CLINICAL REVIEW

Application Type	sNDA
Application Number(s)	022030
Priority or Standard	Priority Review
Submit Date(s)	December 18, 2020
Received Date(s)	December 18, 2020
PDUFA Goal Date	June 18, 2021
Division/Office	Division of Urology, Obstetrics and Gynecology (DUOG), Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Reviewer Name(s)	Agiua Heath, M.D., Medical Officer Mark Hirsch, M.D., Medical Team Leader
Review Completion Date	June 10, 2021
Established/Proper Name	Fesoterodine fumarate
(Proposed) Trade Name	Toviaz
Applicant	Pfizer
Dosage Form(s)	4 mg and 8 mg tablets
Applicant Proposed Dosing Regimen(s)	4 mg tablet by mouth daily in pediatric patients 6 years of age and older weighing (b)(4) to 35 kg. (b)(4) mg tablet by mouth daily in pediatric patients 6 years of age and older weighing > 35 kg.
Applicant Proposed Indication(s)/Population(s)	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 6 years and older with a body weight ≥15 kg
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of neurogenic detrusor overactivity (NDO) in pediatric patients aged 6 years and older with a body weight > (b)(4) kg

Table of Contents

Table of Tables

Table of Figures

Glossary

5-HMT	5-hydroxymethyltolterodine
AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBCL	Childhood Behavior Checklist
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CIC	clean intermittent catheterization
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GPT	Grooved Pegboard Test
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NDO	neurogenic detrusor overactivity
NME	new molecular entity
OAB	overactive bladder
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
QD	once daily
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
UTI	urinary tract infection

1. Executive Summary

1.1. Product Introduction

Toviaz (fesoterodine fumarate) is a competitive, non-selective muscarinic receptor antagonist. Muscarinic receptors are involved in contractions of bladder detrusor muscle. Toviaz inhibits these contractions, thereby improving the symptoms of urge incontinence, urgency, and frequency in patients with overactive bladder (OAB). Toviaz, 4 mg and 8 mg tablets, was initially approved on October 31, 2008 under NDA 022030 for the treatment of overactive bladder (OAB) in adults. In this sNDA data for the pediatric population, data is presented to support the safety and efficacy of Toviaz tablets for the treatment of neurogenic bladder overactivity (NDO) in pediatric patients aged 6 years and older.

The recommended dose for Toviaz in children is based on patient weight. The dose for patients 6 years of age and older, who weigh 25 -35 kg is 4 mg by mouth daily. If needed, this dose may be increased to a maximum dose of 8 mg daily. The dose for patients 6 years of age and older, who weigh > 35 kg is 8 mg by mouth daily.

1.2. Conclusions on the Substantial Evidence of Effectiveness

From the Clinical perspective, the evidence presented in this sNDA is adequate to support the effectiveness of Toviaz in the treatment of pediatric patients with NDO. The evidence is also adequate to support safety for the proposed indication. See later sections of this review for additional information and discussion regarding safety and effectiveness.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Toviaz tablets will be indicated for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients 6 years of age and older, weighing ≥25kg. Neurogenic detrusor overactivity is defined as detrusor overactivity that develops as a result of a neurologic lesion. Tablets are appropriate for children > 25 kg who are capable of swallowing them. The goal of treatment is to preserve renal function and minimize symptoms of incontinence by increasing bladder capacity and the duration of time between incontinence episodes.

At this time, the Clinical review team recommends that this sNDA be APPROVED.

NDO results from neurological lesions often related to congenital anomaly and injury to the spinal cord. In this special pediatric patient population, NDO poses a meaningful burden both physically and socially/emotionally. Physical consequences of untreated NDO are bladder wall injury and renal damage. Interference in social and emotional development results from the limited lifestyle and decreased level of engagement caused by frequent incontinence episodes.

Current oral pharmacologic treatment options for NDO are limited and include four approved options: oxybutynin (tablets and syrup), solifenacin (oral suspension), and mirabegron (tablets and oral suspension), each in combination with clean intermittent catheterization (CIC), and onabotulinumtoxin A (intradetrusor injection). All of the approved products for this indication have side effects. Oxybutynin's side effect profile includes potential central nervous system adverse effects which raises concerns about learning and school performance, as well as more typical side effects associated with anticholinergic medications such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. Solifenacin's anticholinergic side effects consist primarily of constipation and dry mouth. Mirabegron is associated with increases in blood pressure. Side effects of onabotulinumtoxin A intradetrusor injection include bacteriuria, UTI, leukocyturia, and hematuria. There is a need for alternative options that are safe and effective for the treatment of this patient population.

Toviaz is a competitive muscarinic receptor antagonist. After oral administration, fesoterodine is rapidly and extensively hydrolyzed by nonspecific esterases to its active metabolite, 5-hydroxymethyl tolterodine (5-HMT), which is responsible for the antimuscarinic activity of

fesoterodine. Muscarinic receptors play a role in contractions of urinary bladder smooth muscle. Inhibition of these receptors in the bladder is presumed to be the mechanism by which fesoterodine produces its effects. The efficacy of Toviaz in the treatment of NDO in pediatric patients has been demonstrated through clinically meaningful increases in maximum cystometric capacity and supported by improvement in many urodynamic parameters and e-diary recorded bladder volume and leakage measurements. The efficacy of Toviaz does not appear to be associated with any new safety issues. The safety profile of Toviaz for the treatment of NDO in pediatric patients is consistent with the known risks of Toviaz for the treatment of OAB in adults. There were no deaths in the development program, and only one SAE (constipation) that may have been drug-related. In the Phase 3 study there were 6 discontinuations in subjects assigned to Toviaz tablets. Treatment emergent adverse events (TEAEs) leading to discontinuation included urinary incontinence, medication error, fatigue, epiphysiolysis, pyelonephritis, and product dispensing error. None of these TEAEs appeared to be treatment-related. The most commonly reported adverse events were diarrhea, UTI, dry mouth, constipation, abdominal pain, nausea, weight increase and headache, as typically reported for anticholinergic medications. Ophthalmological adverse events, including myopia, accommodation disorder and blurred vision, were reported in 6.1% of pediatric patients with NDO who received Toviaz 4 mg or Toviaz 8 mg. The ophthalmological adverse events did not result in discontinuation of Toviaz in any patient. Increases in heart rate (HR) were reported in pediatric patients with NDO who received Toviaz 4 mg and Toviaz 8. The increases in HR were not associated with clinical symptoms and did not result in discontinuation of therapy with Toviaz. There are no specific concerns for Toviaz in the post-market setting in the indicated pediatric NDO population.

The benefit-risk analysis takes into account that NDO in the pediatric population is a serious condition that is associated with bladder wall changes and renal damage, as well as social and emotional distress that greatly interferes with the development of these children. Toviaz tablets provide an alternative treatment to the currently approved options and a convenient once daily dosing regimen.

