TOVIAZ (FESOTERODINE) RISK MANAGEMENT PLAN

RMP Version number: 10.0

Data lock point for this RMP: 15 November 2020

Date of final sign off: 19 March 2021

Rationale for submitting an updated RMP: The important identified risks, important potential risks, and missing information were evaluated and reassessed to align with the new Guideline on good pharmacovigilance practice (GVP) Module V – Risk management systems (Rev.2). In addition, the paediatric phase 3 clinical trial program has completed and use in children is no longer considered to be important missing information. A summary of significant changes in this RMP are provided in the table below.

RMP converted to the EU RMP template (Revision 2.0.1) in version 10.0.

RMP Part/Module	Major Change(s)
PART I. PRODUCT OVERVIEW	No updates.
PART II. SAFETY SPECIFICATION	
PART II.Module SI. Epidemiology of the Indications and Target Populations	Removed Main Co-Prescribed Medicinal Products Removed Concomitant medication(s) in the target population
PART II.Module SII. Non-Clinical Part of the Safety Specification	Removed conclusions on Nonclinical Data
PART II.Module SIII. Clinical Trial Exposure	Clinical trial exposure updated to the new data lock point (15 November 2020).
PART II.Module SIV. Populations Not Studied in Clinical Trials	Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme Table updated.
PART II.Module SV. Post-Authorisation Experience	Post-marketing exposure updated to the new data lock point (15 November 2020).
PART II.Module SVI. Additional EU Requirements for the Safety Specification	Removed potential harm from overdose; potential for transmission of infectious agent; potential for medication errors; potential for off-label use; specific pediatric issues
PART II.Module SVII. Identified and Potential Risks	The important identified risks, important potential risks, and missing information were evaluated and reassessed to align with the new Guideline on good pharmacovigilance practice (GVP) Module V – Risk management systems (Rev. 2). Following PRAC endorsement (Procedure no.: EMEA/H/C/PSUSA/00001387/202004) the MAH has removed the following safety concerns: Important identified risks: Urinary retention, Angioedema Important potential risks: QT prolongation, Hepatotoxicity, Cognitive function impairment Missing information: Elderly male patients, Paediatric patients, Pregnant or nursing women
PART II.Module SVIII. Summary of the Safety Concerns	Updated following the PRAC endorsement to remove the important identified and potential risks and missing information.

RMP Part/Module	Major Change(s)
PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)	Updated removing the important identified and potential risks and missing information. Removed A0221047 and A0221074[a]as these studies are now complete.
PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES	Removed A0221047 and A0221074[a] as these studies are now complete.
PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)	Updated removing the important identified and potential risks and missing information.
PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN	Updated summary of the RMP.
PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN	Updated the annexes to the RMP.
a. Cohort 2 of A0221047	

Other RMP versions under evaluation: None

Details of the currently approved RMP:

Version number: 9.0

Approved with procedure: EMA/220572/2014

Date of approval (opinion date): 21 November 2013

QPPV name: Barbara De Bernardi, MD

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

LIST OF ABBREVIATIONS

5-HMT	5-hydroxymethyltolterodine
AE	Adverse Event
ADR	Adverse Drug Reaction
ATC	Anatomical Therapeutic Chemical
BACH	Boston Area Community Health
BIC	Beads in Capsule
BPH	Benign Prostatic Hyperplasia
C_{max}	Maximum Concentration
CI	Confidence Interval
CYP	Cytochrome P450
DO	Detrusor Overactivity
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EPINCONT	Epidemiology of Incontinence in the County of Nord-Trøndelag
ER	Extended Release
EU	European Union
FDA	Food and Drug Administration
FORM	Formulation
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
ICD-9-CM	International Classification of Diseases, Eleventh Revision, Clinical Modification
ICS	International Incontinence Society
INN	International Nonproprietary Name
ISC	Intermittent Self Catheterisation
LD_{50}	Lethal Dose 50%
LUTS	Lower Urinary Tract Symptoms
MAA	Marketing Authorization Holder
MAH	Marketing Authorisation Holder
Medi-Cal	California Medicaid Programme
MMSE	Mini-Mental State Examination
MUI	Mixed Urinary Incontinence
NA	North America
NA	Not Applicable
NDO	Neurogenic Detrusor Overactivity
NOAEL	No Observable Adverse Event Level
NOBLE	National Overactive Bladder Evaluation
OAB	Overactive Bladder
OR	Odds Ratio
PK	Pharmacokinetic
PL	Package Leaflet

PSUR	Periodic Safety Update Report
RMP	Risk Management Plan
ROW	Rest of World
SmPC	Summary of Product Characteristics
SS	Safety Set
UNK	Unknown
UK	United Kingdom
US	United States
UTI	Urinary Tract Infection
UUI	Urge Urinary Incontinence
VES	Vulnerable Elderly Survey

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PART I. PRODUCT(S) OVERVIEW

Active substance(s) **(INN or common name)**	Fesoterodine
Pharmacotherapeutic group(s) (ATC Code)	Urinary antispasmodics (G04B D11)
Marketing Authorisation Holder	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	Toviaz
Marketing authorisation procedure	Central
Brief description of the product:	Chemical class: Fesoterodine is a competitive, non-selective muscarinic receptor antagonist.
	Summary of mode of action: N/A
	Important information about its composition: N/A
Hyperlink to the Product Information:	Module 1.3.1
Indication(s) in the EEA	Current: Fesoterodine is indicated for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with Overactive Bladder Syndrome.
	Proposed (if applicable): N/A
Dosage in the EEA	Current: The recommended starting dose is 4 mg once daily. Based on individual response, the dose may be increased to 8 mg once daily. The maximum daily dose is 8 mg.
	Proposed (if applicable): N/A
Pharmaceutical form(s) and strengths	Current: Prolonged-release tablets, 4 mg and 8 mg.

	Proposed (if applicable): N/A
Is/will the product be subject to additional monitoring in the EU?	No

PART II. SAFETY SPECIFICATION

Module SI. Epidemiology of the Indication(s) and Target Population (s)

Indications

Brand name - Toviaz®

Fesoterodine (Toviaz) is indicated for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in adult patients with OAB Syndrome.

Search Strategy

PubMed was searched for primary literature and review articles on incidence, prevalence, and mortality among people with OAB. Because OAB has not been consistently defined in the literature, several search terms were employed to identify articles relevant to OAB including the 2002 ICS definition as well as the individual key symptoms that comprise OAB syndrome, in particular, urgency and urge urinary incontinence. Searches were confined to English language articles involving humans over the age of 18. A special effort was made to identify estimates representative of the EU.

The available epidemiological data of OAB specific to the US and Europe are presented below.

Incidence:

OAB is a chronic medical condition that affects 16.6% or 33 million adults in the US and approximately 100 million worldwide.[1] OAB refers to the collection of bladder storage symptoms, considered to be part of the set of conditions known as the LUTS. According to the 2002 ICS definition, OAB is defined as a syndrome comprised of urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia, and the absence of pathologic or metabolic factors that would explain these symptoms.[2] OAB has been frequently classified as OAB with Urge Urinary Incontinence UUI and OAB without UUI where UUI is defined as involuntary leakage accompanied by or immediately preceded by urgency.[2] Some patients who have both stress urinary incontinence and UUI are classified as having MUI. When urge is predominant then those patients with MUI are considered to have OAB. Much of the published literature focuses on the symptoms that comprise OAB (frequency, nocturia, urgency, and different types of urinary incontinence) rather than the most recent ICS definition of OAB where the emphasis is on the urgency as the underlying symptom of OAB.

