formulation, Astellas developed an optimised suspension formulation (suspension Formulation B), which is the final suspension formulation intended for marketing. Since the modifications to the suspension formulation were limited to excipients that are not expected to impact the adsorption and/or release of solifenacin from the drug-resin complex, no differences in the bioavailability of suspension formulations A and B were anticipated. *In vitro* analysis of these two suspension formulations was conducted and showed no differences in the dissolution profiles. Two relative bioavailability/bioequivalence studies were submitted.

Relative bioavailability/Bioequivalence studies

Study I – oral suspension Formulation A versus 10 mg tablets
The first study used Vesicare oral suspension Formulation A versus Vesicare 10 mg tablets. The 1

mg/ml suspension Formulation A was not bioequivalent with the Vesicare 10 mg tablet under fasting conditions. The suspension showed 20% lower AUC and C_{max} values compared with the Vesicare 10 mg tablets.
Concomitant intake of the suspension with a high fat breakfast showed no statistically significant impact on AUC values. C_{max} was 12% lower. However, 90% CI for AUC and C_{max} were inside the normal criteria of 0.80 – 1.25.

Since Vesicare oral suspension Formulation A is not the final formulation applied for, this study is not considered pivotal.

Study II – oral suspension Formulation A and Formulation B versus 10 mg tablets
In this bioequivalence study both Vesicare Formulation A and the final product, Formulation B, were compared to 10 mg Vesicare tablets (Astellas Pharma, obtained form the United States).

The choice of the US Vesicare tablet formulation in the bioequivalence study has been justified. The composition of Vesicare 10 mg tablets registered in the US is identical to that of the EU registered Vesicare 10 mg tablets. The formula and preparation of the bioequivalence batch is identical to the formula proposed for marketing. The batch size is sufficient.

Design
A single-dose, randomised, three-way crossover comparative bioequivalence study was carried out under fasted conditions in 24 healthy subjects (12 males and 12 females), aged 21-50 years. Each subject received a single dose (10 mg) of one of the three solifenacin succinate formulations in one of the three periods. The formulations were administered with 240 ml water after an overnight fast. There were three dosing periods, separated by a washout period of 13 days.

Blood samples were collected pre-dose and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120, 144, 168, 192, 216 and 240 hours after administration of the products.

The design of the study is acceptable. A study under fasted conditions is in accordance with the applicable guidelines. Despite the expected lack of food effect, the SmPC states that the suspension should be taken orally and should not be ingested together with food and/or drinks. The reason for this is that if the suspension formulation is administered together with food and/or beverages, then the release of solifenacin in the mouth, from the suspended components, cannot be excluded under conditions of a low pH or the presence of cations. Released solifenacin has an unpleasant, bitter taste and may result in a feeling of numbness in the mouth. The recommendation in the proposed SmPC is therefore supported.

Analytical/statistical methods
The analytical method has been adequately validated and is considered acceptable for analysis of the plasma samples. The methods used in this study for the pharmacokinetic calculations and statistical evaluation are considered acceptable.

Results
One healthy volunteer discontinued after receiving period 1 treatment (Formulation A) due to adverse events. Another volunteer received only Formulation A and the tablet formulation, as this subject was withdrawn only from period 2 before dosing due to an adverse event.

As such 24 (Formulation A), 22 (Formulation B) and 23 subjects (tablet) were subsequently eligible for pharmacokinetic analysis.

Table 1. Pharmacokinetic parameters (non-transformed values; arithmetic mean ± SD, t_{max} (median, range)) of solifenacin succinate under fasted conditions.

Treatment	AUC_{0-t} ng.h/ml	$AUC_{0-\infty}$ ng.h/ml	C_{max} ng/ml	t_{max} h	$t_{1/2}$ h
Formulation B N=22	**982 ± 532**	**1075 ± 677**	**15.6 ± 4.4**	**6.0 (4.0 – 12.0)**	**54 ± 21**
Formulation A N=24	**956 ± 534**	**1057 ± 703**	**15.9 ± 4.2**	**7.0 (3.0 – 8.0)**	**54 ± 24**

Tablets N=23	**943 ± 475**	**1023 ± 603**	**16.6 ± 4.4**	**6.0 (3.0 – 8.0)**	**51 ± 19**
***Ratio [B/Ref] (90% CI)**	0.99 (0.94 – 1.05)	0.99 (0.94 – 1.05)	0.91 (0.86 – 0.97)	--	--
***Ratio [A/Ref] (90% CI)**	1.01 (0.96 – 1.07)	1.02 (0.97 – 1.08)	0.97 (0.91 – 1.02)		
***Ratio [A/B] (90% CI)**	0.98 (0.92 – 1.03)	0.97 (0.92 – 1.03)	0.95 (0.89 – 1.00)	--	--
$AUC_{0-\infty}$ area under the plasma concentration-time curve from time zero to infinity **AUC_{0-t}** area under the plasma concentration-time curve from time zero to t hours **C_{max}** maximum plasma concentration **t_{max}** time for maximum concentration **$t_{1/2}$** half-life					

**ln-transformed values*

Conclusion on bioequivalence studies

In the second bioequivalence study all 90% confidence intervals calculated for AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} are within the bioequivalence acceptance range of 0.80 – 1.25. Based on the submitted bioequivalence study the Vesicare 1 mg/ml suspension Formulation A and B are bioequivalent with the Vesicare 10 mg tablet under fasted conditions. In addition, suspension Formulation A and B were also bioequivalent. In the treatment periods for Formulation A and B, two cases of pre-dose concentrations above 5% of C_{max} were reported. The MAH provided pharmacokinetic data and a statistical analysis excluding the data of these two subjects. Bioequivalence was still proven. Therefore no difference in the pharmacokinetics of solifenacin is expected compared to the marketed solifenacin succinate tablet.