Toviaz has benefits that compare favorably against its safety profile. The clinical trials of Toviaz in the pediatric population with NDO provided no safety signals beyond those known for Toviaz in adults with OAB. Labelling is adequate to address the known risks of Toviaz. The safety data submitted supports the use of Toviaz as an additional first line therapy, coupled with CIC, for the treatment of pediatric patients aged 6-17 years with NDO.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurological condition. NDO is a urodynamic observation characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline. • NDO can develop as a result of a lesion at any level in the nervous system. The most prevalent cause of NDO in children is myelodysplasia, which includes such conditions as myelomeningocele, meningocele, and occult spinal dysraphism/spin bifida occulta, and results from neural tube closure defects during fetal development. The most common acquired cause of NDO is cerebral palsy. An injury in the perinatal period (e.g. perinatal infection, anoxia) can produce a neuromuscular disability or a specific cerebral dysfunction. Less common acquired causes include spinal tumors, trauma, or sequelae of transverse myelitis. Because NDO results from a number of different conditions, prevalence is not easily quantifiable. • If untreated, NDO can cause bladder wall changes and renal damage due to hydronephrosis. • Chronic incontinence in children with NDO leads to limited social participation, embarrassment and shame, and decreased independence. These consequences adversely affect the social and emotional development of children and also of adolescents transitioning into adulthood.	This condition is clinically important because of the irreversible kidney damage it can cause without treatment, as well as the severe limitations on daily living and the resulting social and emotional harm it causes during the critical childhood developmental life stage.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• The current first-line treatment option is an antimuscarinic drug coupled with clean intermittent catheterization (CIC). The only approved oral medications are oxybutynin, solifenacin, and mirabegron. Oxybutynin comes in tablets or syrup, is approved for patients with NDO aged 5 years and older, and is dosed 2-3 times a day. Solifenacin oral suspension is approved for patients with NDO aged 2 years and older, and is dosed once daily. Mirabegron comes in extended-release tablets and extended-release oral suspension, is approved for patients with NDO aged 3 years and older, and is dosed once daily. Onabotulinumtoxin A is approved for intradetrusor injection, a more invasive route of administration, requiring anesthesia, in pediatric patients aged 5 and older who have been inadequately managed with anticholinergics. Even more invasive treatment options for those who fail treatment with oral medication and CIC or intradetrusor injection include incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty. • According to approved product labeling, currently approved pharmacotherapies for this condition increase mean maximum cystometric bladder capacity (MCBC) at 24 weeks by 49 mL (oxybutynin), 53 mL (solifenacin) and 87 mL (mirabegron) compared to baseline. Onabotulinumtoxin A intradetrusor injections decreased daily urinary incontinence episodes and increased MCBC by 64 mL after 6 weeks of treatment. • Each approved product has its own side effect profile. For example, the safety profile for oxybutynin includes typical anticholinergic side	There is a need for an additional pharmacotherapy option that offers effective and convenient therapy with a favorable side effect profile.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	effects such as headaches, blurred vision, constipation, altered behavior, dry mouth, and flushed cheeks. There are also potential CNS adverse effects that raise concerns for cognitive effects that could affect learning and school performance in the pediatric demographic. The safety profile of solifenacin includes primarily the typical anticholinergic side effects of constipation and dry mouth. The safety profile of mirabegron includes increases in blood pressure.	
Benefit	• The Phase 3 trial that supported the findings of efficacy for Toviaz in this application was a randomized, open-label, baseline-controlled, multicenter study in pediatric patients aged 6 to 17 years with NDO. The study was comprised of two weight cohorts. Cohort 1 involved subjects > 25 kg, and was a three arm study of Toviaz 4 mg tablets, Toviaz 8 mg tablets, and oxybutynin XL as an informal active comparator. (Cohort 2 involved subjects 15 kg -25 kg, was a study of an investigational fesoterodine fumarate ER beads-in-capsule (BIC) formulation). (b) (4) The study consisted of two investigational periods: The Efficacy phase--a 12 week three arm phase with an informal active comparator (oxybutynin XL). This was followed by the Safety phase--a 12 week two arm extension phase without the active comparator. • The primary endpoint was change from baseline to 12 weeks in mean MCBC. The secondary endpoints were based on urodynamics, patient e-diary responses (bladder volume and leakage measures) and included:	The baseline-controlled open label study demonstrated the efficacy of Toviaz in pediatric patients with NDO, aged 6-17 years old, and weighing ≥ 25 kg. The clinical meaningfulness of the changes in the primary endpoint is supported by secondary endpoint analyses. • The evidence provided meets the evidentiary standard for benefit. • The quality of the evidence is supported by analysis of secondary endpoints which also demonstrate the clinical relevance of the findings. • Comparative analyses with oxybutynin provide supportive information about efficacy and safety relative to a widely used drug.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Change from baseline to week 12 in detrusor pressure at maximum bladder capacity ○ Number and percentage of patients with involuntary detrusor contractions (IDC) at baseline but not at Week 12 ○ Change from baseline to week 12 in bladder volume at first involuntary detrusor contraction (IDC) ○ Change from baseline to week 12 in bladder compliance • In the Phase 3 study (A0221047), the mean change from baseline to week 12 in MCBC was 58.1 mL for patients assigned to Toviaz 4 mg, and 83.4 mL for patients assigned to Toviaz 8 mg. This endpoint is deemed appropriate based on its prior use as a primary efficacy endpoint in the clinical studies that supported approval of oxybutynin, solifenacin and mirabegron for the same indication, and on its routine use in clinical practice as a marker of bladder filling capacity. •Secondary endpoints support the primary efficacy results with improved urodynamic measurements and improvement in e-diary reported bladder volume and leakage measurements that reflect clinical meaningfulness. •Toviaz provides an option in a wide pediatric age group (ages 6 to 17), provides convenient once daily dosing, and has a favorable safety profile.	
Risk and Risk Management	• The extent of exposure and overall safety assessment in this application includes primarily pediatric patients with NDO (and 10 pediatric patients with idiopathic OAB symptoms). The product's safety profile is informed by a Phase 3 trial in pediatric patients with NDO (A0220147), a small safety extension beyond 24 weeks in	The safety results from the Phase 3 study and the Phase 2 study demonstrated the expected adverse reactions to Toviaz, with no new safety signals identified. Toviaz was generally well tolerated in pediatric patients with NDO.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Japanese subjects (A0221109), a small, Phase 2 pharmacokinetic trial in pediatric patients with NDO and pediatric patients with idiopathic OAB symptoms (A0220166). The overall understanding of this product's safety profile is also based on 12 years of post-approval experience with Toviaz in adults with OAB. • Based on the geographic locations of the investigative sites, the safety database population consisted mainly of White and Asian pediatric patients. While an overall diverse population is expected to use the product, there is no reason to presume differences in efficacy or safety based on race or ethnicity. • The most commonly reported adverse events were diarrhea, UTI, dry mouth, constipation, abdominal pain, nausea, weight increase and headache, which are typical of anticholinergic medications. Ophthalmological adverse events, including myopia, accommodation disorder and blurred vision, were reported in 6.1% of pediatric patients with NDO who received Toviaz 4 mg or Toviaz 8 mg. The ophthalmological adverse events did not result in discontinuation of Toviaz in any patient. Increases in heart rate (HR) were reported in pediatric patients with NDO who received Toviaz 4 mg and Toviaz 8. The increases in HR were not associated with clinical symptoms and did not result in discontinuation of therapy with Toviaz. • There are no specific concerns for Toviaz in the post-market setting in the indicated pediatric NDO population.	The safety profile of Toviaz in pediatric patients with NDO was full consistent with the safety profile of approved Toviaz in adults with OAB. There were no new or unresolved safety issues.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	□	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		X	Patient reported outcome (PRO), bladder diary	6.1.1 Study Design 6.1.2 Study Results
		X	Observer reported outcome (ObsRO), bladder diary, Childhood Behavior Checklist	6.1.1 Study Design 6.1.2 Study Results
		X	Clinician reported outcome (ClinRO), Grooved Pegboard Test	6.1.1 Study Design 6.1.2 Study Results
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

NDO is defined by the International Children's Continence Society (ICCS) as detrusor overactivity when there is a relevant neurologic condition. NDO is a urodynamic observation, characterized by involuntary detrusor contractions that are spontaneous or provoked during the filling phase, involving a detrusor pressure increase of greater than 15 cm H_2O above baseline.