US

Studies reporting data on the incidence of OAB as a syndrome in the US were not found. However, several studies provide estimates of the incidence of individual symptoms that comprise OAB. In the Nurses' Health Study cohort, the incidence of UUI and MUI was assessed among 23,792 women in the US.[3] This study consisted of 2 surveys, the baseline survey and the follow-up survey conducted in 2000 and 2002, respectively.[3] Among women

who were aged 54 to 79 and did not report leaking of any urine during the 12 months prior to the baseline survey, 0.7% developed UUI and 0.9% MUI 2 years later.[3] Incidence of different types of urinary incontinence was also assessed in another study of both men and women aged 60 years and older conducted between 1983 and 1984.[4] Among men who reported to be continent at baseline, 4.1% developed UUI and 1.8% developed MUI one year later. Among women who reported to be continent at baseline, 1.7% developed UUI and 9.8% developed MUI one year later.[4] These estimates may not be representative of the true incidence proportions of OAB symptoms because urgency alone was not assessed in participants at baseline. Therefore, it is possible that some of these individuals may have had OAB without UUI (only urgency) at baseline, which was not captured, as well as those who were truly free of urgency. The difference in the incidence proportions in women between two studies are likely to be due to the age difference, definitions used to categorise patients with UUI and MUI, and appreciable loss to follow-up in the second study.[4]

Europe

In a European Community 1998 prospective cohort study, women aged 40 or older were randomly sampled from the registers of 108 General Practices within the Leicestershire Health Authority. Sixty five percent (N = 12,750) responded to a postal questionnaire on urinary symptoms. Responders were then sent three follow-up questionnaires at yearly intervals. In this study the ICS definition of OAB was not used because only those women in whom OAB was "predictive of DO" were classified as OAB cases. DO was not diagnosed via urodynamics. Rather mathematical models based on a small subset that underwent urodynamic testing were used to determine a woman's likelihood of having an OAB predictive of DO.[5] At year one, the incidence of OAB predictive of DO ranged from 6.5% to 9.5% in females depending on age. However, it is difficult to generalise these findings to all OAB patients because this OAB definition is contingent on manifesting DO.

Several other studies conducted in Europe provide estimates of the incidence of individual symptoms that comprise OAB. One (1) study estimated the incidence of women who were free from urgency and voiding symptoms at baseline and then developed urgency and voiding symptoms 1 year later. In this study the annual incidence in women of these symptoms was reported to be 4.1%.[6] Another study reported the incidence of storage symptoms defined as 1 or more symptom of incontinence, urgency, nocturia, and frequency. Among patients who were free of storage disorders at baseline, the overall 1-year incidence was 6.3% for incontinence, and 14.1% for storage disorder.[7]

Prevalence:

US

Prevalence of OAB and symptoms that comprise OAB were estimated in two studies in the US.[8] The first study is that of NOBLE Programme which was initiated to better understand the prevalence and burden of OAB in a study population representative and generalisable to that of the US. This cross-sectional study was conducted via a telephone survey of the US national random sample of the US numbers. In this study, telephone surveys were conducted among 5204 adults aged 18 years and older between November 2000 and January 2001.

OAB without UUI was defined by a feeling of urgency four or more times in the past 4 weeks and either more than 8 micturitions per day or the use of at least 1 of the following coping strategies: restricting fluid intake, locating bathrooms in a new place, limiting travel, or defensive voiding. OAB with urge incontinence was defined as meeting the definition of OAB without urge incontinence plus 3 or more episodes of urinary leakage in the past 4 weeks that was typical (ie, frequency of episodes) and was not exclusively due to stress incontinence. In this study the overall prevalence of OAB was similar between men (16.0%) and women (16.9%). In women, prevalence of OAB with and without UUI was 9.3% and 7.6%, respectively. In men, prevalence of OAB with and without UUI was 13.4% and 2.6%, respectively.

The second study is that of the BACH survey.[9] BACH is a community based epidemiologic study of urologic symptoms and risk factors of American adults living in Boston, Massachusetts, United States of America. This study employed a 2-stage stratified cluster sample design to recruit 5506 adults (2301 men and 3205 women). In this study prevalence of numerous LUTS was assessed including frequency, urgency, urinary incontinence, and OAB. Prevalence of urinary incontinence (involuntary loss of urine at least weekly) was reported to be 5.3% among men and 10.4% among women. Prevalence of frequency (urinating more frequently than every two hours or frequent urination during the day as indicated by responses of fairly often, usually, and almost always or urinating more than 8 times per day) was reported to be 27.8% among men and 36.9% among women. Prevalence of urgency (having difficulty postponing urination or having difficulty a strong urge to urinate in the previous month or experiencing a strong urge to urinate in the previous 7 days) was reported to be 9.3% among men and 14.2% among women. Prevalence of OAB (defined as frequency and urge described above) was reported to be 7.3% among men and 11.7% among women. Prevalence of OAB with UUI (defined as OAB and reporting leaking urine when having a strong feeling of needing to empty the bladder or not getting to the bathroom soon enough) was reported to be 2.8% among men and 6.8% among women. Prevalence of OAB without UUI was reported to be 4.5% among men and 5.0% among women.

Europe

Several population-based studies that estimated the prevalence of OAB in Europe were found. Two (2) largest studies conducted up to date in Europe are summarised below.

In the first study, prevalence of OAB symptoms was assessed among 16,776 participants aged 40 year and older.[10] The study participants were selected from residents of France, Germany, Italy, Spain, Sweden and the UK. The overall prevalence of OAB symptoms (frequency, urgency, urge incontinence, alone or in any combination) was 16.6%, 15.6% among men and 17.4% among women.[10] Prevalence of urgency (a strong urge to urinate with no advance warning) as an individual symptom was reported to be 7.6% among men and 9.7% among women.[11] Prevalence of urge incontinence (feeling unable to get to the toilet in time to urinate or experiencing daytime or nocturnal urinary incontinence) as an individual symptom was reported to be 4.0% among men and 7.4% among women.[11] Prevalence of frequency (urinating 8 or more times during the day or having to get up at least twice at night to urinate) as an individual symptom was reported to be 13.7% among men and 14.6% among women.[11] The prevalence of OAB symptoms varied among the sample

populations of the 6 European countries studied, ranging from 12% among French and Italian respondents to 22% in the Spanish survey.[10]

Prevalence of OAB as defined by ICS was estimated in the most recent population-based cross-sectional survey.[12] The survey was conducted between April and December 2005 in Canada, German, Italy, Sweden, and the UK among 19165 participants. Prevalence of urgency (experiencing a sudden compelling desire to urinate which is difficult to put off) was 10.8% among men and 12.8% among women. Prevalence of frequency (feeling that one urinates too often during the day) was 6.8% among men and 7.4% among women. Prevalence of UUI (leaking urine with a sudden compelling desire to urinate) was 1.2% among men and 1.5% among women. The overall prevalence of symptoms that define OAB was 11.8% (12.8% among women and 10.8% among men).

Demographics of the population in the authorised proposed indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Overall, OAB tends to be more prevalent in women than in men and increases with increasing age. For instance, in one European study[10] prevalence of OAB and of all three symptoms (frequency, urgency and urge incontinence) increased with advancing age in both men and women. The prevalence of OAB symptoms increased with age and ranged from 3.4% in men aged 40 to 44 years old to 41.9% among those aged 75 years old.[10] In women, the prevalence of OAB without UUI ranged from 8.7% among women aged 40 to 44 years to 31.3% among women aged 75 years and older.