No clear indication of the different outcome in results for Formulation A versus the Vesicare tablet between the two bioequivalence studies could be identified. However, bioequivalence is considered proven, as it was demonstrated for Vesicare Formulation B, the final formulation applied for, and the 10 mg tablets. This was the pivotal bioequivalence study.

The MEB has been assured that the bioequivalence studies have been conducted in accordance with acceptable standards of Good Clinical Practice (GCP, see Directive 2005/28/EC) and Good Laboratory Practice (GLP, see Directives 2004/9/EC and 2004/10/EC).

IV.2 Pharmacodynamics

No specific studies were performed with the final Vesicare suspension formulation to evaluate the effects of intrinsic factors on the pharmacokinetics of solifenacin. Since this formulation is bioequivalent to the marketed solifenacin succinate tablet, no difference in the effect of intrinsic factors on the pharmacokinetics of solifenacin is expected between these 2 dosage forms.

IV.3 Clinical efficacy

As the final Vesicare oral suspension formulation is bioequivalent to the marketed solifenacin succinate tablet, no difference is expected compared to the well-established efficacy profile of the marketed solifenacin succinate tablet.

The MAH did not submit any new efficacy data. This is considered acceptable in view of the type of application.

IV.4 Clinical safety

Data on the safety of solifenacin succinate administered as a suspension formulation are available from two bioequivalence studies, in which solifenacin succinate was administered as single doses of either one or both of the suspension formulations (suspension Formulations A and B) and as the marketed solifenacin succinate tablet to a total of 48 healthy subjects (24 subjects in each study). A high-level summary of the safety findings from these studies has been presented in the clinical overview.

Overall the results showed that all tested formulations of solifenacin succinate are well tolerated. No unexpected safety concerns were identified for the marketed solifenacin succinate tablet and no new safety signal was observed for either of the suspension formulations tested versus the well-established safety profile of the marketed solifenacin succinate tablet. The safety sections of the SmPC for the solifenacin succinate tablet are therefore applicable to the suspension formulation of solifenacin succinate.

IV.5 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Vesicare oral suspension.

Summary table of safety concerns as approved in RMP:

Important identified risks	• QT prolongation/ Torsade de Pointes • Urinary retention • Hypertension reactions, including anaphylactic reaction and angioedema • Glaucoma • Ileus
Important potential risks	--
Missing information	• Use in pregnancy • Use of solifenacin in infants and children either exposed to solifenacin directly or exposed via breast feeding

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.6 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with Vesicare film-coated tablets. No new clinical studies were conducted. The MAH demonstrated through a bioequivalence study that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of the original tablet product. Risk management is adequately addressed.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Vesicare film-coated tablets. It has been demonstrated that the only differences pertain to the method of administration due to the difference in pharmaceutical form, and the administrative differences. The layout, font and format of the leaflets are largely the same and justified. The bridging report submitted by the MAH has been found acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Vesicare 1 mg/ml oral suspension is a line extension of Vesicare 5 mg and 10 mg film-coated tablets, which has a proven chemical-pharmaceutical quality. Vesicare is a known medicinal product with an established favourable efficacy and safety profile. The new formulation, developed as an oral suspension, is an approvable addition to the original product. The new formulation is useful for patients experiencing difficulties taking tablets.

Bioequivalence has been shown to be in compliance with the requirements of European guidance documents.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that the line extension for Vesicare oral suspension is approvable and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 10 August 2015.

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
Implementation of acceptance criteria and analytical procedures in the concerned Ph.Eur. monograph	NL/H/0487/ 1-3/IB/039	IB	2-3-2016	1-4-2016	Approved	No
Addition of paediatric indication in children > 5 yr and adolescents was proposed, and at EoP an addition of paediatric information to SmPC section 4.2, 5.1 and 5.2 was accepted (no paediatric indication)	NL/H/0487/ 003/II/037	II	6-10-2015	8-6-2016	Approved	No

ANNEX – TYPE II VARIATION

I. RECOMMENDATION

Based on the review of the data on safety and efficacy, it is considered that the variation for Vesicare 1 mg/ml, oral suspension (solifenacin), for the proposed extension of the indication to include children and adolescents with OAB from 5 to 18 years is not approvable. However, it is accepted to include the results of the paediatric studies in section 4.2, 5.1 and 5.2 of the SmPC.

II. EXECUTIVE SUMMARY

II.1 Introduction

Vesicare 1 mg/ml, oral suspension has been registered as a line extension to Vesicare tablets in the Netherlands by Astellas Pharma Europe B.V. since 25 September 2015 through procedure NL/H/0487/003/DC.

The approved indication is the same as for the tablets: symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder (OAB) syndrome. The product is registered for use in adults.

II.2 Scope of the variation

A Type II variation was submitted in order to make solifenacin oral suspension available for children and adolescents with OAB syndrome (aged 5 years and older). The MAH provided quality, non-clinical and clinical data regarding the use of the oral suspension in children and adolescents with OAB syndrome. Evidence from several studies is referred to, including those that are used as clinical measure for PIP compliance.

II.3 PIP compliance

Vesicare has an approved PIP (EMEA-C-000573-PIP01-09-M05) for the indication “symptomatic treatment of urge incontinence and/or increased urinary frequency and urgency as may occur in patients with overactive bladder syndrome". Four studies, including three paediatric clinical studies, have been completed as clinical measures for the PIP: study 1 (quality-related study), study 905-CL-075 (pharmacokinetic study), study 905-CL-076 (placebo controlled clinical efficacy study), and study 905-CL-077 (long-term safety extension study).

On 22 May 2015 the PDCO adopted the following opinion on PIP compliance for this product: The Paediatric Committee, having reviewed the data submitted in accordance with Article 23 of Regulation (EC) No 1901/2006, is of the opinion, as set out in the appended compliance report, that the measures are in compliance with the agreed above mentioned PIP and that the agreed timelines have been respected accordingly.

III. QUALITY ASPECTS

In support of this variation, the MAH has justified the safety of the excipients and their quantities for use in children from 5-18 years. In general, no issues are foreseen for the use of this formulation in children from a quality point of view.