NDO can develop as a result of a lesion at any level in the nervous system, including the cerebral cortex, spinal cord, or peripheral nervous system. The most prevalent cause of NDO in children is myelodysplasia, a group of developmental abnormalities that occur during neural tube closure. These include myelomeningocele, meningocele, and occult spinal dysraphism (spina bifida occulta). The most common acquired cause of NDO is cerebral palsy. Less common acquired causes include spinal tumors, trauma, or the sequalae of transverse myelitis.

The early management of NDO is focused on optimizing bladder function to prevent hydronephrotic renal damage. Optimizing bladder function prevents the high-pressure detrusor contractions and elevated bladder filling pressures that result in irreversible changes to the bladder wall. The most common pharmacologic treatment for NDO is oxybutynin (oral or intravesical), which suppresses detrusor overactivity. Clean intermittent catheterization (CIC), typically performed 4-5 times daily, improves bladder drainage and reduces bladder pressure during filling. To date, the vast majority of patients are treated successfully with oxybutynin treatment coupled with CIC.

NDO is a condition that significantly impacts a child's social participation because of the need for frequent CIC, and because of the occurrence of episodes of incontinence. Better management of incontinence related to NDO improves quality of life by allowing greater independence and opportunities for social participation. Optimizing quality of life throughout early childhood and in the adolescent years improves social and emotional health and physical development and contributes to a successful transition to adulthood.

2.2. Analysis of Current Treatment Options

The first-line treatment for pediatric NDO is the combination of continuous intermittent catheterization (CIC) and antimuscarinic drugs. Currently there are three approved oral drugs for NDO in pediatric patients, oxybutynin chloride, solifenacin succinate, and mirabegron. Oxybutynin is available as immediate-release tablets, extended-release tablets, and syrup. Solifenacin is available as tablets and oral suspension. Mirabegron is available as extended-release tablets and extended-release oral suspension. All of these products have side effects. For example, oxybutynin has been associated with headaches, blurred vision, constipation, altered behavior, dry mouth, flushed cheeks and effects on the CNS. Solifenacin has been associated with constipation, dry mouth, and less frequently with hypertension, tachycardia, and somnolence. CNS side effects are of particular concern as they can lead to impaired school performance.

Other treatments include intravesical oxybutynin, which has a reduced first pass metabolism in the liver compared to oral anticholinergic therapy, and consequently, may have a more tolerable side effect profile compared to oral oxybutynin. Onabotulinumtoxin A intradetrusor injection was approved on February 9, 2021 for the treatment of NDO in pediatric patients aged 5 and older who have an inadequate response to, or are intolerant of, anticholinergic medications. This invasive treatment requires injection under anesthesia and is intended as a second-line treatment for patients inadequately managed by the currently approved oral treatment options.

Patients who fail treatment with these medications coupled with CIC may be candidates for more invasive procedures such as incontinent urinary diversion or reconstructive bladder surgery with augmentation cystoplasty.

Toviaz can provide another option to use in combination with CIC for pediatric patients with NDO aged 6 and older.

Table 1. Available Treatments for Pediatric Neurogenic Detrusor Overactivity (NDO)

Oral antimuscarinic drugs	Oral β-3 adrenergic agonists	Intradetrusor injection
Approved for NDO in pediatric patients		
Ditropan (oxybutynin chloride) Syrup (5 mg/5 mL) Tablets, immediate-release and extended-release		
VESIcare (solifenacin succinate) LS Oral suspension (1 mg/mL)		
	MYRBETRIQ (mirabegron tablets)	
		Botox (onabotulinumtoxin A)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The reader is referred to Section 3.2 of this review for the regulatory history and activity for this sNDA. The reader is referred to the original NDA Clinical review of Toviaz tablets for additional regulatory history.

3.2. Summary of Presubmission/Submission Regulatory Activity

On October 31, 2008 NDA 022030 was approved for Toviaz for the treatment of overactive bladder in adults. The approval letter included the following Pediatric Research Equity Act (PREA) postmarketing requirement (PMR) for a deferred pediatric study:

> Deferred pediatric study under PREA for the treatment of overactive bladder in the subgroup of pediatric patients with neurologic disease ages 6 to 16 years, 11 months.

On May 5, 2009 a Type C meeting was held to discuss the proposed fesoterodine pediatric drug development program, which would consist of three clinical trials:

- Study A0221066 – a Phase 2, PK/PD study, in pediatric patients aged 11 to 17 years with idiopathic and neurogenic OAB who weigh >35kg. (This study had already been initiated.)
- Study A0221047 – a Phase 3, open-label, safety and efficacy study in pediatric patients aged 11 to 17 years with neurogenic OAB who weigh >35kg
- Study A0221074 – a Phase 2, PK/PD, study in pediatric patients aged 6 to 10 years with idiopathic and neurogenic OAB who weigh ≤35kg

(These studies will heretofore be referred to as, Study 1066, Study 1047, and Study 1074, respectively.)

The Division advised the Sponsor to recruit neurogenic patients, rather than patients with idiopathic OAB, into its studies. The Division also strongly encouraged a concurrent active control (e.g., oxybutynin) in the Efficacy phase of Study 1047, and recommended a 12 week safety extension for Studies 1047 and 1074.

On March 16, 2010 a second Type C meeting was held. Key discussion points from this meeting included:

- The Division agreed to the Sponsor's plan to share PK and safety data from the ongoing Study 1066 prior to initiating the proposed phase 3 Study 1047.

- The Division agreed to the Sponsor's proposal to meet again at such a time as the data from Study 1047 was available to discuss the final study design for Study 1074. The Division concurred that such a "stepwise" process could be built into a Written Request.

- The Division expressed concern that the revised sample size for Study 1074 (n= (b) (4)) might be too small, but that 50 subjects might suffice.

- The Sponsor discussed the development of a pediatric-appropriate formulation for Study 1074 (a beads in capsule [BIC] formulation).

On August 9, 2010, the Sponsor submitted their Proposed Pediatric Study Request (PPSR).

On February 23, 2011, FDA issued a letter stating that the PPSR was inadequate, and recommended that the Sponsor resubmit the PPSR after addressing several issues.

On April 27, 2011, the Sponsor submitted a revised PPSR and revisions to the protocols for Studies 1047 and 1074.

On July 7, 2011, the Sponsor submitted further revisions to the protocol for Study 1074, as well as the final study report for Study 1066 entitled, "*An Open-Label, Dose-Escalating Study of the Pharmacokinetics, Safety and Tolerability of Fesoterodine in Pediatric Overactive Bladder Patients Aged 8-17 Years"*.

On September 9, 2011, the Sponsor submitted final study reports for Study A0221068 (which was a PK/relative bioavailability and food effect study in adults).

On November 14, 2011, FDA issued a pediatric Written Request (WR). The WR requested the following studies:

Study 1: An open label, active control, , 12-week, randomized study with a 12-week safety extension phase evaluating the efficacy, PK, safety and tolerability of two doses of fesoterodine in pediatric patients with neurogenic detrusor overactivity aged 6 to 16 years and weighing >25 kg. In this study, each patient will serve as his/her own control.