Moreover, age patterns of OAB differ by type (OAB with UUI vs. OAB without UUI) and gender. For example, in the NOBLE study, prevalence of OAB with UUI in women increased with age from 2.0% to 19% with a marked increase after 44 years of age. In men, prevalence of OAB with UUI increased with age from 0.3% to 8.9% with a marked increase after 64 years of age.[8] The prevalence of OAB without UUI showed a different pattern than that of OAB with UUI. In men, OAB without UUI showed a steeper increase by age with prevalence increasing from 8.5% in men below 45 years of age to 21.8% in those aged 55 to 64 years. In women, the prevalence of OAB without UUI gradually increased with age and reached a plateau once women reached the age of 44 years.[8]

OAB syndrome has a multifactorial aetiology which is associated with a wide range of risk factors including those that are physiological, neurological, behavioural, dietary, and genetic. The single most strongly correlated risk factor for OAB across multiple studies is increased age.[13] Additionally, some evidence has suggested that OAB is related to obesity, diabetes, depression, and gender related exposures.

The pathophysiology of OAB differs between men and women, and these differences are reflected in a number of sex specific risk factors. Benign prostatic hyperplasia (BPH) and prostate inflammation in men, and uterine prolapsed in women can constrain bladder volume and lead to OAB.[14] The EPINCONT cohort study in Norway (n = 15,307) reported that vaginal births compared to caesarean births were associated with incontinence in mothers (OR = 1.7, 95% CI: 1.3 - 2.1),[15] and cross-sectional studies have suggested that parity may play a role in OAB.[16,17] However, a recent cross-sectional study from Spain (n = 1004

women) produced seemingly contradictory results: women with 3 or more children were predisposed to OAB, but those with 1 or 2 children were protected from OAB.[18]

In both men and women, complications relating to other health conditions can alter the lower urinary tract and result in OAB. Neurological diseases, such as stroke, multiple sclerosis, and Parkinson's disease, can have urological sequelae that bring about OAB.[19] A cross-sectional study published in 2007 with 3962 women in the US-based Kaiser Permanente Health system reported associations between OAB and obesity (OR = 2.67, 95% CI: 2.2 – 3.2). Using the Kaiser Permanente data, an association between OAB and diabetes was also reported (OR = 1.90, 95% CI: 1.5 – 2.5).[20] Obesity may lead to urinary disorders by stressing the pelvic floor,[20] and diabetes may be related to OAB via normal detrusor muscle transformation, urothelial dysfunction, neuronal impairment, and central and peripheral neural damage.[21]

A potential link between OAB and metabolic syndrome remains controversial. In 2005, a large case control study (n = 2372) of American men 60 years and over reported a significant association between LUTS and 3 or more components of metabolic syndrome (OR = 1.80, 95% CI: 1.11–2.94).[22] However, subsequent cross-sectional examinations failed to show a strong statistically significant association between LUTS and metabolic syndrome.[23,24] A cross sectionals study with 1031 men in Japan showed no association between OAB and 3 separate criteria for metabolic syndrome.[25]

A cohort study with 3685 Japanese men and women 65 years of age and over, found metabolic syndrome was not associated with OAB, but that age and depression predicted incident OAB after one year of follow-up. The odds of OAB was 1.8 (95% CI: 1.4 - 2.5) times greater in those who reported depression on the Geriatric Depression scale than among participants who did not report depression.[26] The association between depression and OAB from the Japanese cohort was consistent with earlier findings in cross-sectional settings.[27,28,29] The Japanese cohort study was one of the few longitudinal OAB epidemiology studies to suggest such an association. It is suggested that low serotonin which is related to depression may also be associated with increased risk of OAB. The suggestion that serotonin is important in OAB was supported by data that showed that serotonin reuptake inhibitors, which increase synaptic serotonin concentrations, may also relieve OAB in some patients.[26,30]

Additional studies have reported associations between OAB and other exposures including genetics,[31] alcohol, tobacco,[32] coffee or tea consumption,[33] menopause,[18] erectile dysfunction in men,[34] bed wetting in children,[35] inflammatory markers,[36] and race in the US.[14] However, the majority of studies that examined OAB risk factors were cross-sectional in design and the results were often difficult to interpret or replicate.

The main existing treatment options:

Antimuscarinics are the current pharmacological treatments of choice for OAB and are available as immediate or ER preparations. Other treatment options that may be considered when symptoms are not controlled with conservative (bladder retraining/pelvic floor exercises) or pharmacotherapy methods, include β3-adrenoceptor agonists, bladder wall

injection with botulinum toxin A and surgery such as sacral nerve stimulation and retropubic mid-urethral tape procedures.[37]

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

OAB does not directly lead to mortality; however, OAB affects many dimensions of patients' lives and causes considerable morbidity. OAB is associated with lost productivity in the workplace and unemployment among men.[38] Both men and women who suffer from OAB are likely to report worry over OAB in work related meetings and symptoms of OAB affect their choice of work schedule and work place.[13] A case control study nested within the EPIC cohort investigated morbidity from OAB by comparing 1434 OAB cases to age and gender matched controls in Germany, the UK, Canada, Italy, and Sweden. The nested case control study showed that OAB was significantly associated with not just lost productivity at work and increased unemployment, but also depression, decreased sexual activity, and decreased sexual enjoyment.[39] A subsequent cross-sectional study of female OAB patients in Spain (n = 891), suggested that coital urinary incontinence was high (36%).[40] Urinary incontinence may explain some of the decreased sexual activity and decreased sexual enjoyment that OAB patients have reported.

Important co-morbidities:

Patients with OAB are affected by numerous co-morbidities, ie, conditions that are diagnosed at the same time as OAB. The section below highlights three co-morbidities that are considered to be most clinically relevant: urinary tract infections, dementia, and Alzheimer's disease. Search strategy is presented in the footnote below.[1]

Co-morbidities: UTI

Incidence of UTI

No population-based data on the incidence of UTI in the OAB patient population were found. However, the incidence of UTI was reported in an extensive meta-analysis which examined the efficacy and safety of patients treated with antimuscarinics.[41] The study population for this meta-analysis was comprised of 83 studies including 46 that were placebo-controlled with study lengths ranging from 2 to 52 weeks. Study subjects were adult patients (aged 18 and older) with idiopathic OAB, DO or urinary incontinence (including UUI and MUI). In this study, the incidence of UTI among placebo treated subjects with OAB or UUI or MUI was 3.6%.[41] This estimate needs to be interpreted with caution given that this study population was largely limited to patients with OAB with UUI or OAB with MUI who met

[1] Throughout the literature review, comorbidities were represented by the following Boolean search terms: [urinary tract infection OR UTI OR bacteriuria] and [dementia OR Alzheimer's disease OR Alzheimer Disease OR cognitive impairment OR cognitive function OR cognitive dysfunction OR angioedema OR Quincke's edema OR angioneurotic edema OR Quincke's disease].

numerous inclusion/exclusion criteria. Hence, this estimate may not be generalisable to OAB patients in the real world with varying severity of OAB symptoms.

Prevalence of UTI

Several population-based epidemiologic studies estimated the prevalence of UTI among OAB patients. Overall, prevalence of UTI ranges from 5.8% to 38.9%. This variability is partly due to the time period during which UTI recall was assessed, type of OAB (OAB with UUI vs. OAB without UUI), age, and gender.