The suspension has a pH of 6.3 which raises no concerns regarding tooth decay. No safety issues are foreseen with regards to the excipients present in this formulation, including the components of the natural orange flavour and simethicone emulsion. Although the orange flavour contains alcohol as a solvent, the maximum daily exposure would be so low that this raises no concerns.
With regards to a measuring device, it is noted that no such device is supplied with the pack. It is stated in the SmPC that the suspension can be measured with a commercially available oral syringe.

This has already been approved as part of the line extension for the oral suspension. The minimum single dose volume for children of less than 14 kg would be 1.4 ml. At this single dose volume level no issues with dosing accuracy are foreseen.

IV. NON-CLINICAL ASPECTS

IV.1 Pharmacology, pharmacokinetics and toxicology

The non-clinical dossier for this procedure consists of an addendum overview. This addendum refers to non-clinical studies for solifenacin succinate that have been completed to identify and characterise the pharmacology, safety pharmacology, toxicology and pharmacokinetic profile. As indicated in SmPC section 5.3 of the registered products, Vesicare 5 mg and 10 mg film-coated tablets (NL/H/0487/001-002) and Vesicare 1 mg/ml oral suspension (NL/H/0487/003), these data did not reveal special hazard for humans.

The addendum also refers to four juvenile mice studies that have been submitted as part of a variation application for Vesicare tablets in 2013 (NL/H/487/001-002/II/031). As a result, for this Type II variation, SmPC section 5.3 Preclinical Safety Data was updated. During the extension application for the oral suspension, the MAH has already included the same statement in Section 5.3 of Vesicare 1 mg/ml oral suspension.

No additional non-clinical pharmacology, toxicology and pharmacokinetic studies are needed.

IV.2 Environmental Risk Assessment (ERA)

The ERA of the active ingredient solifenacin succinate for the Vesicare dossier is equal to the ERA concluded for Vesomni in procedure NL/H/2968/001/E/001.

The MAH makes use of the default penetration factor (F_{pen}) in the ERA. The main study results are summarised in table 1.

Table 1 Summary of main study results

Substance (INN): solifenacin			
CAS-number: 242478-38-2 (solifenacin succinate), 242478-37-1 (solifenacin)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow} at pH 4 = -0.1, log D_{ow} at pH 7 = 1.6, log D_{ow} at pH 10 = 3.95. Ion-corrected log D_{ow} is 5.46.	not B
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.46 (ion-corrected log D_{ow})	
	log D_{ow} at pH 7	1.6	not B
Persistence	$DT50_{system}$	244 and 187 d at 20°C	P
Toxicity	NOEC fish	3.1 µg/L	T
	CMR	not investigated	
PBT-statement :	Solifenacin is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surface\ water}$, default F_{pen}	0.08	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	not reported		
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =918 L/kg (sludge) K_{oc} = 2130, 1220, 6750, 2520 L/kg (soil)	
Ready Biodegradability Test	OECD 310	not readily biodegradable	sealed vessel test (OECD 310)
Aerobic and Anaerobic Transformation in Aquatic	OECD 308	$DT_{50,\ water}$ =0.97 d and 1.4 d $DT_{50,\ system}$ = 187 d and 244 d	

Sediment systems		% shifting to sediment = 93-96%			
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *P. subcapitata*	OECD 201	EC10	542	µg/L	growth rate
Daphnia sp. reproduction Test	OECD 211	NOEC	83.9	µg/L	mortality, length and reproduction
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	3.10	µg/L	mortality
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	$22x10^3$	µg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218 Sediment spiked	NOEC	≥ 4.92	mg/kg_{dw}	normalised to 10% organic carbon. Emergence, development rate, sex ratio.

The evaluation of the ERA for solifenacin (as solifenacin succinate), was concluded as follows:

- Solifenacin is not Persistent, Bioaccumulative and Toxic (PBT), nor very Persistent very Bioaccumulative (vPvB).
- No risk is identified for the Sewage Treatment Plant (STP), surface water, ground water and sediment compartment.

IV.3 Overall conclusions on non-clinical aspects

The Member States agreed that no additional studies on pharmacology, pharmacokinetics and toxicology are needed for the proposed extension of the indication to children over 5 years of age. It was accepted to use the approved conclusion of the ERA for procedure NL/H/2968/001/E/001.

V. CLINICAL ASPECTS

V.1 Introduction

In support of this Type II variation, the MAH submitted data from three clinical studies:

- Study 905-CL-075, which is a single-dose study to investigate the pharmacokinetics, safety and tolerability of solifenacin
- Study 905-CL-076, which is a phase III, 12-week, placebo-controlled dose-titration study to investigate the efficacy, safety and pharmacokinetics of solifenacin
- Study 905-CL-077, which is an extension of study 076 designed to investigate the long-term safety and efficacy of solifenacin

These studies were conducted in paediatric patients with OAB syndrome and are included in the approved paediatric investigation plan (PIP) (EMEA 000573-PIP01-09).

V.2 Pharmacokinetics

The pharmacokinetics of solifenacin were investigated in studies 905-CL-075 and 905-CL-076 in paediatric patients with OAB. There was no pharmacokinetic sampling in study 905-CL-077, which was an extension of study 905-CL-076 designed to investigate the long-term safety and efficacy of solifenacin.

Population pharmacokinetic (popPK) analyses were conducted with data from studies 905-CL-075 and 905-CL-076. The population pharmacokinetic model developed with data from study 905-CL-075 was used to determine the doses of solifenacin to be administered in subsequent efficacy and safety studies conducted in paediatric patients with OAB (study 905-CL-076 and 905-CL-077). The data from study 905-CL-076 were used to develop a population pharmacokinetic model to establish the multiple-

dose (steady-state) pharmacokinetics for solifenacin administered as the final oral suspension formulation in paediatric patients with OAB from 5 to less than 18 years of age.
The initial suspension formulation (Formulation A) was used in the single-dose pharmacokinetic study (study 905-CL-075). The approved suspension formulation (Formulation B) was used in the 12-week, placebo-controlled and long-term extension studies (study 905-CL-076 and 905-CL-077).

