19 December 2012

EMA/819408/2012
Committee for Medicinal Products for Human Use (CHMP)

# Toviaz

(fesoterodine)

Procedure No. EMEA/H/C/000723/A46/0025

# CHMP assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No1901/2006, as amended

**Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted**

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# Administrative information

| | |
|---|---|
| Invented name of the medicinal product: | Toviaz |
| INN (or common name) of the active substance(s): | fesoterodine |
| MAH: | Pfizer Ltd. |
| Currently approved Indication: | Treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome. |
| Pharmaco-therapeutic group (ATC Code): | Urinary Bladder, Overactive<br>G04BD11 |
| Pharmaceutical form and strengths: | Prolonged-release tablet, 4 mg, 8 mg |
| Rapporteur: | Name: Concepcion Prieto Yerro |
| Start of the procedure: | 21/08/2011 |
| Date of this report: | 27/10/2011 |

# Introduction

On 19 July 2011, the MAH submitted a completed paediatric study for Toviaz, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

No critical expert overview has been provided.

The MAH stated that no consequential regulatory action is claimed by the applicant at present.

# Scientific discussion

## *Information on the development program*

The active substance of Toviaz is fesoterodine, a competitive, specific muscarinic receptor antagonist. It is rapidly and extensively hydrolysed by non-specific plasma esterases to the 5-hydroxymethyl derivative (5-hydroxy-methyltolterodine; 5-HMT), its primary active metabolite, which is the main active pharmacological substance of fesoterodine.

Toviaz is available as a prolonged release tablet formulation at doses of 4 and 8 mg. It is indicated in adults for the treatment of the symptoms (increased urinary frequency and/or urgency and/or urgency incontinence) that may occur in patients with overactive bladder syndrome. Toviaz is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy. There are no pharmacokinetic data in paediatric patients.

A PIP application for Toviaz was submitted on 5 December 2008 and then voluntaryly withdrawn by MAH on 16 September 2009.
The MAH is submitting new data referring paediatric population in accordance to article 46 of Regulation 1901/2006. This information consist on the results of the study A0221066 (An Open-Label, Dose-Escalating Study of the Pharmacokinetics, Safety and Tolerability of Fesoterodine in Pediatric Overactive Bladder Patients Aged 8-17 Years).

*Assessor comment:*

*At the time of the PIP evaluation Study A0221066 had already started. Two additional studies in paediatric patients were planned: Study A0221047 (safety and efficacy study in neurogenic detrusor overactive patients of ages 6-16 years and body weight >25 Kg) and Study A0221074 in younger and lighter children (>6 yrs of age and <25 Kg). No information regarding these two clinical trials is included in the documentation submitted. The MAH is requested to provide the status of any other existing paediatric study of fesoterodine related with this condition.*

## *Information on the pharmaceutical formulation used in the study*

Fesoterodine fumarate is authorised as 4 mg and 8 mg sustained release tablets for once-daily dose. Fesoterodine is not indicated for use in children and no suitable paediatric formulation is available.

The study drug was provided in the form of 4 mg and 8 mg Sustained Release Tablets. The dose for all subjects was fesoterodine 4 mg once daily (QD) escalated to 8 mg QD.

## *Clinical aspects*

### *1. Introduction*

The MAH submitted a final report for study A0221066: An Open-Label, Dose-Escalating Study of the Pharmacokinetics, Safety and Tolerability of Fesoterodine in Pediatric Overactive Bladder Patients Aged 8-17 Years.

## *2. Clinical study*

**Study A0221066: An Open-Label, Dose-Escalating Study of the Pharmacokinetics, Safety and Tolerability of Fesoterodine in Pediatric Overactive Bladder Patients Aged 8-17 Years.**

This was an 8-week, open label, multicenter, uncontrolled study of fesoterodine 4 mg and 8 mg once daily in male and female paediatric subjects with Overactive Bladder (OAB); approximately 50% of the study population was targeted to be subjects with neurogenic detrusor overactivity (NDO).

**Methods**

- **Objectives**

  Primary

  - To determine the PK of 5-hydroxy-methyltolterodine (5-HMT) in paediatric OAB subjects aged 8 to 17 years.

  Secondary

  - To examine the influence of subject covariates on the PK of 5-HMT.
  - To assess the safety and tolerability of fesoterodine in pediatric OAB subjects aged 8 to 17 years.

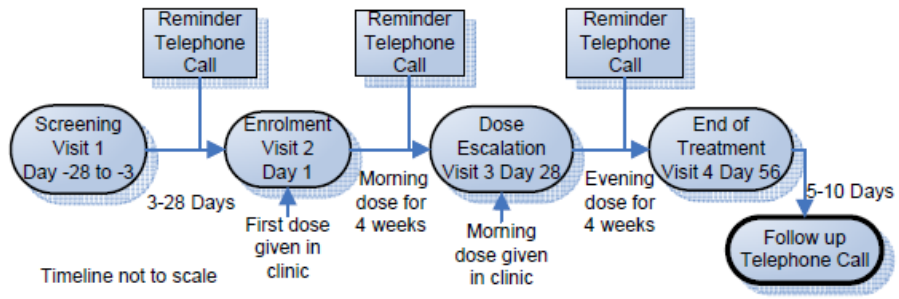
  Exploratory

  - To assess the feasibility and utility of a 3-day bladder diary in pediatric OAB subjects aged 8 to 17 years.