Prevalence of UTI was assessed during the cross-sectional phase of the NOBLE study. Among those who were classified to have OAB with UUI, 27.5% of women and 5.6% of men reported a UTI during the past four weeks. Among those who were classified to have OAB without UUI, 7.7% of women and 38.9% of men reported a UTI during the same time period. In the case control phase of this study which was designed to compare risk factors of individuals with OAB vs. those without OAB,[42] 21.7% of OAB cases reported at least one episode of physician-diagnosed UTI in the past year.

Prevalence of UTI was also quantified among a sub-sample of Medi-Cal enrollees.[43] The study population of this cohort study included patients aged 18 years and older, who were dispensed medications to treat OAB and/or UI between July 1999 and April 2001 and had a diagnosis of either OAB and/or UI. Eighteen (18) and a half percent of OAB and/or UI patients, had claims associated with UTI diagnosis during the study period while 8.1% had claims associated with UTI treatment.[43] It is likely that this estimate is an underestimate since it is possible that not all episodes of UTI come to the medical attention. Moreover, the study population of Medi-Cal may not be representative of all OAB patients.

Prevalence of UTI was quantified among women with urinary incontinence who were enrolled in the Kaiser Permanente Medical Care Programme of Northern California.[44] In this cohort study, of 2109 women aged between 40 and 69 years, age-adjusted prevalence of at least one episode of UTIs in last year among women with urinary incontinence (including UUI) was reported to be 12.7% in White, 17.6% in Hispanic, 9.8% in Black and 9.4% in Asian-American women.

Mortality from UTI

No population-based data on mortality associated with UTI in OAB patients were found.

<u>Comorbidities: Dementia and Alzheimer's Disease</u>

Incidence of Alzheimer's Disease

No population-based data on the incidence of dementia and/or Alzheimer's disease among patients with OAB were found.

Prevalence of Alzheimer's Disease

Data on the prevalence of dementia or Alzheimer's Disease among patients with OAB/urinary incontinence complaints are limited and mostly confined to elderly populations. The prevalence data below are summarised according to the study population: general adult population, general elderly population, and institutionalised elderly population. The emphasis on the study population is necessary because many health conditions differ with age and overall health status (ie, general adults are healthier than general elders and general elders are healthier than institutionalised elders).

Co-morbidities: Alzheimer's Disease in the General Adult Population

Prevalence of cognitive impairment was estimated in a retrospective analysis of a large US managed health care organisation between 01 July 2001 and 31 December 2001. In this study of 11,566 OAB patients aged 18 years and older (mean age 69 years old) cognitive impairment including Parkinson's disease was defined according to the ICD-9-CM codes (290.xx-295.xx, 297.x, 298.x, 311.0-311.2, 332.x). The prevalence of cognitive impairment and / or Parkinson's disease was estimated to be 5.4%.[45]

Co-morbidities: Alzheimer's Disease in the General Elderly Population

Published literature suggests that up to one-third of the population of elderly community residents with urinary incontinence may exhibit some degree of cognitive impairment.[46,47,48] In 1 cross-sectional survey of 14,621 elderly individuals aged 75 years and older selected from 106 general practices in England, Scotland and Wales, 4.7% (N = 694) reported urinary incontinence problems. Of them, 31.3% (95% CI 27.5-35.4) had cognitive impairment as suggested by the assessment conducted with mini-mental state examination, commonly used screening instrument for cognitive impairment.[48] In another survey of elderly general practice patients in UK (aged 75 years and older, N = 1203) estimated the prevalence of urinary incontinence at 12%.[46] Of those with urinary incontinence complaints, proportion of demented patients ranged from 15% to 24% (depending on whether cases with plausible but unconfirmed dementia were included in the estimate).

Co-morbidities: Alzheimer's Disease in the Institutionalised Elderly Population

There is a suggestion that prevalence of cognitive impairment may be significantly higher in institutionalised elderly. In a cross-sectional study of urinary incontinence among a representative sample of American nursing home residents aged 60 years and older (N = 2014), 49% of study participants were classified as incontinent.[49] Dementia was found in 83.6% of incontinent nursing home residents; 26.1% were diagnosed to have delirium. In another study of US nursing home residents (N = 430) estimated the prevalence of urinary incontinence at 39% two weeks after admission.[50] The prevalence of dementia among incontinent residents was 43%.

Co-morbidities: Mortality from Alzheimer's Disease

Data on mortality associated with cognitive impairment in the population of patients with OAB/urinary incontinence are unavailable.

Module SII. Nonclinical Part of the Safety Specification

Fesoterodine has been studied in a range of nonclinical pharmacology, PK and toxicology studies. Overall, the nonclinical safety profile of fesoterodine is comparable to that of other approved antimuscarinic drugs.

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
Single and repeat-dose toxicity: Results from single dose toxicity indicate a NOAEL of 100 mg/kg in both mice and rats. The estimated LD_{50} values were greater than 300 mg/kg. Clinical signs at high doses were mainly related to the antimuscarinic effects of fesoterodine such as reduced motility, ataxia, dyspnoea, and mydriasis. Signs of toxicity after subchronic and chronic treatment with fesoterodine were mainly limited to mortality and reduced body weight in the high dose groups. The liver was a target organ only in the rat; increased liver weights with corresponding bile duct proliferation with focal hepatocellular necrosis, inflammation, and diffuse fatty infiltration of hepatocytes along with changes in clinical pathology parameters were observed in female rats. Findings in the dog after subchronic and chronic treatment were mainly related to the antimuscarinic activity of fesoterodine. Mydriasis, reduced lacrimal secretion leading to conjunctivitis, and an increased heart rate were observed, and are known effects of antimuscarinic drugs. In addition, an increased platelet count and slightly increased urea blood levels were seen. Reduced body weights in the chronic study, resulting from apparent discomfort of the animals due to conjunctivitis, normalised after artificial lacrimal fluid was instilled into the eyes. Histopathological evaluation of the eyes, especially the retina, of dogs treated for 9 months did not show any morphological effect of fesoterodine on the eyes.	Signs of toxicity after subchronic and chronic treatment with fesoterodine were mainly limited to mortality and reduced body weight in the high dose groups and were considered to be related to supra-pharmacologic anticholinergic activity. Because the metabolite pattern in the rat was different from that in mouse, dog and man, and because similar findings were not observed in mice and dogs, the liver toxicity was considered to be specific to the rat. Mydriasis, reduced lacrimal secretion leading to conjunctivitis, and an increased heart rate were observed in dogs, and are known effects of antimuscarinic drugs in dogs.
• Genotoxicity No potential for mutagenic activity or genetic toxicity in bacterial or mammalian cells in vitro or in the in vivo micronucleus assay in mice.	No issues regarding mutagenic or tumorigenic potential were identified.
• Carcinogenicity Fesoterodine did not induce a tumorigenic response in the 2-year bioassays in mice and rats.	No issues regarding mutagenic or tumorigenic potential were identified.
Reproductive Toxicity: In all mouse studies, the number of live foetuses was reduced in the highest dose group (45 to 75 mg/kg). Fesoterodine had no effect on fertility at non-maternally toxic doses in mice, although the number of corpora lutea and implantation sites was reduced at the highest dose.	Fesoterodine had no effect on fertility in mice at non-maternally toxic doses.
Developmental toxicity: In a segment II (embryo-foetal development) study in mice, no teratogenic properties of fesoterodine were seen, even at maternally toxic doses. Foetal body weights were reduced	Overall, reproduction studies have shown minor embryotoxicity at doses close to maternally toxic ones (increased number of resorptions, and post-implantation losses).