Population pharmacokinetic analysis
Three different population pharmacokinetic models were developed to describe the plasma concentrations of solifenacin in adults and/or in children. The model developed using adult and paediatric data following administration of formulation A aimed to further investigate the differences in the apparent clearance (CL/F) observed. Further, the model using adult data following administration of formulation B and the model using paediatric data following administration of formulation A were developed to be used in the determination of the paediatric equivalent dose (PED).
The PED was determined using a combination of results obtained from two population pharmacokinetic models: one to describe the data following administration of formulation B in adults (study 905-CL-080) and another to describe the age-dependent changes on CL/F following administration of formulation A in children (study 905-CL-075). Both approaches led to comparable PED and comparable expected exposures in children. In addition, the expected exposures in children were found to be equivalent to the simulated exposures in adults. Overall, incorporating results from study 905-CL-075 is considered appropriate to estimate PED for subsequent safety and efficacy studies. In addition, from a safety perspective, results of study 905-CL-075 showed that C_{max} values in children are within the expected range of C_{max} at steady state observed in clinical pharmacology studies in healthy adults.

The approach used is based on similar PK-PD relationship in adults and children and the starting dose in the subsequent paediatric studies is targeted to achieve equivalent exposures in children to those obtained in adults after the recommended starting dose of 5 mg. Up and down dose titration to a PED of 2.5, 7.5 or 10 mg was incorporated to ensure treatment at an efficacious dose level on an individual basis and therefore limit the potential risks of under-dosing.

The doses that were predicted and subsequently used in studies 905-CL-076 and 905-CL-077 are shown in the table below:

Table 2

Pediatric weight range (kg)	PED2.5 (mg) †	PED5 ‡ (mg)†	PED7.5 (mg) †	PED10 (mg) †
< 14	0.6	1.4	2.2	2.8
14–20	1.0	1.8	2.8	3.6
21–31	1.2	2.6	3.8	5.2
32–50	1.8	3.4	5.2	7.0
51–69	2.2	4.6	6.8	9.0
> 69	2.4	5.0	7.4	10.0

Weight was determined at screening. Body weight decimal places between 0.0 and 0.4 kg rounded down to the nearest kg. Body weight decimal places between 0.5 and 0.9 kg rounded up to the nearest kg.
† With a suspension strength of 1 mg/mL, the amounts listed also applied for the volumes (mL) administered.
‡ PED5 (or placebo in Study 905-CL-076) was the starting dose.

Applying the predicted popPK starting dose to achieve equivalent exposures in children to those obtained in adults and further up and down dose titration to a PED of 2.5, 7.5 or 10 mg resulted in a majority of paediatric patients being within the target exposure range derived from adults.
The PED2.5 dose was excluded, taking into account that only 2 of the patients in the efficacy and safety studies have been titrated to PED2.5 as an optimal dose level.

V.3 Clinical efficacy

Study 905-CL-076
Design

The phase 3 study 905-CL-076 was a multi-centre, randomised, double-blind, placebo-controlled sequential dose titration study to assess efficacy and safety of solifenacin succinate suspension in paediatric subjects from 5 to less than 18 years of age with OAB. A total of 219 children and 59 adolescents were screened. Four weeks prior to randomisation, patients started with urotherapy, the standard first line therapy for paediatric OAB patients. After the first 2 weeks of urotherapy, a single-blind 2-week placebo run-in period was started in combination with the ongoing urotherapy. Eligible patients were randomised to 12 weeks of double-blind treatment with solifenacin succinate oral suspension or placebo. 148 children (75 in the placebo group and 73 in the solifenacin group) and 41 adolescents (19 in the placebo group and 22 in the solifenacin group) were randomised. There were 8 site visits in total. Patients completed a 7 day patient diary prior to visits 2, 3, 4, 5, 6 and 7 (week -2 to week 12).

Efficacy endpoints
The primary efficacy variable was change from baseline to end of therapy (EoT) in mean volume voided (MVV) per micturition.

Secondary efficacy variables were change from baseline to EoT in each of:
- Daytime maximum volume voided (DMaxVV) per micturition
- Mean number of incontinence episodes per 24 hours
- Mean number of daytime incontinence episodes per 24 hours
- Mean number of night time incontinence episodes per 24 hours
- Number of dry (incontinence-free) days per 7 days
- Number of dry (incontinence-free) night times per 7 days
- Mean number of micturitions per 24 hours
- Mean number of daytime micturitions per 24 hours
- Mean number of night time micturitions per 24 hours
- Mean number of grade 3 or 4 urgency episodes per 24 hours in adolescents

Methods
The change from baseline to EoT in MVV per micturition in the full analysis set (FAS) was summarised and analysed using an analysis of covariance (ANCOVA) model including treatment (placebo or solifenacin succinate oral suspension) gender and region as fixed-effects, and the baseline MVV as a covariate. No further covariates were included in the model. Least squares (LS) mean estimates within and between the 2 treatment groups, together with 95% CIs, were provided.

Results
The median and range of exposures (AUC_{tau}) for children and adolescents were similar, and the majority of the patients were within the target exposure range derived from adults. At final visit, the change from baseline in MVV (SD) per micturition was 14.40 (32.48) ml in placebo-treated children vs 26.25 (38.24) ml in solifenacin-treated children and 16.67 (45.51) ml in placebo-treated adolescents vs 17.64 (61.51) ml in solifenacin-treated adolescents (table 3).