- **Study design**

This was an 8-week open label, uncontrolled study in male and female patients with OAB (see Figure 1).

**Figure 1. Study Overview**




Screening evaluations (Visit 1) were to occur within 28 days prior to the first dose. If the subjects were previously receiving anticholinergic or other medications for OAB, there was a washout of 1 week, or other appropriate period as determined by the investigator prior to the enrolment visit.

- **Study population /Sample size**

*Inclusion Criteria*

Subjects must meet all of the following inclusion criteria to be eligible for enrolment into the study:

1. Male or female subjects between the ages of 8 and 17 years inclusive and total body weight >25 kg.
2. OAB as defined by:
   - Symptoms of urinary frequency (8 micturitions on average per 24 hours) and urgency (defined as a sudden and compelling desire to pass urine which is difficult to defer), with or without urgency incontinence, for at least 6 months prior to enrolment,

   OR
   - Subjects with stable neurological disease and urodynamically confirmed detrusor overactivity, who may require intermittent catheterization for management of urinary drainage.

*Exclusion Criteria*

1. General exclusion criteria

Patients with evidence or history of clinically significant disease; a positive urine drug screen; clinically significant abnormality in ECG or laboratory values; any condition possibly affecting drug absorption, previous treatment with an investigational drug (4 weeks or 5 half-lives); history of recreational use of drugs of abuse, alcohol and tobacco, were excluded from the study.

Subjects required to take concomitant medications that can interact with the pharmacokinetics and/or pharmacodynamics of fesoterodine or patients who have received any electrostimulation therapy or bladder retraining within 4 weeks of Visit 1 or who are expected to start such therapy during the study period, were already excluded.

2. Urinary exclusion criteria

Subjects with monosymptomatic nocturnal enuresis or giggle incontinence, a relevant disease with which their urinary symptoms may be associated, continuous use of indwelling urinary catheter; a clinically significant urinary tract infection at screening; subjects with greater than 1+ hematuria on dipstick test and subjects not requiring intermittent catheterization who have a post-void residual volume >40 mL were excluded.

*Sample size*

A total of 20 paediatric OAB subjects, aged between 8 and 17 years, were to be enrolled in the study. Approximately 50% of the study population was targeted to be subjects with neurogenic detrusor overactivity.

- **Treatments**

For Weeks 1 to 4, the dose for all subjects was to be fesoterodine 4 mg QD. Based on the investigator's assessment of individual subjects' tolerability and safety, the study dose was to be escalated to 8 mg QD for the next 4 weeks.

- **Outcomes/endpoints**

<u>Endpoints</u>

- Primary

Model-based pharmacokinetic parameter estimates for absorption rate constant, apparent oral clearance and volumes of distribution to predict the AUC, Cmax, Tmax and half-life of 5-HMT in pediatric OAB patients aged 8-17 years, and weighing more than 25 kg.

- Secondary

Laboratory tests, post-void residual volume, ECG, and adverse events.

- Exploratory

Change from baseline in:

- mean number of micturitions or catheterizations per day
- mean number of incontinence episodes per day
- mean urgency episodes per day
- mean volume voided per micturition or mean volume per catheterization

<u>Measures</u>

- Pharmacokinetic measures
    - Individual concentration data: plasma 5-HMT concentrations
    - PK parameter estimates: absorption rate constant (Ka), apparent oral clearance (CL/F), volumes of distribution (VC/F)
    - PK parameters predicted: AUC, Cmax, Tmax, half-life of 5-HMT.

Blood samples (2 mL each) were collected according to the following schedule: Visit 3 (Week 4) predose and at 0.5-2, 2-4, 4-6 hours postdose (relative to dose on that morning), Visit 4 (Week 8) at 8-10, 10-14, and 14-16 and 16-20 hours postdose (relative to dose on the previous night).

In order to limit the blood sampling in paediatric subjects, PK samples at earlier time points postdose (absorption phase) were to be collected after dosing in the morning up to Visit 3 (Weeks 1 to 4), and the samples at later time points postdose (terminal elimination phase) were to be collected after dosing in the evening after Visit 3 up to Visit 4 (Weeks 5 to 8).

Variations in the CYP2D6 gene play a role in metabolism of active metabolite of fesoterodine. The alleles which were to be genotyped are *3, *4, *5, *6,*7, *8, *10, *14, *18, *21, *36, *41, and duplication. Homozygous or combination of *3,*4, *5, *6, *7, *8, *14, *18, and *21 were classified as a poor metabolizer of CYP2D6; all other genotypes were classified as an extensive metabolizer.

- Efficacy measures

A bladder diary, noting the number of micturitions/catheterizations events, volume of urine of each micturition or catheterization, urinary urgency and incontinence episodes, was to be completed for 3 consecutive days during the week prior to Visits 2, 3, and 4.

- Safety measures

Safety parameters included clinical laboratory evaluations, physical examination, vital signs, post-void residual volume (PVR) in subjects who were not performing clean intermittent bladder catheterization (CIC) and the frequency and intensity of AEs were collected according to the Schedule of Activities..