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
starting at the intermediate dose (45 mg/kg), and at the high dose (75 mg/kg), resorptions rate and post-implantation loss was increased. In a segment III (pre- and postnatal development) study in mice, slight effects on maternal body weight were noted for F0 dams at 30 and 60 mg/kg. Pup survival was decreased during the postnatal period at 30 and 60 mg/kg. Delayed physical development was demonstrated at 30 and 60 mg/kg by reduced pup body weight gain during the preweaning period, delayed age at ear opening, and a reduction in the number of pups demonstrating an auditory reflex on postnatal Day 14. Pup body weights at 30 and 60 mg/kg normalised during the post-weaning period and there were no effects noted on other landmarks of physical and central nervous system development. There was no effect on reproductive development or competency of the F1 offspring. There were no effects on central nervous system function, including learning and memory. In rabbits, no malformations or variations were found after oral or subcutaneous treatment with fesoterodine. In these segment II studies, increased foetal incidences of retardation of ossification were observed after oral treatment with 27 mg/kg fesoterodine, but not after subcutaneous treatment with lower dosages and higher systemic exposure.	Fesoterodine did not have a teratogenic effect in mice and rabbits up to the dose levels tested.
General safety pharmacology: The safety pharmacology studies conducted in mice, rats, and dogs have shown that fesoterodine exerts antimuscarinic effects on the eye, heart, autonomic nervous system, and the urinary bladder and to a limited extent on the central nervous system. No effect was observed on intestinal transport following single oral administration. Supratherapeutic concentrations of the active metabolite of fesoterodine, 5-HMT, have been shown to inhibit K+ current in cloned human ether-a-go-go-related gene channels and prolong action potential duration (70% and 90% repolarisation) in canine isolated Purkinje fibres. However, in conscious dogs, infused 5-HMT had no effect on the QT interval and QTc interval, and similarly, orally administered fesoterodine had no effect on QT or QTc interval in the repeat-dose 13- and 39-week toxicity studies.	The safety pharmacology studies showed that fesoterodine exerts antimuscarinic effects on the eye, heart, autonomic nervous system, and the urinary bladder and to a limited extent on the central nervous system. Although adverse effects related to inhibition of muscarinic receptors in those organs and systems cannot be disregarded, safety pharmacology studies concerning the effect of fesoterodine on cardiac repolarisation as well as additional studies targeting vital functions do not raise special concern and support its use in humans. Although in vitro assays suggested a potential for QT prolongation, an in vivo study of infused 5-HMT in dogs at peak unbound plasma exposures of at least 26x human exposure (5-HMT Cmax in poor metabolisers following an 8 mg dose) did not show a QT prolongation effect.
Pharmacokinetics: Fesoterodine and its primary in vivo metabolite, 5-HMT are specific but non-selective muscarinic receptor antagonists. Nonclinical PK and toxicokinetic studies confirmed the rapid de-esterification of fesoterodine to its active metabolite 5-HMT both in vitro and in vivo with rapid absorption after oral administration. [14C] fesoterodine	Studies of the specificity and tissue selectivity of fesoterodine and/or 5-HMT demonstrate antimuscarinic activity with preferred action at the urinary bladder. Nevertheless, as a consequence of the blockade of muscarinic receptors on secretory glands and smooth muscles, typical antimuscarinic side effects

Table 1. Key Safety Findings and Relevance to Human Usage

Key Safety findings from Non-clinical Studies	Relevance to Human Usage
derived radioactivity was rapidly absorbed following oral administration with a bioavailability of greater than 50%, 14%, and 87% of the radioactivity in mice, rats, and dogs, respectively. Penetration into the central nervous system was low. Neither pharmacology nor drug metabolism studies in juvenile animals have been conducted.	such as dry mouth and dry eyes or constipation may be expected. Clinical data shows that these antimuscarinic effects are generally mild to moderate in severity, reversible on discontinuation, and do not represent a significant risk to patients. They are listed adverse reactions in the Product Label, but do not merit inclusion in the summary of safety concerns.
Other toxicity-related information or data Studies on local tolerance showed that fesoterodine is irritating to the eyes following ocular administration in rabbits but is non-irritating to the skin. No sensitising or immunotoxic properties have been observed in the relevant studies. Photo-safety studies with the active metabolite 5-HMT, including in vitro assessment of phototoxicity, photosensitisation, and in vitro photo-mutagenicity revealed no photo-safety potential issues.	No issues were identified relevant to human usage; the eye irritation observed following ocular administration in rabbits is not relevant to orally administered fesoterodine in humans.

Module SIII. Clinical Trial Exposure

SIII.1. Brief Overview of Development

Each fesoterodine tablet contains either 4 or 8 mg fesoterodine fumarate. During the clinical development programme to support the MAA filing, an immediate-release formulation of fesoterodine was used in 2 initial Phase 1 studies conducted in healthy subjects and a Phase 2a, double-blind, placebo-controlled pilot study in subjects with detrusor instability. Subsequently, an ER formulation of fesoterodine suitable for once daily administration was developed and further optimised in parallel with the clinical development programme.

Following the identification of efficacious and well-tolerated doses of fesoterodine in Studies SP582 and SP668, daily doses of fesoterodine 4 and 8 mg were investigated in 2 double-blind Phase 3 studies to determine the efficacy and safety of fesoterodine as an antimuscarinic agent in subjects with OAB (with or without UUI, and with urgency and urinary frequency). Studies SP583 and SP584 were similar in that each had a multicenter, randomised, double-blind, placebo-controlled, parallel-group, fixed-dose design. In addition to a placebo control, Study SP583 also included an active control arm (tolterodine 4 mg). Study SP583 was conducted in Europe, South Africa, Australia, and New Zealand; Study SP584 was conducted in the US. One (1) Phase 2 study (SP668) used a central assessment of urodynamic examination at Baseline and End-of-Treatment. Subjects enrolled in this study were stratified into 2 groups based on the presence or absence of involuntary detrusor contractions at Baseline urodynamics. The treatment outcome was compared between these 2 groups.

Study number/clinical development phase/study design/dosage	No. of Subjects receiving fesoterodine[a]	No. of Subjects receiving placebo[a]	No. of Subjects receiving active control[a]	Treatment duration for fesoterodine
SP583/Phase 3/ multicenter, randomised, double-blind, double-dummy, placebo- and active controlled, parallel-group study to investigate efficacy and safety in OAB/ fesoterodine 4 mg and 8 mg doses once daily and tolterodine 4 mg once daily	4 mg: 272 8 mg: 287	283	Tolterodine 4 mg: 290	12 weeks
SP584/Phase 3/ multicenter, randomised, double-blind, placebo-controlled, parallel-group study to investigate efficacy and safety in OAB/ fesoterodine 4 mg and 8 mg doses once daily	4 mg: 282 8 mg: 279	271	NA	12 weeks
Total	1120	554	290	—

a. These exposures are based on the SS for each study.

The open-label extension studies for Studies SP668, SP583, and SP584 (SP669, SP738, and SP739, respectively) provided evidence of long-term safety and maintenance of treatment benefit over time. To allow for additional 1-year exposures, new subjects not previously participating in Study SP668, were allowed to enter the study until February 2004, when the US Phase 3 study, SP584, began enrollment.