Study 2: An open label, 12-week, randomized study with a 12-week safety extension phase, assessing the efficacy, PK, safety and tolerability of two doses of fesoterodine in pediatric patients with neurogenic detrusor overactivity aged 6 to 16 years and weighing ≤25 kg. Each patient will serve as his/her own control.

Study 2 was to be initiated after data from Study 1, including population PK and exposure-response modeling, were shared with the Agency. Study 2 was to use the beads-in-capsule (BIC) formulation.

The first WR was followed by WR amendments in May 19, 2014, October 3, 2016, and June 27, 2019. These amendments were to extend the submission date for study 1047 due to enrollment, recruitment, and manufacturing process challenges.

On October 30, 2013, the Sponsor requested a meeting to discuss their proposed protocol amendment to Study 1047 to re-structure Study 1047 into two cohorts, whereby Cohort 1 would include subjects weighing ≥25 kg and treated with Toviaz tablets, while Cohort 2 would include subjects weighing < 25 kg in body weight and treated with the new beads-in capsule formulation. The Sponsor also proposed to include 17-year-olds in Cohort 1 of Study 1047.

On January 14, 2014, FDA sent comments to the Sponsor, stating the changes to the protocol would be acceptable, and the meeting request was withdrawn.

(b) (4)

On September 10, 2020, a Type B pre-sNDA meeting was held. Discussion items included how to provide safety data summaries, including pooling of safety data from Studies 1047 and 1066. The Sponsor also inquired as to whether they could fulfill the terms of the pediatric WR with submission of the sNDA for Toviaz tablets, (b) (4)

On October 16, 2020, the Sponsor submitted clarifications and requests for feedback regarding the sNDA data package that had been discussed at the September 10, 2021, Pre-sNDA meeting. (b) (4)

(b) (4)

On December 18, 2020, the Sponsor submitted for review a supplemental NDA to market Toviaz tablets 4 and 8 mg for the treatment of NDO in pediatric patients 6 years of age and older with a body weight ≥ (b) (4) kg.

(b) (4)

3.3. Foreign Regulatory Actions and Marketing History

On April 20, 2007, Toviaz tablets received approval in the European Union (E.U.) for the treatment of OAB in adults with the symptoms of increased urinary frequency, urgency, and urgency incontinence. Marketing approval for the same indication was granted in the US on October 31, 2008. Toviaz has since received marketing authorization in 47 countries, and is currently marketed in 33 countries. Toviaz is not yet marketed for use in pediatric patients.

Information from the worldwide clinical trials, with focus on the pediatric development program, was included in the Periodic Safety Update Report (PSUR) that was submitted by Sponsor on March 12, 2021. Data relating to the worldwide postmarketing experience with Toviaz through January 4, 2021, with focus on use in the pediatric population, was also submitted. According to the PSUR, for the time period September 1, 2020 through January 4, 2021, no actions had been taken worldwide for safety reasons.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Due to the ongoing COVID-19 global pandemic and the resulting challenges in completing on-site, good clinical practice (GCP) inspections prior to this application's action due date, DUOG determined that the review of this application could proceed without the need for clinical site inspections. No irregularities were observed in the data that would require for-cause inspections, and there was no reason to be concerned about study conduct or data quality.

4.2. Product Quality

For Toviaz tablets, there are no outstanding CMC issues. The CMC team recommended that the application be approved.

4.3. Clinical Microbiology

There were no Clinical Microbiology issues for this application.

4.4. Nonclinical Pharmacology/Toxicology

No juvenile animal studies were requested prior to the initiation of clinical pediatric studies,

and no new nonclinical data was submitted with this sNDA. Initial pediatric study design and doses/exposures for the pediatric NDO population were based on prior adult OAB study designs and doses/exposures for OAB. No revisions to the nonclinical-related sections of the original label or the new parts of the label were recommended by the Pharm/Tox review team.

4.5. Clinical Pharmacology

There were several Clinical Pharmacology review issues, and for a comprehensive review, the reader is referred to the Clinical Pharmacology review.

Based on the results of efficacy and safety from Study, 1047, as well as modeling and simulation analyses, the Sponsor proposed Toviaz 4 and 8 mg tablets as the recommended pediatric formulation with a dosing regimen of Toviaz 4 mg daily for patients with a body weight ≥ (b) (4) kg to ≤ 35 kg and of Toviaz 8 mg daily for patients with a body weight >35 kg. The Sponsor's rationale for this dosing recommendation is based on maintaining 5-HMT exposures (maximum observed concentration at steady state [Cmax,ss] and area under the concentration time curve at steady state [AUCtau,ss]) in pediatric patients receiving Toviaz 4 and 8 mg daily doses within a range of exposure close to adult values.

The Pharmacometrics review team verified the Sponsor's analyses and concluded that the analyses support the proposal of changing the weight threshold for dose (b) (4) 35 kg. However, as outlined below, the Clinical Pharmacology review team (including the Pharmacometrics review team) did not concur with all of the Sponsor's proposed Dosage & Administrations recommendations. The Clinical Pharmacology review team provided the following recommendations for changes to the Sponsor's proposal:

(b) (4)

Pediatric patients weighing greater than 25 kg up to 35 kg:
Recommendation: While the Sponsor proposed only the Toviaz 4 mg daily dose for patients weighing > 25 kg to 35 kg, the Clinical Pharmacology review team recommended that the dose of 4 mg daily may be increased to 8 mg daily if needed.

Rationale: For this group, both Toviaz 4 mg and 8 mg daily treatments were evaluated in Study 1047. Treatments with both 4 mg or 8 mg daily resulted in improvements from baseline to Week 12 in the primary efficacy endpoint, maximum cystometric bladder capacity (MCBC), with numerically higher changes from baseline for the 8 mg daily treatment than for the 4 mg daily treatment. However, according to the modeling and simulation analyses, some patients in this group receiving Toviaz 8 mg daily may have higher Cmax,ss compared to adults. Therefore, the Clinical Pharmacology review team recommended the dose of 4 mg daily for this group, and if needed, the dose in this group may be increased to 8 mg daily.

Pediatric patients weighing greater than 35 kg:
Recommendation: The proposed (b) (4) mg daily dose for pediatric patients weighing >35 kg should be revised to have a starting dose at 4 mg daily and increase to 8 mg daily after one week.

Rationale: All subjects who received Toviaz 8 mg in Study 1047 increased to the 8mg dose after receiving a week of Toviaz 4 mg. Therefore, the Clinical Pharmacology review team recommended the starting dose of 4 mg daily, to be taken for one week, and after 1 week, the dose should be increased to 8 mg daily, as Study 1047 was conducted.

4.6. Devices and Companion Diagnostic Issues

There were no devices and no companion diagnostics included in this application.

4.7. Consumer Study Reviews

Toviaz is available by prescription only. Therefore, over-the-counter, pre-marketing consumer behavior studies are not relevant to this application.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The principal analyses of efficacy and safety included in this sNDA involve data from a Phase 3 efficacy and safety clinical study. Supportive exposure and safety data were obtained from a Phase 2 PK study in pediatric patients with NDO and OAB. Table 1. below lists the studies relevant to this sNDA.