- **Statistical Methods**

Four populations were considered:

- Pharmacokinetic Analysis Sets:
    - the PK concentration population was defined as all subjects randomized and treated who had at least 1 concentration during the study.
    - the PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of primary interest during the study.
- Full Analysis Set (FAS): The FAS consisted of all randomized subjects who had taken at least 1 dose of study medication. This was a secondary analysis population. Withdrawn subjects might have been included in these analyses if considered appropriate.
- Per Protocol Analysis Set (PPAS): The PPAS consisted of all randomized subjects who have completed the study and who were not serious protocol violators. This was also a secondary analysis population. The PPAS was defined prior to unblinding the study.

Pharmacokinetic Analysis

The population PK (PPK) modelling approach was used to analyze the plasma concentration-time data for the fesoterodine 4 mg QD and 8 mg QD doses for the estimation of PPK parameters (apparent systemic clearance [CL/F], Ka, and apparent volumes of distribution [VC/F]) in paediatric subjects. Population mean estimates for the PK parameters were obtained by fitting the PK and variance models to the whole data set of all individuals. Confidence intervals (CIs) were computed for means and variances of estimates. Individual estimates of PK parameters were obtained using an empirical Bayesian Estimation Method.

The inter-subject variability was estimated and 95% CIs were reported for all population parameter estimates. For the residual variability, various models were fitted, including but not restricted to additive and proportional models.

Exploratory analyses were performed to investigate the effect of covariates including, but not limited to, age, weight, CYP2D6 status, and sex. The PK parameter estimates in paediatric subjects were compared descriptively to those previously obtained in the adult population.

Nonlinear Mixed-Effects Modelling: Modelling PPK analyses were conducted via nonlinear mixed-effects modelling with the NONMEM® software, Version VII (ICON Development Solutions, Ellicott City, MD). The first-order conditional estimation (FOCE) method in NONMEM was employed for all model runs, assuming that convergence was successful. If convergence was problematic, the first-order (FO) method was employed.

Base Model: Different structural models such as 1- or 2- compartment PK models for fesoterodine were considered as dictated by the data. In all models, estimation of CL/F and VC/F were of primary interest. Model selection was driven by the data and based on various goodness of fit indicators, including comparisons based on the minimum objective function value (OFV), Akaike Information Criterion (AIC), visual inspection of diagnostic scatter plots and evaluation of estimates of population.

Final Model: The population modelling approach was used to analyze plasma concentration time data for the fesoterodine 4 mg and 8 mg doses for the estimation of PPK parameters (CL/F, Ka, and VC/F) in paediatric subjects. Population mean estimates for the PK parameters were obtained by fitting the PK and variance models to the whole data set of all individuals. CIs were computed for means and variances of estimates. Using NONMEM, the FO or FOCE methods were employed for all model building. Individual estimates of PK parameters were obtained using POSTHOC, an empirical Bayesian Estimation Method.

Assessment of Model Adequacy (Goodness of Fit): The inter-subject variability was estimated and 95% CIs reported for all population parameter estimates. For the residual variability, various models were fitted, including but not restricted to additive and proportional models. Adequacy of model fitting was judged by the objective function, goodness of fit plots and parameter precision estimates.

Safety analyses

No formal hypothesis testing of safety data was performed. Results from the safety assessments and any AE were presented in tabular and/or graphical format adhering to the Sponsor's standards.

Exploratory analyses
No formal efficacy evaluations were conducted in this study, although the bladder diary assessment provided exploratory measures of clinical effect.

- **Changes on the conduct of the study / planned analyses**

The protocol, finalized 10 December 2008, was amended 3 times. The date of the initiating of the study is March 2009. Last subject visit was done on December 2010

- First amendment (23 November 2009):Change in inclusion criteria: expansion of the age range in Study A0221066 to 8 to 17 years, as long as the patient body weight is above 35 kg.
- Second amendment (26 May 2010): Change in exclusion criterion 15 to allow participation of subjects who are incapable of independent toileting or have assistance with intermittent catheterization.
- Third amendment (28 July 2010): Change in inclusion criteria: the body weight requirement for inclusion in this study is lowered from 35 kg to 25 kg.

Changes on the planned analyses:
- To update the age-range of subjects in the study, in line with the amended protocol.
- To clarify how gaps in diary completion were handled.
- To clarify the derivation of diary endpoints.

This amendment was made following the review of unblinded tables (as this was an open label study), however, all updates were to provide further detail and clarification, and not to change any of the planned analyses.

**Results**

- **Recruitment/ Number analysed**

A total of 20 subjects were planned, and 21 subjects were assigned to study treatment and treated (Table S3). Twenty subjects completed the study; 1 subject was no longer willing to participate and discontinued from the study. All enrolled and treated subjects were analyzed for safety.

**Table S3. Subjects Included in Pharmacokinetics, Efficacy, and Safety Analyses**

| No. of Subjects | Fesoterodine | |
|---|---|---|
| | 4 mg QD | 8 mg QD |
| Analyzed for Pharmacokinetics | | |
| PK Concentration | 19 | 18 |
| Analyzed for Efficacy* | | |
| Full Analysis Set | 21 | 20 |
| Per Protocol Set | 17 | 17 |
| Analyzed for Safety | | |
| Adverse events | 21 | 20 |
| Laboratory data | 21 | 20 |

Abbreviations: PK=pharmacokinetics, QD=once daily, No.=number

* Analyzed for Exploratory Diary Endpoints

- **Baseline data**

There were 12 (57.1%) males and 9 (42.9%) females in the study (Table 6). The average body weight was 51.9 kg (range 31.8 kg to 83.9 kg), and the average body mass index was 23.2 kg/m2 (range 15.3 kg/m2 to 33.8 kg/m2). The mean age of all subjects was 13.1 years (range 9 years to 17 years). Eighteen (85.7%) of the subjects were white.