Study number/clinical development phase/study design/dosage	No. of Subjects receiving fesoterodine[a]	Treatment duration for fesoterodine
SP669/Extension of SP668/ 2-phase multicenter, double-blind and open-label, long-term study to assess safety and efficacy in OAB/ fesoterodine 4, 8, and 12 mg doses once daily in the double-blind phase; fesoterodine 4 mg and 8 mg doses once daily in the open-label phase	186 (125 new fesoterodine exposures/ subjects[b])	Up to 4 years or until commercially available
SP738/Extension of SP583/ multicenter, open-label, long-term safety and efficacy in OAB; fesoterodine 4 mg and 8 mg doses once daily	417 (218 new fesoterodine exposures)	Up to 3 years or until commercially available
SP739/Extension of SP584/ multicenter, open-label, long-term safety and efficacy in OAB; fesoterodine 4 mg and 8 mg doses once daily	473 (158 new fesoterodine exposures)	Up to 3 years or until commercially available
Total	1076	—

a. These subject exposures are based on the enrolled set.
b. Includes 105 subjects who did not participate in SP668 and 20 subjects who were randomised to placebo in SP668.

New Population - Paediatric NDO:

Initially, PK and safety were assessed favourably in older/heavier children with idiopathic OAB and NDO (study A0221066). The Phase 3 Study A0221047 was initiated after receipt of the FDA Written Request. Cohort 1 of this open-label, active comparator, study investigated the efficacy, tolerability and safety of fesoterodine in an NDO population aged 6-17, >25 Kg, and includes an active comparator (oxybutynin XL). 124 subjects were assigned to treatment (42 in the fesoterodine 4 mg arm, 42 in the fesoterodine 8 mg arm and 40 in the oxybutynin arm). Efficacy was demonstrated in the primary urodynamic assessment and a number of secondary endpoints. At the request of the FDA a 12-week safety extension

phase was conducted in which subjects in the oxybutynin arm were allocated to 4 mg or 8 mg fesoterodine by the Investigator, and following this 2 subjects (randomised to fesoterodine 8 mg) were included in a further 6-month Japanese safety extension study (A0221109).

Cohort 2 of study A0221047 (originally study A0221074) is an open-label safety and efficacy study in lighter NDO subjects, aged 6-17 years and ≤25 kg. The study consisted of a 12-week efficacy phase followed by a 12-week safety extension phase, mirroring cohort 1 but without a comparator group. 57 subjects were randomised and assigned to treatment (28 to 2 mg BIC and 29 to 4 mg BIC). 7 of the subjects from the 2 mg BIC group and 3 from the 4 mg BIC group were included in a further 6-month Japanese safety extension study (A0221109). The overall conclusion from both cohorts and the Japanese extension study is that the benefit-risk profile of fesoterodine is positive in paediatric patients with NDO over 6 years old. The benefit-risk is optimal at the higher of the two dose ranges, i.e. 8 mg tablets in cohort 1 and 4 mg BIC in cohort 2.

Overall, 10871 adult and pediatric subjects have received fesoterodine (2 mg BIC, 4 mg BIC, or 4 mg, 8 mg or 12 mg tablets) in double-blind and open-label clinical studies. For the purpose of the tables below, subject-year is defined as the total exposure in days divided by 365. Overall fesoterodine exposure refers to end of treatment. Each subject is counted only once starting from onset of exposure to end of treatment, regardless of dose.

Table 2. Duration of Exposure[a] (Overall Fesoterodine Exposure)

Duration of Exposure	Subjects	Subject-Years
Both OAB/NDO		
>0 months	10871	4193.0
>6 months	1071	2000.3
>12 months	808	1817.4
>18 months	617	1608.8
>24 months	539	1476.2
Total person time	10871	4193.0
OAB		
>0 months	10683	4120.5
>6 months	1041	1979.3
>12 months	800	1809.3
>18 months	617	1608.8
>24 months	539	1476.2
Total person time	10683	4120.5
NDO		
>0 months	188	72.5
>6 months	30	21.1
>12 months	8	8.1
Total person time	188	72.5

a. Pooled Double-Blind Protocols: SP582, SP583, SP584, SP668, A0221005, A0221008, A0221009, A0221014, A0221045, A0221046, A0221064, A0221048, A0221049, A0221095
Open Label Protocols: SP669, SP738, SP739, A0221006, A0221007, A0221045, A0221058, A0221059, A0221094, A0221047, A0221066, A0221109

Table 3. Exposure by Gender[a] (Overall Fesoterodine Exposure)

Gender	Subjects	Subject-Years
Both OAB/NDO		
Male	2850	984.8
Female	8021	3208.1
Total person time	10871	4192.9
OAB		
Male	2751	946.3
Female	7932	3174.2
Total person time	10683	4120.5
NDO		
Male	99	38.6
Female	89	33.9
Total person time	188	72.5

a. Pooled Double-Blind Protocols: SP582, SP583, SP584, SP668, A0221005, A0221008, A0221009, A0221014, A0221045, A0221046, A0221064, A0221048, A0221049, A0221095
Open Label Protocols: SP669, SP738, SP739, A0221006, A0221007, A0221045, A0221058, A0221059, A0221094, A0221047, A0221066, A0221109

Table 4. Exposure by Age and Gender[a] (Overall Fesoterodine Exposure)

Age Group	Subjects		Subject-Years	
	Male	Female	Male	Female
Both OAB/NDO				
Children (6 to 11 years)	64	71	28.0	26.6
Adolescents (12 to 17 years)	41	24	11.5	8.4
Adults (18 to 64 years)	1251	4995	463.2	2075.2
Elderly (≥65 years)	1490	2926	481.3	1096.7
Elderly (≥75 years)	519	916	151.9	309.5
Total	2846	8016	984	3206.9
OAB				
Children (6 to 11 years)	1	0	0.2	0.0
Adolescents (12 to 17 years)	5	6	0.8	1.0
Adults (18 to 64 years)	1251	4995	463.2	2075.2
Elderly (≥65 years)	1490	2926	481.3	1096.7
Elderly (≥75 years)	519	916	151.9	309.5
Total	2747	7927	945.5	3172.9
NDO				
Children (6 to 11 years)	63	71	27.8	26.6
Adolescents (12 to 17 years)	36	18	10.7	7.3
Total	99	89	38.5	33.9

a. Pooled Double Blind Protocols: SP582, SP583, SP584, SP668, A0221005, A0221008, A0221009, A0221014, A0221045, A0221046, A0221064, A0221048, A0221049, A0221095
Open Label Protocols: SP669, SP738, SP739, A0221006, A0221007, A0221045, A0221058, A0221059, A022194, A0221047, A0221066, A0221109
Nine subjects [redacted] from study A0221059 are excluded from this table because their birth date was recorded as either on or later than the baseline visit date.

Table 5. Exposure by Race[a] (Overall Fesoterodine Exposure)

Race	Subjects	Subject-Years
Both OAB/NDO		
White	8686	3399.2
Black	541	196.1
Asian	1346	457.3
Other	298	140.5
Total person time	10871	4193.1
OAB		
White	8592	3368.6
Black	536	194.9
Asian	1261	417.9
Other	294	139.1
Total person time	10683	4120.5
NDO		
White	94	30.6
Black	5	1.2
Asian	85	39.4
Other	4	1.3
Total person time	188	72.5

a. Pooled Double Blind Protocols: SP582, SP583, SP584, SP668, A0221005, A0221008, A0221009, A0221014, A0221045, A0221046, A0221064, A0221048, A0221049, A0221095
Open Label Protocols: SP669, SP738, SP739, A0221006, A0221007, A0221045, A0221058, A0221059, A022194, A0221047, A0221066, A0221109

Table 6. Dose of Exposure[a] (NDO Indication only)