Table 2. Listing of Clinical Trials Relevant to this sNDA

Study ID NCT# Phase	Objective/Study Endpoints	Study Design	Test Product and Dosage Regimen	Number of Subjects	Study Population	Countries
Controlled Studies to Support Efficacy and Safety						
A0221047 **NCT01557244** **Phase 3**	To determine the safety and efficacy of fesoterodine following qd treatment for 12 weeks/Primary endpoint was the mean change in maximum cystometric bladder capacity. (This was followed by a 12 week Safety extension phase.)	Cohort 1: Phase 3, open-label, baseline-controlled, multicenter, comparing 2 doses of drug and active comparator.	Cohort 1: Toviaz 4 mg tablet qd/Toviaz 8 mg tablet qd/ oxybutynin XL qd (In the Safety extension phase subjects on oxybutynin were allocated to either 4 or 8 mg of Toviaz)	Cohort 1: Enrolled: 124 Treated: 124 Completed: 101	Cohort 1: Subjects aged 6-17 years with NDO, and weighing greater than 25 kg	21 Countries: North America: USA, Canada Asia: Japan, Korea, Malaysia, Taiwan Europe: Belgium, Estonia, Finland, France, Greece, Italy, Poland, Russia, Slovakia, Spain, Sweden, Switzerland, Turkey, United Kingdom Africa: South Africa
		Cohort 2: Phase 3, open-label, baseline-controlled multicenter, comparing 2 doses of drug	Cohort 2: Fesoterodine 2 mg BIC qd/ fesoterodine 4 mg BIC qd	Cohort 2: Enrolled: 57 Completed:47	Cohort 2: Subjects aged 6-17 years with NDO, and weighing 15 kg-25 kg	
Uncontrolled Studies to Support Safety						
A0221109 **NCT02501928** **Phase 3**	To investigate the safety and tolerability of fesoterodine following qd long-term treatment for a total of 52 weeks	Phase 3, open-label, long-term treatment study	Cohort 1: Toviaz 4 mg tablet qd/ Toviaz 8 mg tablet qd	Cohort 1: Enrolled:2 Completed: 2 (Both subjects received Toviaz 8 mg)	Subjects aged 6-17 years with NDO, who had completed 24 weeks of Study A0221047 (Cohorts as in Study A0221047)	7 centers in Japan (only 2 of the 12 subjects in this study were on Toviaz tablets)
			Cohort 2: Fesoterodine 2 mg BIC/ fesoterodine 4	Cohort 2: Enrolled: 10 Completed:9		

			mg BIC			
Clinical Pharmacology Studies						
A0221066 **Phase 2**	8 week study to determine the PK of 5-HMT in pediatric OAB patients	An open-label, dose-escalation study	Toviaz 4 mg tablet qd/ Toviaz 8 mg tablet qd	Enrolled: 21 Completed: 21	Subjects aged 8-17 11 with OAB 10 with NDO	

5.2. Review Strategy

The efficacy review focused on urodynamic and bladder diary parameters from Study A0221047 (which will be referred to as Study 1047). The primary efficacy endpoint was the change from baseline in the maximum cystometric bladder capacity at Week 12. Study 1047 contained 2 cohorts based on weight. Cohort 1 was composed of children weighing >25 kg, who were treated with Toviaz tablets. Subjects in Cohort 1 were randomized to 1 of 3 treatment arms: Toviaz 4 mg tablets , Toviaz 8 mg tablets, and oxybutynin XL as an active comparator. Cohort 2 was composed of subjects ≤ 25 kg, who were treated with the new fesoterodine beads-in-capsule (BIC) formulation. Subjects in Cohort 2 were assigned to 1 of 2 treatment arms: fesoterodine 2 mg BIC and fesoterodine 4 mg BIC. The current sNDA submission requests approval of Toviaz tablets only. (b) (4) this Clinical review of efficacy shows the Cohort 1 data only.

For Efficacy, the reader is also referred to the final Statistical reviewer. Both the Sponsor and the statistical review team conducted the primary efficacy analysis and a number of secondary efficacy analyses that included sensitivity analyses using the Baseline observations carried Forward (BOCF) method to impute any missing observations.

For our Safety review, we primarily analyzed safety data from Cohort 1 of Study 1047. We also reviewed pooled data from Study 1047 Cohort 1 and Study 1066 subjects with NDO. We considered the safety data from Study 1047 Cohort 2. Finally, we also reviewed data from Study 1109, the 12-month long-term safety study conducted in Japan with subjects who had participated in Study 1047.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study A0221047

6.1.1. Study Design

Overview and Objective

The primary objective of Study A0221047 was to evaluate the safety and efficacy of Toviaz in pediatric subjects aged between 6 and 17 years with symptoms of NDO.

The secondary objectives were to evaluate the pharmacokinetics (PK) and tolerability of Toviaz in pediatric subjects aged between 6 and 17 years with symptoms of NDO.

Trial Design

Study 1047 was a Phase 3, open-label, multi-region study in pediatric subjects aged 6 years to 17 years with the symptoms of NDO. The study was comprised of two weight cohorts. Cohort 1 involved subjects > 25 kg, and was a three, parallel-arm study of Toviaz 4 mg tablets, Toviaz 8 mg tablets, and oxybutynin XL as an active comparator.

The study consisted of two investigational periods:

- The Efficacy phase--a 12-week three arm phase with an active comparator (oxybutynin XL)

- The Safety phase--a 12-week two arm extension phase without the active comparator, which followed the Efficacy phase

After a screening and medication washout period of up to 12 weeks, subjects were randomized in a 1:1:1 ratio to one of three arms: 4 mg or 8 mg/day of Toviaz tablets or oxybutynin XL at a starting dose of 5 mg once daily.

Reviewer's comment: Because effective treatment existed, a placebo arm was not ethically possible. In this study subjects acted as their own controls. The use of an active comparator provided additional information regarding benefit and risk of the study drug.

Subjects assigned to the Toviaz 8 mg arm started at 4 mg daily for 1 week, and then escalated to 8 mg daily. If subjects could not tolerate the doses they were randomized to, they were to be withdrawn from the study. Subjects who were unable to tolerate a minimum total dose of oxybutynin XL 10 mg once daily were to be withdrawn. Subjects who withdrew from the oxybutynin treatment arm for reasons of tolerability, and who fulfilled all continuation criteria, could be allocated by the investigator to Toviaz treatment at either 4 or 8 mg/day for the remaining 12-week Safety Extension Phase.

At 12 weeks (or earlier if appropriate), subjects in the oxybutynin arm of the study were allocated by the investigator to Toviaz at either 4 mg or 8 mg per day. Subjects underwent a minimum 2-day washout period from oxybutynin prior to starting treatment with Toviaz. All those assigned to the Toviaz 8 mg arm started at 4 mg daily for 1 week and then escalated to 8 mg daily.

Key inclusion criteria for the study were:

1. Age 6-17 years 11 months (at time of first dose)
2. Weight > 25 kg
3. Subjects with stable neurological disease and clinically- or urodynamically-demonstrated

NDO, confirmed urodynamically at Visit 2, by detrusor overactivity or decreased bladder compliance, with decreased maximum cystometric bladder capacity.

4. Subjects >25 kg had to already have the ability to swallow tablets whole, without chewing or crushing. The first dose of medication was given in clinic under observation, and any subject not able to swallow tablets was excluded from the study.

Reviewer's comment: In response to an Information Request from the Division, the Sponsor stated that swallowability was not a cause of any screen failures, and that there were no problems with swallowing documented in the study. However, in a subsequent Information Request the Sponsor reported a survey of factors contributing to difficulties with subject enrollment in Study 1047. In this survey 16.7% of investigators stated that patients' difficulty swallowing the study medication was a reason for enrollment difficulties.