**Table 6. Demographic Characteristics**

| No. of Subjects | Fesoterodine | | |
|---|---|---|---|
| | Male N=12 | Female N=9 | Total N=21 |
| Age (years) | | | |
| 9 – 12 | 6 | 4 | 10 |
| >12 – 17 | 6 | 5 | 11 |
| Mean (SD) | 13.2 (2.6) | 13.1 (3.0) | 13.1 (2.7) |
| Range | 9 – 17 | 9 – 17 | 9 – 17 |
| Race | | | |
| White | 10 | 8 | 18 |
| Black | 2 | 1 | 3 |
| Weight (kg) | | | |
| Mean (SD) | 54.0 (18.5) | 49.2 (14.5) | 51.9 (16.7) |
| Range | 31.8 – 83.9 | 33.6 – 77.1 | 31.8 – 83.9 |
| Body Mass Index ($kg/m^2$) | | | |
| Mean (SD) | 22.8 (5.8) | 23.7 (4.4) | 23.2 (5.1) |
| Range | 15.3 – 33.8 | 18.4 – 31.3 | 15.3 – 33.8 |
| Height (cm) | | | |
| Mean (SD) | 153.1 (18.8) | 143.1 (12.7) | 148.8 (16.9) |
| Range | 118.0 – 188.0 | 128.0 – 165.0 | 118.0 – 188.0 |

Source: Table 13.2.1 and Appendix B2.1
Abbreviations: SD=standard deviation, kg=kilogram, m=meter, N=number of subjects, cm=centimeter, No.=number
Body Mass Index calculated as $Weight/(Height/100)^2$.

The primary diagnosis for 10 subjects was idiopathic OAB (hypertonic bladder), with a mean duration since onset of 9.5 years (range 4.3 years to 17.5 years). The primary diagnosis for 11 subjects was neurogenic bladder, with a mean duration since onset of 9.0 years (range 0.6 years to 17.4 years).

Each of the 21 subjects enrolled and treated received at least 1 dose of study medication. Subjects 10051002 and 10111004 were <80% compliant with study medication. Subject 10051002 discontinued prior to escalation to the 8 mg dose. Seven subjects missed no doses of study medication, while other subjects missed occasional doses.

- **Pharmacokinetic results**

The results excluding the concentrations in the three 17-year-old subjects were evaluated to assess the influence of these subjects on the overall interpretation of study results for paediatric subjects across the age range of 8 years to 16 years and 11 months. As expected, based on the mature development stage across this age range, there was no apparent difference in the PK results when the 17-year-old subjects were included in the analysis dataset (Table S5). Based on these findings, it was further decided to include these subjects in the PPK analysis dataset to allow robust modelling of 5-HMT population PK.