Dose of Exposure	Subjects	Subject-Years
2 mg BIC	54	14.4
4 mg BIC	29	13.9
4 mg tablet	130	20.9
8 mg tablet	72	22.3

a. Pooled Open Label Protocols A0221047, A0221066, A0221109

Module SIV. Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion Criteria which remain as Contraindications			
Criterion	**Reason for Exclusion**	**Missing Information?**	**Rationale**
Hypersensitivity to fesoterodine fumarate or to peanut or soy or any of the excipients.	To avoid risk to patients with known hypersensitivity	No	Hypersensitivity is an established adverse reaction

Urinary retention; Bladder outlet obstruction evidenced by previous history of acute urinary retention requiring catheterisation, use of an indwelling catheter or an ISC programme, urodynamic evidence of obstruction or severe voiding symptoms including a previously measured post void residual volume of greater than 200 ml which has not subsequently been appropriately managed.	To avoid risk to patients with urinary retention	No	Urinary retention is an established adverse reaction
Uncontrolled narrow angle glaucoma.	To avoid risk of visual loss in patients with uncontrolled narrow angle glaucoma	No	Uncontrolled narrow angle glaucoma is contraindicated per product label
Exclusion Criteria Which are NOT Proposed to Remain as Contraindications			
Criterion	**Reason for Exclusion**	**Missing Information?**	**Rationale**
Paediatric subjects under 6 years old	Children under 6 are not part of the target population.	No	Per product labelling, fesoterodine should not be used in children under 6 years of age.
Pregnant or nursing women	Avoid risk to pregnant mother, fetus or infant.	No	Per product labelling, fesoterodine is not recommended in pregnant or nursing women.
Gastric Retention	To avoid risk of antimuscarinic effects exacerbating gastric retention via further delay of gastric emptying	No	Antimuscarinic effects on the GI tract are well established. Per product labelling, there is a warning to use with caution in patients with reduced GI motility.
Myasthenia gravis	To avoid risk of antimuscarinic effects exacerbating myasthenia gravis.	No	Per product labelling, there is a warning to use with caution in patients with myasthenia gravis.
Severe hepatic impairment (Child-Pugh C)	Higher risk population; hepatic metabolism contributes significantly to elimination of fesoterodine.	No	Per product labelling, fesoterodine is not recommended in patients with severe hepatic impairment.
Severe ulcerative colitis	Antimuscarinic effects on the gastrointestinal tract might exacerbate ulcerative colitis	No	Per product labelling, there is a warning to use with caution in patients with reduced GI motility.
Toxic megacolon	Antimuscarinic effects on the gastrointestinal tract might exacerbate toxic megacolon.	No	Per product labelling, there is a warning to use with caution in patients with reduced GI motility.

Neurologic conditions such as spinal dysraphism, stroke, multiple sclerosis, spinal cord injury, or Parkinson's disease, which are known or suspected of influencing the subject's bladder function.	Higher risk population with potential urinary retention.	No	Post-marketing data do not indicate any particular risk associated with these neurological conditions.

The interventional clinical trial program in adults and paediatrics has now completed. No further sponsored studies are planned at the current time therefore there are no exclusion criteria which are planned not to remain as contraindications.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

The clinical development programme is unlikely to detect certain type of ARs such as rare ARs, ARs with a long latency, and ARs caused by prolonged exposure.

SIV.3. Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 7. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the MAH's clinical development programme.
Breastfeeding women	
Patients with other relevant co-morbidity	
Patients with hepatic impairment	A single oral dose of 8mg fesoterodine was administered to 8 male subjects with moderate hepatic impairment (Stage B according to Child-Pugh Classification) and 8 healthy male subjects matched for age and body weight.
Patients with renal impairment	In a single-dose, non-blind, non-randomized, non-controlled trial, 4mg fesoterodine was administered to 32 subjects assigned to one of 4 defined groups (n = 8 per group). Subjects were stratified according to their creatinine clearance values (CL_{cr}) within 1 week prior to dosing: Group 1: $CL_{cr} \geqslant 80$mL/min (healthy controls) Group 2: 80mL/min $> CL_{cr} \geqslant 50$mL/min (mildly impaired) Group 3: 50mL/min $> CL_{cr} \geqslant 30$mL/min (moderately impaired) Group 4: $CL_{cr} < 30$mL/min (severely impaired; not on dialysis between 2 weeks prior to enrollment visit and end of trial).
Patients with cardiovascular disease	Not included in the MAH's clinical development programme.

Table 7. Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Immunocompromised patients	Not included in the MAH's clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trial population	Fesoterodine has been studied across the range of symptom severity. Due to the nature of the condition there is no expected correlation with disease severity and treatment emergent ADRs.
Patients of Different Racial and/or Ethnic Origin	In the OAB development programme, there were 8592 White subjects (3368.6 subject-years), 536 Black subjects (194.9 subject-years), 1261 Asian subjects (417.9 subject-years), and 294 Other subjects (139.1 subject-years). In the NDO development programme, there were 94 White subjects (30.6 subject-years), 5 Black subjects (1.2 subject-years), 85 Asian subjects (39.4 subject-years), and 4 Other subjects (1.3 subject-years).
Subpopulations carrying known and relevant genetic polymorphisms	Fesoterodine was studied in extensive and poor metabolisers for cytochrome 2D6 (CYP2D6) in Phase 1, Phase 2, and Phase 3 trials. 900/2859 (31%) subjects were genotyped as extensive metabolisers for CYP2D6, and 89/2859 (3%) were genotyped as poor metabolisers for CYP2D6.
Children and Adolescents	In the OAB development programme there was 1 male and no female children subjects ([6 to 11 years]; subject-years 0.2 and 0.0, respectively). There were 5 males and 6 female adolescent subjects ([12 to 17 years]; subject-years 0.8 and 1.0, respectively). In the NDO development programme there were 63 male and 71 female children subjects ([6 to 11 years]; 27.8 and 26.6 subject-years, respectively). There were 36 male and 18 female adolescent subjects ([12 to 17 years];38.5 and 33.9 subject-years, respectively).
Elderly	In the OAB development programme, there were 1490 male and 2926 female elderly subjects ([≥65 years]; 481.3 and 1096.7 subject-years, respectively). There were 519 male and 916 female elderly subjects ([≥75 years]; 151.9 and 309.5 subject-years, respectively).

Module SV. Post-Authorisation Experience

SV.1. Post-Authorisation Exposure

SV.1.1. Method Used to Calculate Exposure

Cumulative exposure calculations have been made based upon sales data provided by IQVIA.

SV.1.2. Exposure

It is estimated that 5,080,907 patients were exposed to fesoterodine worldwide since the product was first approved. US cumulative exposure was projected from sample patient data obtained from IQVIA's Total Patient Tracker, a validated source for estimating patient level data, which includes 97.0% coverage of US pharmacies. Since patient data are not available outside the US, to calculate non-US patient exposure, IQVIA standard units were used to extrapolate the number of non-US fesoterodine patients, with assumptions that usage and treatment patterns were consistent worldwide. One standard unit equated to one tablet. US and non-US fesoterodine standard units were obtain from IQVIA Midas from 20 April 2007 through 15 November 2020. The IQVIA standard unit data from 01 July 2020 to 15 November 2020 was extrapolated by taking the average of sales of the previous 4 quarters. Overall cumulative patient exposure (5,080,907 patients) has been obtained by adding previous cumulative patient exposure (20 April 2007 through 19 April 2020; 4,421,985 patients) to the balance reporting interval patient exposure (20 April 2020 through 15 November 2020; 658,922 patients).

Cumulative estimated exposure by indication, gender, age group dose, formulation and region extrapolated from applicable data provided by IQVIA Health Prescribing Insights Medical are summarized in Table 8.