Key exclusion criteria for the study were:

1. Any comorbid condition that, in the opinion of the investigator, would confound study results or increase the risk to subjects e.g., current history of bladder calculus.
2. Subjects required to take or expected to initiate concomitant medications that could interact with the pharmacokinetics and/or pharmacodynamics of fesoterodine or oxybutynin.
3. Subjects with a clinically significant urinary tract infection (UTI) at screening.
4. Subjects with hypocontractile bladder, detrusor underactivity, or a "flaccid" bladder.
5. Subjects with a history of an indwelling urinary catheter within 4 weeks of participation in the study.
6. Subjects not requiring intermittent catheterization who had a post-void residual volume greater than 20 mL as determined by transabdominal ultrasound immediately after urination.

Dose selection

For a thorough discussion of pediatric dose selection for Toviaz, see the ClinPharm review. The Sponsor based dosing for study 1047 on safe and effective exposures in adult patients with OAB, and PK results from study 1066 (a Phase 2 dose-escalation trial), along with modeling and simulation (M&S) analyses. Pharmacokinetic (PK) simulations were conducted based on adult 5-HMT population PK parameters, and allometric scaling of the adult population parameters applied to a distribution of pediatric patients 6-17 years of age and body weights >25 kg. The M&S analyses predicted that plasma 5-HMT exposures of children aged 6-17 years and weighing >25 kg, who were given Toviaz 4mg and Toviaz 8 mg once daily would be similar to 5-HMT exposures in adults given those same doses. This was confirmed by the plasma concentrations from Study 1066.

Reviewer's comment: The Sponsor ultimately proposed dosing of Toviaz 4 mg once daily for pediatric patients weighing (b) (4) kg to 35 kg, and Toviaz 8 mg daily for pediatric patients weighing over 35 kg. We note that neither Study 1066 nor Study 1047 exposed children weighing (b) (4) kg to Toviaz tablets at either the 4 mg or 8 mg dose.

Table 1 provides an overview of the main study design and conduct characteristics:

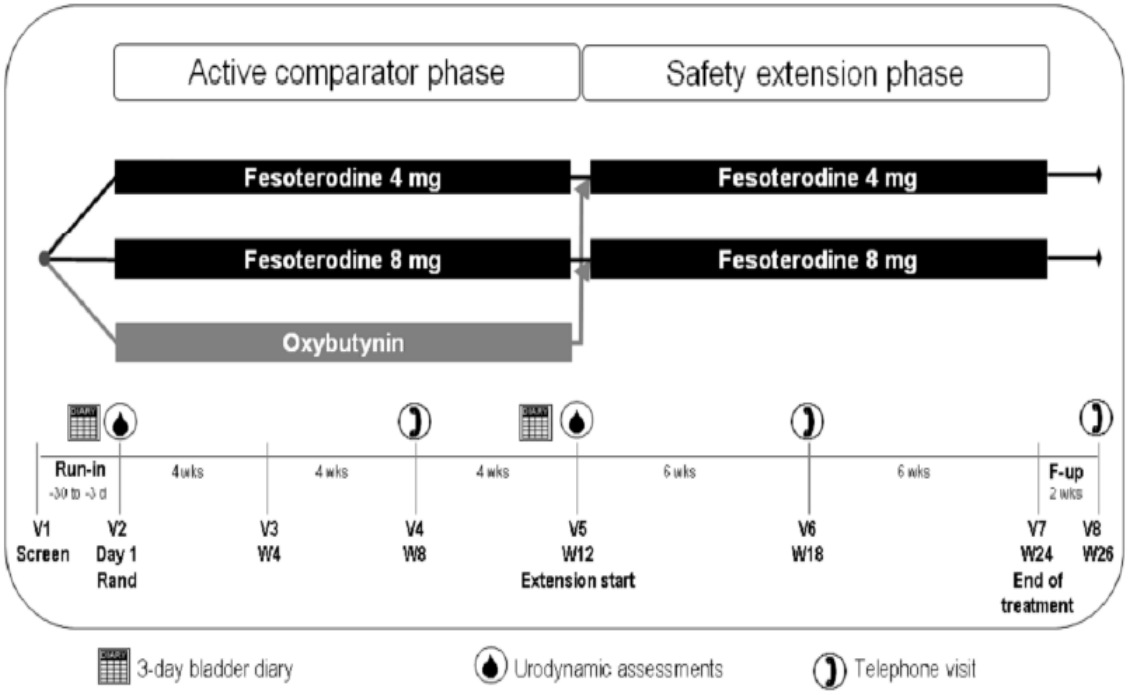
Table 1.Main Study Design and Conduct Characteristics	
Study Drugs	**Cohort 1 (>25 kg):** Toviaz 4 mg or 8 mg/day tablet Oxybutynin ≥10 mg/day tablet Cohort 2 (15 kg -25 kg): Fesoterodine 2 or 4 mg /day BIC
Number of Study Sites	65 sites across North America, Europe, Asia, and South Africa
Number of Patients Enrolled/ Treated	**Cohort 1 (>25 kg): tablets** 124 total enrolled/124 treated Toviaz 4 mg: 42 enrolled/42 treated Toviaz 8 mg: 42 enrolled/42 treated Oxybutynin XL tablet: 40 enrolled/40 treated Cohort 2 (≤25 kg): BIC (b) (4) total enrolled/ (b) (4) treated Fesoterodine 2 mg BIC: (b) (4) enrolled (b) (4) treated Fesoterodine 4 mg BIC: enrolled treated
Primary Efficacy Endpoint	Maximum cystometric bladder capacity (MCBC), defined as maximal tolerable cystometric bladder capacity or until voiding/leaking begins, or at 40 cm H_2O
Secondary Efficacy Endpoints	Additional urodynamic measurements: • Detrusor pressure at MCBC • Presence of involuntary detrusor contraction (IDC) • Bladder volume at first IDC • Bladder compliance Bladder diary assessments: • Mean number of catheterizations and/or micturitions/24 hours • Mean number of incontinence episodes/24 hours • Mean urgency episodes/24 hours (only for sensate subjects) • Mean volume voided per catheterization or micturition

Assignment to Treatment

The study used an automated tele-randomization system incorporating a central randomization scheme. At Visit 2, randomization, subjects were randomly assigned to their treatment group

according to a computer-generated pseudorandom code using the method of random permuted blocks. At Visit 5, start of extension period, subjects in the oxybutynin group were allocated to Toviaz 4 or 8 mg, according to the investigator's judgment. In order to ensure an appropriate balance of subjects in each treatment group across the body weight spectrum, subjects were stratified at randomization into 2 groups depending on their body weight. The lower weight group included all those with a weight of 50 kg or less, and the higher weight group included all those with a weight above 50 kg.

Figure 1. Study Design Schematic



Source: Study 1047 Protocol Amendment 5, p.20

Treatment compliance

Compliance with study medication was assessed using electronic methods. Subjects' compliance was recorded as a protocol deviation if compliance with medication was less than 80% of doses prescribed as measured by pill counts. Subjects with persistently poor compliance were withdrawn. Compliance with medications was assessed by subjects completing a daily electronic dosing log, and by pill counts at Week 12 (Visit 5) and Week 24 (Visit 7). Additionally, compliance with dosing was assessed for at least 3 days prior to PK sampling at Week 4 (Visit 3) and one day prior to urodynamic evaluation at Week 12 (Visit 5).