**Table S5. Plasma 5-HMT Concentration Versus Time Summary, With and Without Inclusion of 17-Year-Old Subjects**

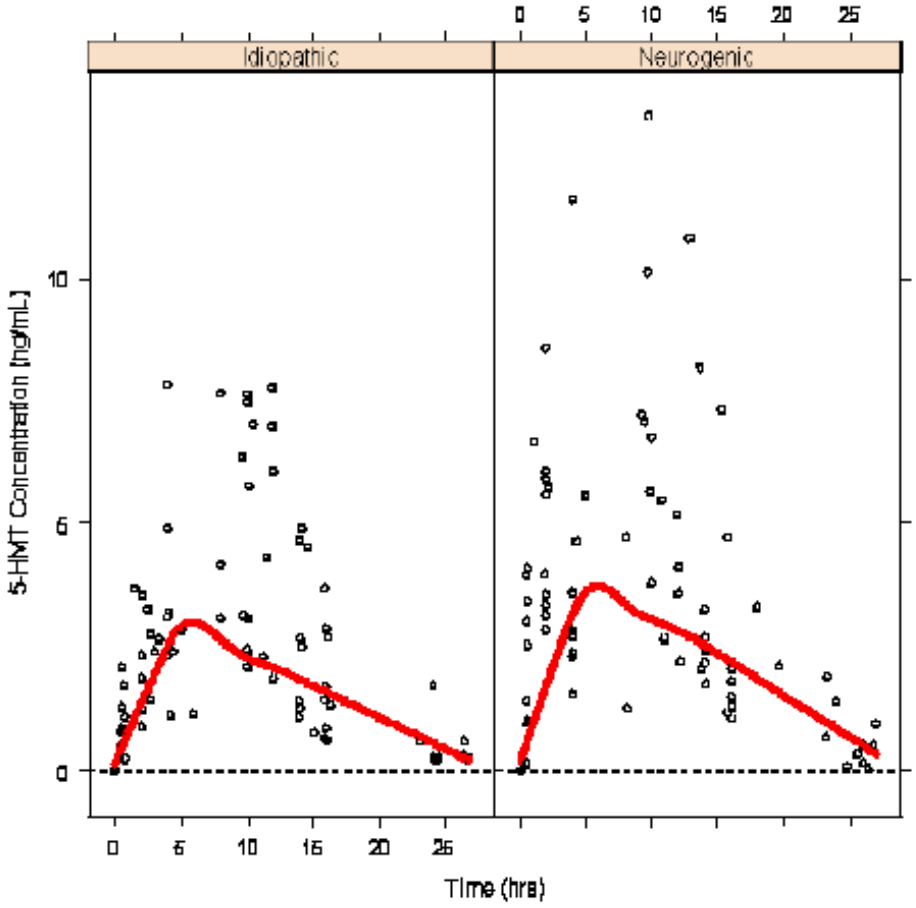
| Planned Time Postdose (hours) | N | Plasma 5-HMT Concentration (ng/mL) | | | | |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Median | Min | Max |
| **Subjects Aged 8-17 Years Old** | | | | | | |
| **Fesoterodine 4 mg once daily** | | | | | | |
| **Visit/hours postdose** | | | | | | |
| Visit 3/0 | 19 | 0.5569 | 101 | 0.3170 | 0.000 | 1.90 |
| Visit 3/0.5 | 14 | 1.722 | 64 | 1.350 | 0.506 | 3.96 |
| Visit 3/2 | 14 | 3.613 | 56 | 3.455 | 0.867 | 8.60 |
| Visit ¾ | 16 | 3.693 | 71 | 2.780 | 1.12 | 11.6 |
| **Fesoterodine 8 mg once daily** | | | | | | |
| Visit 4/8 | 7 | 5.179 | 42 | 4.750 | 2.24 | 7.64 |
| Visit 4/10 | 12 | 4.368 | 46 | 3.960 | 1.89 | 7.77 |
| Visit 4/14 | 18 | 2.718 | 68 | 2.335 | 0.000 | 7.33 |
| Visit 4/16 | 17 | 1.568 | 64 | 1.280 | 0.000 | 3.68 |
| **Subjects Aged 8-16 Years Old Only** | | | | | | |
| **Fesoterodine 4 mg once daily** | | | | | | |
| Visit 3/0 | 17 | 0.5122 | 98 | 0.3170 | 0.000 | 1.90 |
| Visit 3/0.5 | 12 | 1.752 | 67 | 1.350 | 0.506 | 3.96 |
| Visit 3/2 | 13 | 3.648 | 58 | 3.560 | 0.867 | 8.60 |
| Visit 3/4 | 14 | 3.937 | 69 | 2.960 | 1.12 | 11.6 |
| **Fesoterodine 8 mg once daily** | | | | | | |
| Visit 4/8 | 5 | 5.182 | 43 | 4.750 | 2.24 | 7.64 |
| Visit 4/10 | 10 | 4.449 | 47 | 3.960 | 1.89 | 7.77 |
| Visit 4/14 | 16 | 2.850 | 67 | 2.490 | 0.000 | 7.33 |
| Visit 4/16 | 15 | 1.642 | 63 | 1.310 | 0.000 | 3.68 |

Abbreviations: CV=coefficient of variation; Min=minimum, Max=maximum; 5-HMT=5-hydroxy-methyltolterodine; PK=pharmacokinetic, N=Number of observations (non-missing concentrations)
Summary statistics were calculated by setting concentration values below the lower limit of quantification to zero.
The lower limit of quantification is 0.0200 ng/mL.
PK samples were collected at Visit 3 (Week 4) and Visit 4 (Week 8).
Subjects with <80% compliance with dosing, or concentrations with sampling time deviation >20% from nominal time were excluded for summary statistics; these data were included in Population PK analysis if dosing on 3 days prior to PK sampling was confirmed and accurate PK sampling was recorded.
Two subjects were excluded due to <80% compliance with study drug.

Subjects with NDO did not appear to have any remarkable differences in 5-HMT PK when compared with subjects with idiopathic OAB (Figure 3). Somewhat higher exposures in NDO subjects may have been due to the generally lower body weights in this subject group compared with idiopathic subjects.

PPK analyses were conducted via nonlinear mixed-effects modelling with NONMEM® software; the data were adequately described by a one-compartment model with first-order absorption and elimination. PPK parameters (CL/F, VC/F) were standardized to a 70 kg person, using the allometric size model. Age and sex were not included as covariates in the final PPK model due to convergence failure and lack of improvement to explain PK variability. Importantly, the available data from this study contained a small number of children with a limited age range.

**Figure 3. Plasma 5-HMT Concentrations Following Once Daily Doses of Fesoterodine 4 mg and 8 mg Administered to Pediatric Subjects With Idiopathic OAB and NDO**




Source: Appendix A14.1
Abbreviations: hrs=hours; 5-HMT=5-hydroxy-methyltolterodine, OAB=overactive bladder, NDO=neurogenic detrusor overactivity
The red line indicates Loess (multi-dimensional scatter plot smoother) Local Regression Model.

In the PPK analysis (Table S6), all PK parameters, intersubject´s variability, and residual variability were well estimated as reflected in reasonable % relative standard error (RSE). Inter-individual variability in PK parameters calculated as the square root of inter-individual variance (ω2) and expressed as % coefficient of variation (CV), ranged from 38% (CL/F) to 43% (VC/F).