Table 3 Summary of change from baseline in MVV per micturition (ml) by study week (FAS)

Visit/Statistic	Children (Aged 5 to less than 12 Years)		Adolescents (Aged 12 to less than 18 Years)	
	Placebo	Solifenacin	Placebo	Solifenacin
Baseline				
n	70	73	19	21
Mean (SD)	94.06 (38.12)	96.88 (40.98)	169.06 (63.65)	159.55 (61.21)
Week 3				
n	68	72	18	18
Mean (SD)	104.86 (49.70)	105.65 (43.67)	171.58 (58.30)	179.95 (67.77)
Mean (SD) Change from Baseline	9.97 (27.87)	8.56 (26.71)	6.83 (40.19)	14.18 (56.14)
Week 6				
n	69	67	19	16
Mean (SD)	105.33 (46.43)	114.47 (45.97)	183.43 (69.76)	167.58 (51.87)
Mean (SD) Change from Baseline	11.48 (28.34)	14.49 (28.19)	14.38 (53.75)	1.03 (47.85)
Week 9				
n	64	65	17	18
Mean (SD)	102.62 (38.35)	116.96 (53.80)	188.85 (74.34)	184.62 (59.56)
Mean (SD) Change from Baseline	8.38 (26.50)	19.73 (37.64)	18.47 (52.43)	20.47 (64.41)
Week 12				
n	61	61	15	16
Mean (SD)	109.03 (45.57)	125.24 (54.77)	197.69 (46.97)	183.68 (59.60)
Mean (SD) Change from Baseline	16.08 (32.82)	27.61 (39.83)	19.37 (50.27)	12.89 (64.92)
Final Visit				
n	70	73	19	21
Mean (SD)	108.46 (44.91)	123.13 (53.24)	185.73 (59.61)	177.19 (65.30)
Mean (SD) Change from Baseline	14.40 (32.48)	26.25 (38.24)	16.67 (45.51)	17.64 (61.51)

FAS: full analysis set; MVV: mean volume voided.

Source: Tables 12.3.1.1.1 and 12.3.1.2.1

The secondary endpoints “mean number of incontinence episodes per 24 hours”, and “daytime and nighttime incontinence episodes per 24 hours” did not show statistical significant difference (table 4). However nominally changes in these parameters indicated some improvement.

Table 4 Change from baseline to EoT in Mean Number of Incontinence Episodes per 24 h (FAS)

Statistics	Placebo (n = 70)	Solifenacin (n = 73)	Difference (Solifenacin – Placebo)‡
n†	70	73	N/A
Baseline Mean (SE)	3.0 (0.3)	2.5 (0.3)	
EoT Mean (SE)	1.6 (0.2)	1.5 (0.1)	
Mean Change (SE)	-1.3 (0.3)	-1.0 (0.3)	
Change from Baseline‡			
Adjusted Mean (SE)	-1.2 (0.2)	-1.1 (0.2)	0.0 (0.2)
95% CI	(-1.5, -0.9)	(-1.5, -0.8)	(-0.3, 0.4)
P-value§	N/A		0.763

Study 905-CL-077

Design

Patients who completed study 905-CL-076 could be included into study 905-CL-077; a 40-week open-label, multi-centre, sequential dose titration, long-term extension study to assess safety and efficacy of solifenacin succinate suspension in paediatric subjects with OAB.

Eligible patients were treated once daily with open-label solifenacin oral suspension for 40 weeks. The study commenced with a titration phase of up to 12 weeks during which the patients could be up or down titrated at predefined time points based on a combination of efficacy and safety parameters followed by a fixed-dose phase during which no dose adjustments were allowed.

The starting dose of solifenacin oral suspension (as determined by modelling the results of studies 905-CL-075, 905-CL-066 and 905-CL-080) was adjusted based on weight in order to deliver a plasma

drug exposure equivalent to the 5 mg once daily oral tablet dose of solifenacin in adults. This was referred to as the paediatric equivalent dose (PED) of 5 mg (PED5).

One to 3 titration steps of 3 weeks duration each were foreseen to reach the optimal dose (doses to achieve exposures equivalent to adult exposures at 2.5 mg (PED2.5), 5 mg (PED5), 7.5 mg (PED7.5) and 10 mg (PED10) once daily). To ensure that patients who did not require drug therapy were discontinued from the study during the titration phase, down titration to “no treatment” (i.e., interruption of treatment) for a period of 3 weeks could be performed in patients with a complete response. Patient with as sustained response on “no treatment” were to be withdrawn from the study.

The first visit of study 905-CL-077 was labelled visit 8 and coincided with visit 8 (end of study visit) of study 905-CL-076. Last treatment in study 905-CL-076 was taken on visit 7, which was scheduled 2 to 3 days before visit 8, the first visit of study 905-CL-077. Hence, patients were off-treatment for 2 to 3 days when rolling over from study 905-CL-076 to study 905-CL-077.

The baseline values measured for study 905-CL-076, were also taken as the baselines for the present study.

There were 7 visits in total:
- Visit 8 (2 to 3 days after visit 7 of study 905-CL-076): the day before start of open-label treatment;
- Visit 9 (week 15), visit 10 (week 18) and visit 11 (week 21): opportunity to up or down titrate open-label treatment;
- Visit 12 (week 24) and visit 13 (week 36): fixed-dose steady state of individualised doses for all patients;
- Visit 14 (week 52): end of study visit.

At least 120 patients (at least 100 children and at least 20 adolescents) were to be evaluable for the primary endpoint i.e., the incidence and severity of adverse events (AEs). All children and adolescents who chose to participate were considered eligible and received open-label solifenacin (119 children and 29 adolescents).

The study population consisted of male and female children (5 to less than 12 years old) and adolescents (12 to less than 18 years old) with OAB, who completed study 905-CL-076. The age of the patient upon signing the informed consent or assent form of study 905-CL-076 determined the age group.

The investigational drug (solifenacin succinate oral suspension 1 mg/mL) was provided as 100 mL suspension. Dose volumes corresponded with PED2.5, PED5, PED7.5 or PED10 solifenacin once daily.