If a subject withdrew from the study prior to Week 12, the same assessments were performed as were performed at Week 12, if possible. However, urodynamic assessments were only performed in subjects who had been on a stable dose of study medication for at least 2 weeks, and who had not missed any doses in the 3 days prior to the visit. If a subject withdrew from the study after Week 12, the same assessments as at Week 24 were performed, if possible. Subjects who withdrew from the study and who had taken at least 1 dose of study medication were contacted by telephone approximately 2 weeks after stopping study medication, had the same assessments performed as at Week 26.

In regard to "rescue" medications and on-treatment dose adjustment, rescue medication was not discussed. For subjects randomized to the oxybutynin arm only, dose adjustment was possible until the end of Week 4, at which time all subjects were to be on a minimum daily dose of oxybutynin XL 10 mg. After that time, no further dose adjustments were made.

Study Endpoints

The primary efficacy endpoint was the change from baseline to week 12 of treatment in maximum cystometric bladder capacity (MCBC), which was defined as the maximum tolerable cystometric capacity or until voiding/leaking begins or at 40 cm H_2O.

The secondary efficacy endpoints included additional urodynamic measures, symptom measures from voiding diaries, and urine volume measures.

Additional urodynamic measures included:

- Detrusor pressure at maximum bladder capacity
- Bladder volume at first involuntary detrusor contraction (IDC)
- Bladder compliance

Symptom measures from voiding diaries included:

- Mean number of micturitions per 24 hours
- Mean number of catheterizations per 24 hours
- Mean number of incontinence episodes per 24 hours
- Mean number of urgency episodes per 24 hours if applicable (only for sensate subjects)

Urine volume measures included:

- Mean volume voided per micturition
- Mean volume voided per catheterization

Safety endpoints included tests of visual acuity and accommodation, cognitive function testing via the Childhood Behavior Checklist (CBCL) and the Grooved Pegboard Test (GPT), and post-

void residual volume in subjects not performing CIC, or with > 1 urinary tract infection (UTI) during the study.

Reviewer's comment: We re-consulted the Division of Neurology 1 in regard to the neuropsychiatric (cognitive function) monitoring measures for Study 1047. In developing Study 1047, the Sponsor proposed the CBCL and GPT as measures for cognitive function in children because these assessments had been widely employed as cognitive endpoints in clinical studies of school-age children. At that time, the Division of Neurology 1 agreed that these were reasonable, though limited, measures for the purpose intended. The Division sought some measure of assurance that fesoterodine did not have an adverse effect on cognitive function. While there have been concerns raised about the effects of anticholinergics, such as fesoterodine, on cognitive function, there is no widely established neuropsychological profile of anticholinergic-induced cognitive impairment in either children or adults. At the time, it was believed that the CBCL and GPT would provide a degree of assurance concerning adverse effects on cognition. Although a memory-specific measure may have provided additional information, this would have added a burden to the study population. Thus, the CBCL and GPT were assessed to be acceptable for the purpose of providing a cognitive-based safety assessment for Study 1047.

Statistical Analysis Plan

For a detailed review of the Applicant's statistical analysis plan, see the Statistical Review. The statistical plan was finalized before the data were unblinded. The primary analysis set was the full analysis set (FAS), which included all subjects who were randomized and received at least one dose of study medication and who provided baseline data for the primary efficacy endpoint. The Per Protocol Analysis Set (PPAS) included all subjects who completed the active comparator phase of the study, who had no violations of the inclusion/exclusion criteria, and no protocol violations that could affect the efficacy outcome of the study. This group was defined prior to unblinding of the study. The primary analysis was based on the full analysis set (FAS), which consisted of subjects who had had one dose of treatment and one measurement of the primary efficacy endpoint, MCBC. A Baseline Observation Carried Forward (BOCF) and a Last Observation Carried Forward (LOCW) algorithm was used for missing data. No imputation techniques for missing data were employed for the PPAS. All randomized subjects were used for summarizing discontinuations in the Active Comparator Phase and overall, and for data collected at baseline.

Protocol Amendments

There were five amendments to the protocol. For a complete listing and description, see the original NDA submission. Two protocol amendments are most important to the Clinical review:

Amendment 2, dated October 7, 2011, provided for vision testing, cognitive function testing, a telephone call for all treatment groups at Week 1, removal of the PinQ questionnaire, laboratory evaluations at baseline, Week 12 and Week 24,and PK sample collection at Week 4 instead of Week 12.

Amendment 5, dated March 3, 2014, specified an enrollment target that would result in approximately 99 evaluable subjects at Week 12, and extended the enrollment to subjects aged 17 years old. This amendment also allowed for the enrollment of subjects ≤25 kg as a separate cohort within the study (rather than in an entirely separate study, as originally planned), to receive a new fesoterodine beads-in-capsule (BIC) formulation.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant has provided attestation that all studies were conducted in accordance with Guides of Good Clinical Practice (GCP), the Declaration of Helsinki, and in compliance with FDA regulations for informed consent and protection of patient rights.

Financial Disclosure

The Sponsor submitted Form FDA 3454 ("Certification: Financial Interests and Arrangements of Clinical Investigators"), dated November 10, 2020, and completed by J.R. Meloro, Global Data Dissemination, Publications and Transparency Lead, Pfizer Inc. Form 3454 was submitted with an attached list of investigators and certifies that for those investigators, the Sponsor does not have any financial arrangements whereby the value of compensation to the investigator could be affected by the outcome of the study; that the investigators were required to disclose whether they had a propriety interest in the product or a significant equity in the Sponsor, and did not disclose such interests; and that none of the investigators in the list of investigators were the recipient of significant payments. Form 3454 also certifies due diligence in attempts to contact one investigator, from whom the Sponsor was unable to obtain financial information.

Reviewer's comment: The lack of information from this one investigator does not affect the overall study integrity, as the affected study site contributed only (b) (6) *to Study 1047.*

The Sponsor also submitted Form FDA 3455 ("Disclosure: Financial Interests and Arrangements of Clinical Investigators"), dated November 10, 2020, and completed by J.R. Meloro, Global Data Dissemination, Publications and Transparency Lead, Pfizer Inc. This form lists 3 investigators for Study 1047 who received payments greater than the threshold of $24,999. These three investigators worked at clinical investigative sites that enrolled (b) (6) subjects, respectively, into Study 1047. Of these, a total of 3 subjects were randomized in Cohort 1. Of these, 1 subject was randomized to the oxybutynin chloride XL group during the 12-Week efficacy phase, and so does not affect efficacy results for Toviaz. 2 subjects were randomized to receive Toviaz 8 mg during the 12-Week Efficacy phase.

Reviewer's comment: We analyzed the efficacy data for Study 1047, omitting the contributions from the 2 subjects in question, and found no impact on study efficacy conclusions. The data for this analysis is presented in Table 6 below (Efficacy Results-Primary Endpoint).

Patient Disposition

Of the 166 subjects who were screened, 124 (85.5%) were enrolled. Of these 120 (96.8%) were included in the full analysis set (FAS), and 84 (67.7%) were included in the per protocol analysis set (PPAS). Exclusions from the FAS were due to subjects having no maximum cystometric bladder capacity measurement at baseline (1 subject each [2.4%] in the Toviaz 4 and 8 mg arms and 2 subjects [5.0%] in the oxybutynin chloride XL arm.)