**Table S6. Final Model Parameters**

| Parameter | Point Estimate | SEE | %RSE | 95% CI Lower Limit | 95% CI Upper Limit |
|---|---|---|---|---|---|
| CL/F (L/h) | 86.70 | 11.4 | 13.15 | 63.9 | 98.1 |
| VC/F (L) | 10.10 | 222 | 21.98 | 566 | 1232 |
| Ka (1/h) | 0.44 | 0.14 | 32.95 | 0.15 | 0.58 |
| CYP effect on CL | 1.33 | 0.18 | 13.38 | 0.97 | 1.51 |

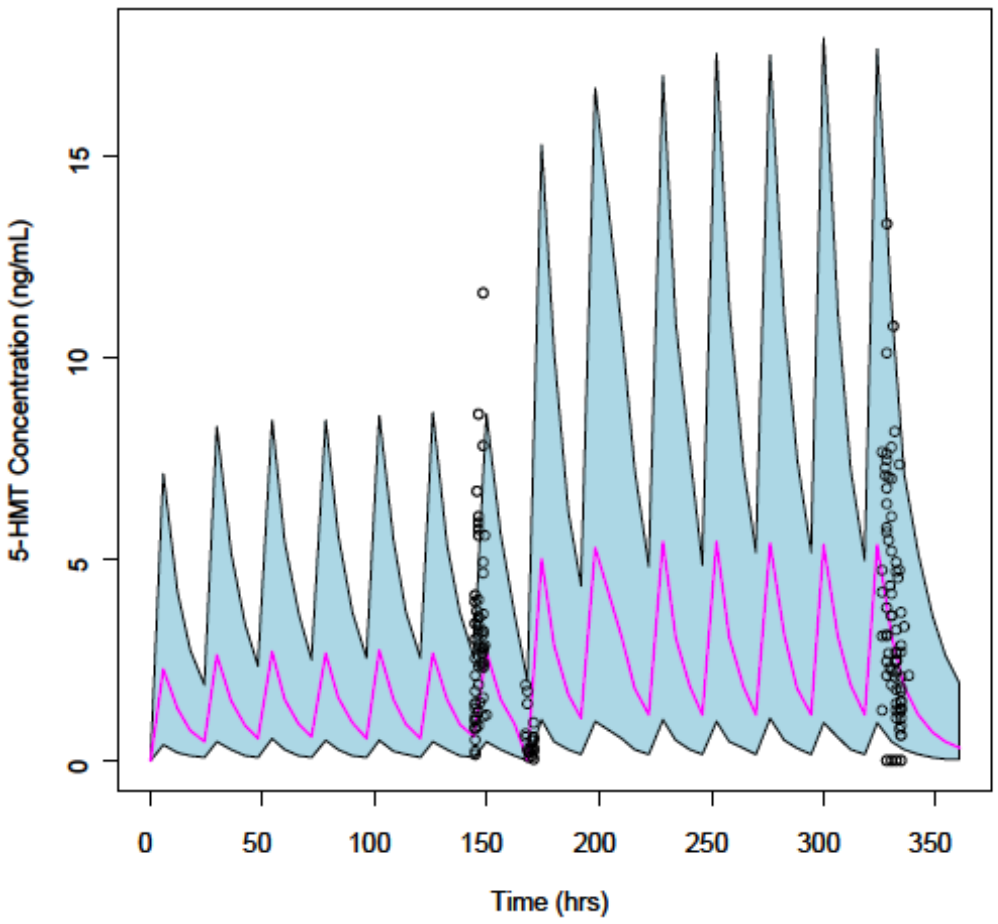
Abbreviations: SEE=Standard Error of Estimate, CI=confidence interval, % RSE=Relative Standard Error, =100*(SEE/Estimate), Ka=absorption rate constant, VC/F=apparent volumes of distribution, CL=clearance, CL/F=apparent systemic clearance, h=hour

The actual observed plasma concentrations from this study were in agreement with the simulation results, based on the adult population PK parameters and allometric scaling of the adult population parameters applied to a distribution of paediatric subjects meeting the age and body weight criteria for this study, that were used to determine paediatric doses. This agreement of the simulated and observed concentration value represents an external validation of the model used to predict exposures.

Pharmacokinetic Modelling Results
PK modelling and simulation (M&S) results, based on the adult population PK parameters and allometric scaling of the adult population parameters applied to a distribution of paediatric patients meeting the age and body weight criteria for this study, were used to determine paediatric doses. These M&S analyses predicted that following administration of fesoterodine 4 mg and 8 mg QD to children aged 6 to 16 years and >25 kg, exposures would be similar to those in adults given the same doses.

Clinical trial simulation with this study design was performed. Figure 5 shows the projected outcome of 1000 virtual clinical trials (median and 95% prediction intervals) for fesoterodine 4 mg QD followed by fesoterodine 8 mg QD doses in the intended population. The actual observed 5-HMT plasma concentrations from this study (open circles in Figure 5) were in agreement with the simulation results.

**Figure 5. Median and 95% Prediction Intervals for Predicted Steady-State 5-HMT Exposures Compared With Observed Values in Pediatric Subjects 8-17 Years of Age and Weighing >25 kg**




- **Pharmacogenomic results**

The CYP2D6 metabolizer status based on genotyping results was classified as poor metabolizer for 1 subject, missing for 2 subjects (due to lack of sample), and extensive or ultra-rapid metabolizer in all others.

- **Safety results**

There were no deaths, severe adverse events , or permanent withdrawals due to adverse events (AEs) reported. One subject receiving fesoterodine 8 mg QD temporarily discontinued study treatment due to a serious AE (SAE) (Table S7). A total of 8 subjects receiving fesoterodine 4 mg QD and 13 subjects receiving fesoterodine 8 mg QD reported AEs (all causalities).