Efficacy endpoints
Efficacy variables were secondary and were change from baseline of study 905-CL-076 to end of this study in:
- Mean number of micturitions/24 hours
- Mean number of grade 3 or 4 urgency episodes per 24 hours in adolescents
- Mean number of incontinence episodes/24 hours
- Mean number of dry (incontinence-free) days/7 days

Methods
The changes from baseline to each solifenacin treatment duration window for each efficacy variable were summarised and analysed using a repeated measures analysis of covariance (ANCOVA) model including region, gender, time and randomised treatment group in study 905-CL-076 as fixed-effects, and baseline as a covariate. No further covariates were included in the model.

The efficacy endpoints were assigned to 1 of several intervals, or windows, based on the duration of solifenacin treatment at the study day (i.e., the number of days from the date of the first dose of solifenacin in either study 905-CL-076 or 905-CL-077 up to and including the study day, irrespective of any interruptions to treatment). This was required so that data from those patients who received solifenacin in study 905-CL-076 could be combined in a meaningful way with that from the patients who received placebo and hence did not start solifenacin until visit 8/week 12.

Results
119 children and 29 adolescents received open-label solifenacin in study 905-CL-077 (table 5). 20 children and 6 adolescents discontinued the study.117 children and 29 adolescents were eligible for repeated measures analysis.

The mean number of incontinence episodes per 24 hours decreased over the course of the study. After 52 weeks of treatment, the adjusted mean reduction in number of incontinence episodes per 24 hours from baseline was 1.9 for children and 2.0 for adolescents. The mean number of dry (incontinence-free) days per 7 days increased over the course of the study. After 52 weeks of treatment, the adjusted mean increase in number of dry (incontinence-free) days per 7 days from baseline was 2.8 for children and 3.9 for adolescents (0.6 in children and 1.2 in adolescents at baseline) (table 6).

Table 5 Results of Repeated Measures Analysis of Change From Baseline in Number of Incontinence Episodes per 24 h (FAS)

Duration of Solifenacin Treatment†	Statistics	Children (Aged 5 to Less Than 12 Years) Total Solifenacin n = 117	Adolescents (Aged 12 to Less Than 18 Years) Total Solifenacin n = 29
Baseline	n	117	29
	Mean (SE)	2.70 (0.22)	2.69 (0.43)
3 Weeks	n	114	28
	Mean Change From Baseline (SE)	-0.92 (0.18)	-1.05 (0.34)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-0.95 (0.12)	-0.93 (0.35)
	95% 2-sided CI	(-1.19, -0.71)	(-1.62, -0.23)
6 Weeks	n	116	26
	Mean Change From Baseline (SE)	-1.11 (0.17)	-1.40 (0.33)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-1.11 (0.12)	-1.38 (0.36)
	95% 2-sided CI	(-1.34, -0.88)	(-2.09, -0.68)
9 Weeks	n	115	29
	Mean Change From Baseline (SE)	-1.28 (0.19)	-1.48 (0.38)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-1.26 (0.13)	-1.40 (0.35)
	95% 2-sided CI	(-1.53, -1.00)	(-2.09, -0.70)
12 Weeks	n	111	29
	Mean Change From Baseline (SE)	1.39 (0.20)	-1.66 (0.39)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-1.39 (0.12)	-1.58 (0.35)
	95% 2-sided CI	(-1.63, -1.16)	(-2.27, -0.88)
24 Weeks	n	108	27
	Mean Change From Baseline (SE)	-1.61 (0.19)	-1.73 (0.39)
	Adjusted Change From Baseline †		
	Adjusted Mean (SE)	-1.54 (0.11)	-1.80 (0.35)
	95% two-sided CI	(-1.76, -1.32)	(-2.50, -1.10)
40 Weeks	n	97	23
	Mean Change From Baseline (SE)	-1.66 (0.23)	-1.49 (0.36)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-1.56 (0.13)	-1.57 (0.36)
	95% 2-sided CI	(-1.81, -1.31)	(-2.29, -0.85)
52 Weeks	n	44	11
	Mean Change From Baseline (SE)	-1.56 (0.22)	-1.34 (0.38)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	-1.93 (0.13)	-2.00 (0.42)
	95% 2-sided CI	(-2.19, -1.67)	(-2.83, -1.17)

† From a repeated measures ANCOVA considering the change in the total number of incontinence episodes from the baseline mean value.

The model includes duration of all (double-blind and/or open-label) solifenacin treatment (mapped to 3 weeks, 6 weeks, 9 weeks, 12 weeks, 24 weeks, 40 weeks, and 52 weeks), gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate, and with "duration" repeated within subject.

ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set.

Source: Table 12.3.1.3

The study drug dose was up-titrated individually. At week 3 (first titration opportunity), the dose was up-titrated from PED5 to PED7.5 in 57 (78.1%) placebo-treated vs 51 (69.9%) solifenacin-treated children and 16 (84.2%) placebo-treated vs 19 (86.4%) solifenacin-treated adolescents. The majority of patients were further up-titrated at week 6 (2nd titration opportunity) or week 9 (third or final titration opportunity) to PED10 and remained on PED10 until the end of the study. PED10 was the final dose in 52 (71.2%) placebo-treated vs 47 (64.4%) solifenacin-treated children and 12 (63.2%) placebo-treated vs 16 (72.7%) solifenacin-treated adolescents.