Table 8. Cumulative Estimated Exposure for Fesoterodine (20 April 2007 – 15 November 2020) – Number of Patients

Indication	Age (years)				Gender			Region				Form	Dose		
	0-16	17-65	>65	UNK	Female	Male	UNK	EU	Japan	NA	ROW	Oral	4 mg	8 mg	UNK
Neuromuscular dysfunction of bladder, not elsewhere classified	14,454	768,242	3,028,747	20,639	2,499,133	1,328,618	4,332	219,873	3,540,493	71,638	79	3,832,082	3,408,782	421,641	1,660
Unspecified urinary incontinence	535	123,514	225,619	-	271,949	77,719	-	261,866	28,705	59,096	-	349,668	199,685	138,351	11,632
Other disorders of urinary system	-	105,531	122,111	-	185,097	42,545	-	203,147	19,474	5,020	-	227,641	133,561	88,675	5,406
Hyperplasia of prostate	-	37,620	119,981	-	986	156,615	-	95,987	61,419	-	195	157,601	106,230	51,371	0
Polyuria	156	27,790	95,057	-	70,082	52,920	-	28,973	66,666	27,364	-	123,003	86,272	28,869	7,862
Other disorders of bladder	-	55,606	48,219	-	83,555	20,269	-	99,956	1,121	2,405	342	103,824	48,518	55,306	0
Total Others	142	88,061	198,872	13	185,801	101,286	-	245,634	29,329	12,125	-	287,087	195,402	91,686	0

Module SVI. Additional EU Requirements for the Safety Specification

SVI.1. Potential for misuse for illegal purposes

Antimuscarinics do not have the potential for abuse or dependence. Abuse potential and dependence of fesoterodine have not been evaluated.

Module SVII. Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

None.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new important identified or potential risks have been observed for fesoterodine since the last EU RMP (version 9.0, dated 21 November 2013).

The important identified risks were evaluated and reassessed to align with the revised Guideline on good pharmacovigilance practice (GVP) Module V – Risk management systems (Rev. 2) and the Guidance on the format of the risk management plan (RMP) in the EU – in integrated format (Rev. 2.0.1 accompanying GVP Module V Rev. 2).

As a result of the re-evaluation, all of the safety concerns have been removed, namely the important identified risks of Urinary retention and Angioedema, the important potential risks of QT prolongation, Hepatotoxicity[2], Cognitive function impairment, and the missing information of elderly male patients, paediatric patients, and pregnant or nursing women. The MAH proposed the removal of these safety concerns from the next RMP update in the PSUR report number 12 covering the period from 20 April 2017 to 19 April 2020, and this proposal

[2] The MAH renamed the important potential risks Liver enzyme elevation to Hepatotoxicity based upon a request from the LMS (Spain) of the EMA PRAC in the PSUR FAR (Procedure no.: EMEA/H/C/PSUSA/00001387/201704) for the Fesoterodine 2017 PSUR (reporting period 20 April 2014 to 19 April 2017).

was endorsed by PRAC in their Assessment Report Procedure no.: EMEA/H/C/PSUSA/00001387/202004).

The rationale for removal, based upon the approach to the evaluation of the risks as described in the guideline is that the risks are followed up via routine pharmacovigilance, without the need for additional risk minimisation activities, and do not require further characterisation via additional pharmacovigilance activities.

The important identified risks of urinary retention and angioedema are well-recognised and characterised adverse reactions that are associated with antimuscarinics as a class. There is insufficient evidence to support a causal association between QT prolongation and hepatotoxicity despite the extensive real-world exposure to fesoterodine. Therefore, these are no longer considered to be risks. Cognitive function impairment remains as a potential risk not important, but no additional risk minimization measures or pharmacovigilance activities are required.

There is a large volume of post-marketing safety data involving elderly male patients, with estimated exposure being over 1,000,000 patient-years, and therefore use in elderly males is no longer missing information. Similarly, use in paediatric patients is no longer considered missing information following completion of the paediatric programme. Use in pregnancy and lactation is not recommended and based upon the very low number of case reports of pregnancy and lactation in the safety database, the product labelling is effective in preventing such use. Therefore, use in pregnancy and lactation no longer meets the criteria for important missing information.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

There are no important identified or potential risks for fesoterodine.

SVII.3.2. Presentation of the Missing Information

There is no missing information for fesoterodine.

Module SVIII. Summary of the Safety Concerns

Table 9. Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	None

PART III. PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

III.1. Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond ADRs reporting and signal detection:

- **Specific adverse reaction follow-up questionnaires for safety concerns:**

None

- **Other forms of routine pharmacovigilance activities for safety concerns:**

None.

III.2. Additional Pharmacovigilance Activities

There are no additional pharmacovigilance activities for fesoterodine.

III.3. Summary Table of Additional Pharmacovigilance Activities

III.3.1. On-Going and Planned Additional Pharmacovigilance Activities

There are no on-going or planned additional pharmacovigilance activities for fesoterodine.

PART IV. PLANS FOR POST AUTHORISATION EFFICACY STUDIES

There are no post-authorisation efficacy studies being conducted or planned with fesoterodine.

PART V. RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

RISK MINIMISATION PLAN

V.1. Routine Risk Minimisation Measures

Routine risk minimisation measures, which include the use of the SmPC and PL are sufficient to manage the product.

V.2. Additional Risk Minimisation Measures

Routine risk minimisation activities are sufficient to manage the safety concerns of the medicinal product. No additional risk minimisation measures are proposed.

V.3. Summary of Risk Minimisation Measures

Routine risk minimisation measures, which include the SmPC and PL are sufficient to manage the product. There are no additional risk minimisation measures proposed or additional pharmacovigilance activities proposed.

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the RMP for Toviaz. The RMP details the important risks of Toviaz, how these risks can be minimised, and how more information will be obtained about Toviaz;s risks and uncertainties (missing information).

Toviaz's SmPC and its PL give essential information to healthcare professionals and patients on how Toviaz should be used.

This summary of the RMP for Toviaz should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

I. The Medicine and What It Is Used For

Toviaz is authorised for treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome (see SmPC for the full indication). It contains fesoterodine as the active substance and it is given by oral route of administration.

Further information about the evaluation of Toviaz's benefits can be found in Toviaz's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/en/medicines/human/EPAR/toviaz

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

There are no important identified or potential risks for Toviaz and no missing information. Routine risk minimisation activities, which include the use of SmPC and PL for these products are sufficient to manage the product. In addition, information about adverse events is collected continuously analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A List of Important Risks and Missing Information

Not applicable.

II.B Summary of Important Risks

Not applicable.

II.C Post-Authorisation Development Plan

There are no Post-Authorisation studies.

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies, which are conditions of the marketing authorisation or specific obligation of this product.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for fesoterodine.

PART VII. ANNEXES TO THE RISK MANAGEMENT PLAN

Annex 2 – Tabulated summary of planned, on-going, and completed pharmacovigilance study programme

Annex 3 - Protocols for proposed, on-going, and completed studies in the pharmacovigilance plan

Annex 4 - Specific Adverse Drug Reaction Follow-Up Forms

Annex 5 - Protocols for proposed and on-going studies in RMP Part IV

Annex 6 - Details of Proposed Additional Risk Minimisation Activities (if applicable)

Annex 7 - Other Supporting Data (Including Referenced Material)

Annex 8 – Summary of Changes to the Risk Management Plan over Time

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ANNEX 4. SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable.

ANNEX 6. DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Not Applicable.