**Table S7. Treatment Emergent Adverse Events (All Causalities)**

| No. of Subjects | Fesoterodine | |
|---|---|---|
| | 4 mg QD | 8 mg QD |
| Subjects evaluable for AEs | 21 | 20 |
| Number of AEs | 22 | 23 |
| Subjects with AEs | 8 | 13 |
| Subjects with serious AEs | 0 | 1 |
| Subjects with severe AEs | 0 | 0 |
| Subjects discontinued due to AEs | 0 | 0 |
| Subjects with dose reduction or temporary discontinuation due to AEs | 0 | 1 |

Abbreviations: AE=adverse event, No.=number, MedDRA=Medical Dictionary for Regulatory Activities, v=version, QD=once daily
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
MedDRA (v13.1) coding dictionary applied.
Includes data up to 7 days after last dose of study drug.

A total of 2 subjects receiving fesoterodine 4 mg QD reported 3 treatment related AEs and a total of 5 subjects receiving fesoterodine 8 mg QD reported 5 treatment-related AEs (Table S8).

**Table S8. Treatment Emergent Adverse Events (Treatment Related)**

| No. of Subjects | Fesoterodine | |
|---|---|---|
| | 4 mg QD | 8 mg QD |
| Subjects evaluable for AEs | 21 | 20 |
| Number of AEs | 3 | 5 |
| Subjects with AEs | 2 | 5 |
| Subjects with serious AEs | 0 | 1 |
| Subjects with severe AEs | 0 | 0 |
| Subjects discontinued due to AEs | 0 | 0 |
| Subjects with dose reduction or temporary discontinuation due to AEs | 0 | 1 |

Abbreviations: AE=adverse event, No.=number, MedDRA=Medical Dictionary for Regulatory Activities, v=version, QD=once daily
Except for the Number of Adverse Events subjects are counted only once per treatment in each row.
Serious Adverse Events - according to the investigator's assessment.
MedDRA (v13.1) coding dictionary applied.
Includes data up to 7 days after last dose of study drug.

There was 1 treatment-related SAE: a 15-year-old female subject temporarily discontinued study drug fesoterodine 8 mg QD due to constipation. Study drug was temporarily stopped during hospitalization; the subject recovered and the event resolved. The event was considered an important medical event and related to study drug by the investigator.

Treatment-related AEs were 1 AE each of dry mouth (mild), constipation (moderate), dry eye (mild), and blurred vision (moderate), and 2 AEs each of nausea (mild) and residual urine volume increased (mild).

Post-Void Residual volumes at baseline and following treatment with fesoterodine 4 mg QD and 8 mg QD doses in subjects not performing clean intermittent bladder catheterization are summarized in Table S9.

**Table S9. Summary of Post-Void Residual (PVR) Urine Volume (Subjects not Performing CIC)**

| Post-Void Residual (PVR) Urine Volume (mL) | Baseline (n=10) | Week 4 (n=12) Feso 4 mg QD | Week 8 (n=10) Feso 8 mg QD | Change from Baseline | |
|---|---|---|---|---|---|
| | | | | Week 4 (n=10) Feso 4 mg QD | Week 8 (n=10) Feso 8 mg QD |
| Mean | 15.50 | 25.42 | 24.40 | -2.60 | 8.90 |
| SD | 20.74 | 37.52 | 25.13 | 29.09 | 39.14 |
| Median | 6.00 | 4.00 | 25.00 | 0.00 | 12.50 |
| (Min, Max) | (0.00, 65.00) | (0.00, 90.00) | (0.00, 70.00) | (-65.0, 54.00) | (-65.0, 60.00) |
| 95% CI | (0.66, 30.34) | (1.58, 49.25) | (6.42, 42.38) | (-23.4, 18.21) | (-19.1, 36.90) |

Abbreviations: n=number of subjects, CIC=clean intermittent bladder catheterization, Feso=fesoterodine , QD=once daily, Min=minimum, Max=maximum, CI=confidence interval, SD=standard deviation
Baseline is defined as the measurement taken at Screening.

Treatment-related AEs of the central nervous system, such as behavioural change, aggression, drowsiness or cognitive dysfunction were not reported by patients in this study. Intermittent inattentive behaviour was observed on Days 2-5 of treatment with 4 mg fesoterodine in one subject (10111005); the causality of this AE was not deemed treatment-related by the principal investigator as it was consistent with the patients behaviour history.

The mean increase from baseline pulse rate was 14.6 bpm (Week 1, 4 hours post-dose), 4.6 bpm (Week 4, 0 hours post-dose), 12.4 bpm (Week 4, 4 hours post-dose) during fesoterodine 4 mg treatment and 8.2 bpm (Week 8, 4 hours post-dose) during fesoterodine 8 mg treatment. The increase did not appear dose-related. Following fesoterodine 4 mg, two subjects had pulse rates >120 bpm. Patient heart rate will be monitored in the planned paediatric studies with fesoterodine.

There were no ECG abnormalities of clinical significance at Screening or at the end of treatment.

- **Efficacy results**

No efficacy evaluations were performed in this study.

Based on feedback from investigators and subjects, and qualitative assessment of usable diary data, the 3-day bladder diaries in this study were deemed feasible and useful for assessing OAB symptoms in paediatric subjects (see Table S4). However, considering the small number of subjects in this study, these results should be interpreted with caution.