Table 6 Results of Repeated Measures Analysis of Change From Baseline in Number of Dry (Incontinence-Free) Days per 7 Days (FAS)

Duration of Solifenacin Treatment†	Statistics	Children (Aged 5 to Less Than 12 Years) Total Solifenacin n = 117	Adolescents (Aged 12 to Less Than 18 Years) Total Solifenacin n = 29
Baseline	n	117	29
	Mean (SE)	0.56 (0.10)	1.16 (0.24)
3 Weeks	n	114	28
	Mean Change From Baseline (SE)	1.17 (0.16)	1.69 (0.53)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	1.35 (0.19)	1.53 (0.69)
	95% 2-sided CI	(0.97, 1.73)	(0.17, 2.89)
6 Weeks	n	116	26
	Mean Change From Baseline (SE)	1.28 (0.19)	2.21 (0.56)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	1.43 (0.20)	1.90 (0.70)
	95% 2-sided CI	(1.02, 1.83)	(0.52, 3.27)
9 Weeks	n	115	29
	Mean Change From Baseline (SE)	1.59 (0.21)	1.94 (0.50)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	1.72 (0.22)	1.75 (0.69)
	95% 2-sided CI	(1.27, 2.16)	(0.39, 3.10)
12 Weeks	n	111	29
	Mean Change From Baseline (SE)	1.60 (0.21)	2.89 (0.51)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	1.80 (0.22)	2.69 (0.69)
	95% 2-sided CI	(1.36, 2.24)	(1.34, 4.05)
24 Weeks	n	108	27
	Mean Change From Baseline (SE)	2.09 (0.22)	3.19 (0.51)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	2.21 (0.23)	3.07 (0.69)
	95% two-sided CI	(1.74, 2.67)	(1.70, 4.43)
40 Weeks	n	97	23
	Mean Change From Baseline (SE)	2.15 (0.25)	2.71 (0.59)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	2.28 (0.25)	2.45 (0.71)
	95% 2-sided CI	(1.79, 2.77)	(1.05, 3.85)
52 Weeks	n	44	11
	Mean Change From Baseline (SE)	2.57 (0.40)	3.27 (0.73)
	Adjusted Change From Baseline†		
	Adjusted Mean (SE)	2.84 (0.33)	3.93 (0.81)
	95% 2-sided CI	(2.19, 3.49)	(2.34, 5.53)

† From a repeated measures ANCOVA considering the change in the total number of dry days from the baseline value.

The model includes duration of all (double-blind and/or open-label) solifenacin treatment (mapped to 3 weeks, 6 weeks, 9 weeks, 12 weeks, 24 weeks, 40 weeks, and 52 weeks), gender, geographic region and randomized treatment group in Study 905-CL-076 as fixed effects, baseline as a covariate, and with "duration" repeated within subject.

ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set.

Source: Table 12.3.2.3

Although formally not an efficacy study (i.e. lacking a control arm and not powered to demonstrated differences in efficacy) results show decrease in incontinence episodes and an increase in dry days as compared to baseline. This change as compared to baseline is maintained over the 52 weeks study period.

V.4 Clinical safety

Study 905-CL-076
Safety endpoints
Safety variables were:

- Treatment-emergent adverse events (TEAEs) (frequency, severity, seriousness, and relationship to study drug)
- Clinical laboratory variables (haematology, biochemistry including liver function tests, and urinalysis)
- Post Void Residual (PVR) volume
- Vital signs (systolic and diastolic blood pressure and pulse rate)
- 12-lead electrocardiogram (ECG)

Results
The most common drug-related treatment-emergent adverse events (TEAEs) in placebo-treated children were constipation and ECG QT prolonged (2 patients each). The most common drug-related TEAEs in solifenacin-treated children were constipation, ECG QT prolonged (4 patients each) and dry mouth (2 patients). The safety profile of solifenacin appears comparable with that in the adult population. Considering the QT prolongation in adults this is not studied in the adult phase 3 studies. Previously a QT study in healthy adults was performed. The QT study did not reveal any clinically relevant changes.

Study 905-CL-077
Safety endpoints
Primary safety variables:

- Incidence and severity of AEs

Secondary safety variables:

- Clinical laboratory variables (haematology, biochemistry including liver function tests, and urinalysis)
- Post Void Residual (PVR) volume
- Vital signs (systolic and diastolic blood pressure (SBP and DBP) and pulse rate)
- 12-lead electrocardiogram (ECG) parameters

Analytical methods
All analyses of safety were performed on the safety analysis set (SAF) for each age group.
The secondary safety endpoints (urinalysis laboratory data, PVR volume, vital signs, and ECG) were also assigned to 1 of several intervals, or windows, based on the duration of solifenacin treatment at the study day.

Results
The most commonly reported drug-related TEAEs in children were constipation and ECG QT prolonged (14 and 10 patients, respectively). The most commonly reported drug-related TEAEs in adolescents were ECG QT prolonged (4 patients) and nausea (2 patients). TEAE of constipation, which is an expected adverse drug reaction in the treatment of adults with solifenacin and other antimuscarinic agents, had a reported incidence of 2.8% in adolescents.

The overall safety profile and overall tolerability in this study are consistent with that reported for adults. No new or unexpected safety results were observed.

V.5 Risk Management Plan

The Risk Management Plan has been updated in view of adding the paediatric population (5-18 years) to the indicated population.

No changes have been made to the summary of safety concerns. This is acceptable.
No post-authorisation efficacy studies are planned for solifenacin.

V.6 Discussion on the clinical aspects

The use of the MVV as a primary endpoint for determining efficacy and safety is in line with the Guideline on the clinical investigation of medicinal products for the treatment of urinary incontinence (CPMP/EWP/18/01/Rev.1). However, to assess the clinical relevance of this pharmacodynamic endpoint the guideline advises to include a diary evaluating the effect on daytime incontinence episodes/24 hours, night-time incontinence episodes/24 hours, dry (incontinence-free) days/7 days, day-time micturition/24 hours, urgency episodes per 24 hours as a co-primary endpoint. Although the design of the study (including the primary endpoints) were defined and accepted as part of the PIP, these are not in line with the current guideline as diary results on incontinence and micturition frequency are lacking as primary endpoint. This hampers the assessment of the clinical relevance of the found effect on MVV. Further it is stated in the guideline that OAB in adults is from a pathophysiological perspective considerably different from the condition observed in children.