**Table S4. Summary Statistics of Exploratory 3-Day Bladder Diary Endpoints**

| Diary Variable (PPAS) | Mean (SD) (95% Confidence Interval) | | |
|---|---|---|---|
| | Baseline | Change from Baseline | |
| | | Feso 4 mg QD Week 4 | Feso 8 mg QD Week 8 |
| Mean number of micturitions or catheterizations/day (N=17)[a] | 6.05 (1.776) (5.14, 6.97) | -0.31 (1.519) (-1.09, 0.47) | -0.22 (1.643) (-1.06, 0.63) |
| Mean number of catheterizations/day (N=8)[a,b] | 4.99 (0.842) (4.28, 5.69) | 0.00 (0.626) (-0.52, 0.53) | -0.07 (0.861) (-0.79, 0.65) |
| Mean number of incontinence episodes/day (N=13)[a] | 1.85 (1.211) (1.12, 2.58) | -0.41 (0.961) (-0.99, 0.18) | -0.81 (0.962) (-1.39, -0.22) |
| Mean number of urgency episodes/day (N=12)[a] | 3.21 (1.881) (2.02, 4.41) | -0.76 (1.394) (-1.64, 0.13) | -0.51 (1.758) (-1.62, 0.61) |
| Mean volume voided per micturition or mean volume per catheterization (N=17) (mL) | 183.1 (79.07) (142.5, 223.8) | 31.50 (57.99) (1.69, 61.32) | 45.03 (72.94) (7.53, 82.54) |
| Mean volume per catheterization (N=8)[b] (mL) | 172.2 (95.97) (91.97, 252.4) | 36.61 (82.57) (-32.4, 105.6) | 84.09 (84.49) (13.45, 154.7) |

Abbreviations: N=number of subjects, SD=standard deviation, NDO=neurogenic detrusor overactivity, PPAS=Per Protocol Analysis Set, Feso=fesoterodine, QD=once daily

[a]Only subjects reporting >0 episodes at baseline are included in these summaries.

[b]Subjects with NDO only.

## 1. Discussion on clinical aspects

Fesoterodine is indicated for the treatment of the overactive bladder in adults. The use was restricted for children and no pharmacokinetic data for paediatrics were available.

The MAH has submitted the results of a open label study to characterize the pharmacokinetics of 5-HMT in children aged to 8-17 years following 4 and 8 mg once-daily regimens, and identify potential covariates that could explain the inter-individual variability in 5-HMT pharmacokinetics in this paediatric population.

Plasma concentrations data from 21 paediatric patients (10 suffering idiopathic OAB, 11 with neurogenic detrusor overactivity) from 9 to 17 years were collected and used for a population pharmacokinetic analysis. The PK of 5-HMT following the administration of fesoterodine once daily to paediatric patients were simulated using an allometric scaling method via nonlinear mixed-effects modelling using the final adult population PK parameters. Pediatric patients, aged 8-17 years and body weight >25 kg, representing the population of study A0221066 were used for PK simulations to select paediatric doses.

Results of modelling and simulations predicted that 5-HMT exposures in paediatric patients (aged 11-17 years, weighing >35 kg or aged 6-16 years, weighing >25 kg) are within the range of exposures observed in adults given the same doses in Phase 2-3 studies. Patients with NDO did not appear to have any remarkable differences in 5-HMT PK when compared with patients with idiopathic OAB. Somewhat higher exposures were observed in NDO patients, which may be due to the generally lower body weights in this patient group compared with idiopathic patients.

Currently, the wording of the SmPC of fesoterodine reflects the lack of data in paediatric population. No amendment derived from this study is proposed by the MAH in this application.

However, there seems to be two ongoing additional studies in paediatric population: Study A0221047 (safety and efficacy study in neurogenic detrusor overactive patients of ages 6-16 years and body weight >25 Kg) and Study A0221074 in younger and lighter children (>6 yrs of age and <25 Kg). No information regarding these two clinical trials is included in the documentation. Since the results of these two studies could impact the current assessment, the MAH is requested to address this issue, i.e, whether the SPC may be updated with the information already provided or whether it should be preferable to wait for the outcome of these two trials.

In the assessor's view, the results of Study A0221066, although limited, could be of use for prescribers when a treatment with fesoterodine is considered for a paediatric patient. Safety data and pharmacokinetic results of patients treated in this study can allow a better dose approach in this population. The inclusion of this information in the SmPC (Section 5.2 Pharmacokinetic properties) if appropriate (please see above), should be discussed by the MAH.

## Rapporteur's overall conclusion and recommendation

Having assessed the data submitted for this procedure, it is considered that the information provided could be of help for prescribers. Whether it is more appropriate to include the data in this moment in section 5.2 of the SPC or whether it would be preferable to wait for the results of the two ongoing studies related to this procedure should be discussed by the MAH.

Also, a short clinical overview, lacking in the current submission, should be provided by the MAH.

**NOTE FOR READER'S:** After circulating PAR, Pfizer informed of the following timelines: study A0221047 is planned to start 2Q2012 with CSR availability 1Q2014 and Study A0221074 is planned to start 2Q2014 with CSR 1Q2016. As proposed by the EMA it is agreed that this procedure can be considered concluded (no additional clarifications are therefore requested) and that the results of the two remaining studies as well as any potential update of the SPC will be discussed in a future commitment, once the data are available.

**Recommendation**

☒ **Fulfilled**

☐ **Not fulfilled**:

# Additional clarifications requested

N/A