A meta-analysis made by Lee (Lee et al., 2009) clearly demonstrated that there is a strong correlation between MVV, micturition frequency and incontinence episodes in adults. Therefore the MAH analysed the effect on MVV in children and compared (indirect comparison) the changes in MVV reported for adults with those observed in the paediatric study. The effect size observed for MVV in paediatric subjects in the pivotal placebo-controlled study (study 905-CL-076), when scaled relative to age-expected bladder capacity, is in the range of the effect size reported for solifenacin and other approved treatments for OAB in adults. The clinical beneficial effects as reported for adults are extrapolated by the MAH, however without scientific argumentation. The observation that the diagnosis of OAB in children according to the same definition results in a more or less comparable clinical manifestation does not give any information of the pathophysiological basis of the disease. Further a correlation between changes in MVV and clinically relevant improvement is not reported in general literature for children. As OAB in children has a different etiology from the condition seen in adults some justification for the extrapolation should be given. The loosecorrelation as demonstrated for study 905-CL-076 using a regression model with change from baseline in MVV, treatment group, and baseline number of incontinence episodes per 24 hours as predictors might indicate some effect. However given the magnitude of the effect on incontinency related parameters this effect can not be considered clinically relevant.

The lack of effect on the relevant incontinence endpoints was explained by the MAH by assuming that the small sample size, the concomitant effect of urotherapy and an imbalance in baseline incontinence parameters between the treatment groups prohibited the demonstration of a statistically significant effect.

VI. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

This variation application was discussed in the Board meeting of the RMS on 26 November 2015. The MAH requested to extend the indication of Vesicare 1 mg/ml, oral suspension to the treatment of OAB syndrome in paediatric patients (5 to 18 years of age). After having considered the available evidence, the Board concluded that the benefit-risk balance of Vesicare in the treatment of OAB syndrome in paediatric patients is negative. The clinical benefit in children is not sufficiently demonstrated. As the available analysis provides information relevant for the prescriber the RMS and Concerned Member States agree that inclusion of information concerning the paediatric clinical studies is appropriate in sections 4.2, 5.1 and 5.2 of the SmPCs of Vesicare. The added text is indicated below in Section VII. The variation procedure was finalised on 8 June 2016.

VII. CHANGES IN PRODUCT INFORMATION

The changes to SmPC and PL in the context of this variation are presented below. Added text is underlined, strike-through text was deleted.

- **SmPC**

4.2 Posology and method of administration

~~*Paediatric population*~~
~~The safety and efficacy of Vesicare in children have not yet been established. Therefore, Vesicare should not be used in children.~~

Paediatric population
The efficacy of Vesicare in children and adolescents has not yet been established. Therefore, Vesicare should not be used in children and adolescents below 18 years of age. Currently available data are described in Section 5.1 and 5.2.

4.6 Fertility, pregnancy and lactation

Fertility
There are no clinical data available on effect of solifenacin on fertility. No effects on fertility were observed in animals.

5.1 Pharmacodynamic properties

Pharmacodynamic effects

Adults:
Treatment with Vesicare in doses of 5 mg and 10 mg daily was studied in several double blind, randomised, controlled clinical trials in men and women with overactive bladder.
As shown in the table below, both the 5 mg and 10 mg doses of Vesicare produced statistically significant improvements in the primary and secondary endpoints compared with placebo. Efficacy was observed within one week of starting treatment and stabilises over a period of 12 weeks. A long-term open label study demonstrated that efficacy was maintained for at least 12 months. After 12 weeks of treatment approximately 50% of patients suffering from incontinence before treatment were free of incontinence episodes, and in addition 35% of patients achieved a micturition frequency of less than 8 micturitions per day. Treatment of the symptoms of overactive bladder also results in a benefit on a number of Quality of Life measures, such as general health perception, incontinence impact, role limitations, physical limitations, social limitations, emotions, symptom severity, severity measures and sleep/energy.

Special populations:

Children and adolescents (age 5 years and older):
Treatment with Vesicare oral suspension was studied in two clinical studies. A 12-week double-blind, randomised, placebo-controlled, clinical trial (Study 905-CL-076) was performed in 189 paediatric patients with OAB (73 children aged 5-11 years and 22 adolescents aged 12-17 years were treated with solifenacin). This was followed by a 40-week long-term open-label extension study (Study 905-CL-077) in 148 paediatric patients (119 children and 29 adolescents were treated with solifenacin). In both studies, the majority of patients were up-titrated to the weight-based equivalent of 10 mg in adults.
In Study 905-CL-076 Vesicare oral suspension did not show a statistically significant improvement in the primary endpoint of mean volume voided per micturition compared with placebo in the overall population.
In children (aged 5-11 years) a statistically significant difference was observed for this primary endpoint. No statistically significant improvement was observed in the secondary endpoints of micturition frequency, number of incontinence episodes per day and number of dry days per week. No unexpected or unlisted adverse events were reported for the entire dose range tested.
In the open-label extension study, no unexpected or unlisted adverse events were reported. The safety profile for solifenacin in paediatric patients during long-term exposure was comparable to that observed in adults.

5.2 Pharmacokinetic properties

~~The pharmacokinetics of solifenacin have not been established in children and adolescents.~~

Children and adolescents (age 5 years and older):

The pharmacokinetics of solifenacin following weight-adjusted dosing in children and adolescents with OAB were similar to those observed in adults, with a slightly shorter t_{max} and $t_{1/2}$; these differences were not considered clinically significant.

- **PL**

1. What Vesicare is and what it is used for

The active substance of Vesicare belongs to the group of anticholinergics. These medicines are used to reduce the activity of an overactive bladder. This enables you to wait longer before having to go to the bathroom and increases the amount of urine that can be held by your bladder.

Vesicare is used to treat the symptoms of a condition called overactive bladder. These symptoms include: having a strong, sudden urge to urinate without prior warning, having to urinate frequently or wetting yourself because you could not get to the bathroom in time.

Vesicare is used to treat overactive bladder in adults.