Table 3. Summary of Patient Disposition

	Toviaz 4 mg	Toviaz 8 mg	Oxybutynin	Total
	N (%)	N (%)	N (%)	N (%)
Screened: 166				
Screen Failure: 42				
Assigned to Treatment	42 (100)	42 (100)	40 (100)	124 (100)
Treated	42 (100)	42 (100)	40 (100)	124 (100)
Completed	30 (71.4)	36 (85.7)	35 (87.5)	101 (81.5)
Discontinued	12 (28.6)	6 (14.3)	5 (12.5)	23 (18.5)
Analysis for Efficacy:				
Full Analysis Set	41 (97.6)	41 (97.6)	38 (95.0)	120 (96.8)
Per Protocol Analysis Set	26 (61.9)	31 (73.8)	27 (67.5)	84 (67.7)

Source: 1047 Clinical Study Report Table 14.1.1.1a

Protocol Violations/Deviations

There were numerous protocol deviations in Study 1047 for Cohort 1. The most common

categories of deviations were procedure/test not done or procedure/test not performed per protocol. These deviations were evenly distributed between subjects randomized to the Toviaz 4 mg (N=44) and Toviaz 8 mg (N=43) arms. Most of these involved incomplete or untimely bladder diary entries. Other common deviations involved improper testing of visual acuity and visual accommodation, and incomplete or missing CBCL testing. Two subjects in the Toviaz 4 mg arm and one subject in the Toviaz 8 mg arm had protocol deviations involving urodynamic testing, which resulted in their exclusion from the study.

Reviewer's comment: Review of the various protocol deviations does not show a pattern likely to have an impact on the efficacy results of Study 1047. Problems in visual testing and CBCL testing did affect interpretability of these safety findings, as discussed in later sections of this review.

Demographic and Baseline Characteristics

Subjects were randomized in 65 clinical sites worldwide. Overall, of the 124 total patients age 6 to 17 years, 55.6% were male and 44.4% were female. The mean patient age was 11.0 years (with 72% aged 6-12, and 29.8% aged 13-17). The mean patient weight was 42.9 kg. 52.4% of subjects were White, 43.5% were Asian, 2.4% were Black/African American. 4.8% were Hispanic/Latino. 13 (10.5 %) subjects were from the U.S. Most subjects were from Europe (55%) or Asia (52%).

Reviewer's comment: Study 1047 was conducted predominantly outside the U.S. The racial distribution of subjects in the study does not represent the racial distribution of children with NDO in the U.S. However, in response to an Information Request from the Division, the Sponsor stated that since there are no racial differences in the PK of 5-HMT, the study findings are applicable to the U.S. population. In response to a second Information Request from the Division on this issue, the Sponsor further explained how they made efforts towards enrolling a diverse population.

Generally, baseline characteristics were evenly distributed among treatment arms, but there were more male subjects than female subjects in the Toviaz 4 mg and oxybutynin chloride XL arms. Additionally, the proportion of White subjects was lower in the oxybutynin chloride XL arm than in the Toviaz arms, and the proportion of Asian subjects was higher in the oxybutynin chloride XL arm than in the Toviaz arms.

Table 4. Table of Demographic Characteristics

Demographic Parameters		Treatment Group		
	Toviaz 4 mg (N=42) n (%)	Toviaz 8 mg (N= 42) n (%)	Oxybutynin (N=40) n (%)	**Total** (N=124) n (%)
Sex				

Male	26 (61.9)	20 (47.6)	23 (57.5)	69 (55.6)
Female	16 (38.1)	22 (52.4)	17 (42.5)	55 (44.4)
Age				
Mean years (SD)	10.7 (2.6)	11.2 (2.7)	11.5 (2.9)	11.0 (2.8
Min, max (years)	7.0, 17	6.0, 16.0	6.0, 17	6.0, 17.0
Age Group				
≥6-9	15 (35.7)	15 (35.7)	15 (37.5)	45 (36.3)
≥10-12	15 (35.7)	14 (33.3)	13 (32.5)	42 (33.9)
≥ 13-17	12 (28.6)	13 (31.0)	12 (30.0)	37 (29.8)
Weight (kg)				
Mean (SD)	43.3	42.0	43.2	42.9
Min, max	25.5, 96	25.1, 73	25.9, 73	25.1, 96.0
Weight Group				
≤ 50 kg	30 (71.4)	31 (73.8)	29 (72.5)	90 (72.6)
>50 kg	12 (28.6)	11 (26.2)	11 (27.5)	34 (27.4)
Race				
White	24 (57.1)	24 (57.1)	17 (42.5)	65 (52.4)
Black or African American	2 (4.8)	0	1 (2.5)	3 (2.4)
Asian	14 (33.3)	18 (42.9)	22 (55.0)	54 (43.5)
Other*	2 (4.8)	0	0	2 (1.6)
Ethnicity				
Hispanic or Latino	3 (7.1)	2 (4.8)	1 (2.5)	6 (4.8)
Not Hispanic or Latino	39 (92.9)	40 (95.2)	39 (97.5)	118 (95.2)
Region				
United States	4 (9.5)	5 (11.9)	4 (10.0)	13 (10.5)
Rest of the World	38 (90.5)	37 (88.1)	36 (90.0)	111 (89.5)
North America	5 (11.9)	5 (11.9)	4 (10.0)	14 (11.3)
South America	0	0	0	0
Europe	20 (47.6)	21 (50)	14 (35)	55 (44.4)
Asia	14 (33.3)	16 (38.1)	22 (55)	52 (41.9)
Africa	3 (7.1)	0	0	3 (2.4)

**Data on race and/or ethnicity were not collected because of local regulations.*
"Other" includes 1 subject classified as "North American Indian," and 3 subjects classified as "Mixed."

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All patients had NDO, defined as per the eligibility criteria in the study protocol. The average length of time that a patient had previously experienced NDO was approximately 7 years. Medical history was generally evenly distributed between treatment groups. The following neuro problems were reported in some children: congenital hydrocephalus, developmental hip dysplasia, lipomeningocele, meningocele, meningomyelocele, microcephaly, neural tube defect,

spina bifida, spina bifida occulta, syringomyelia.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Mean treatment compliance during the Active Comparator Phase was similar across all treatment arms: 96.7% for the Toviaz 4 mg arm; 96.6% for Toviaz 8 mg arm; and 97.4% for oxybutynin arm.

Concomitant medications during the Active Comparator Phase included antibacterials for systemic use in 59.5% and 38.1% of subjects in the Toviaz 4 mg and Toviaz 8 mg arms respectively; drugs for constipation in 19% and 31% of subjects in the Toviaz 4 mg and Toviaz 8 mg arms respectively; and ophthalmological in 33.3% and 26.2% of subjects in the Toviaz 4 mg and Toviaz 8 mg arms respectively.

During the Active Comparator Phase in the Toviaz 4 mg group three subjects took oxybutynin, and one took trospium chloride. In the Toviaz 8 mg group one subject took solifenacin and one subject took terazosine.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the change from baseline in maximum cystometric bladder capacity (MCBC) after 12 weeks of treatment. Treatment with Toviaz 4 mg and 8 mg tablets resulted in improvements from baseline to Week 12 in MCBC, with greater changes from baseline for Toviaz 8 mg than for Toviaz 4 mg. The improvement from baseline in the primary efficacy endpoint observed for Toviaz 8 mg was of comparable magnitude to that of oxybutynin chloride XL.

Table 5. Change from Baseline in Maximum Cystometric Bladder Capacity (mL) at Week 12

MCBC (mL) -Mean Baseline and Change from Baseline to Week 12			
	Toviaz 4 mg	Toviaz 8 mg	Oxybutynin XL
N	41	41	38
Baseline (mean)	195.1	173.3	164.1
Change from Baseline LS mean (95% CI)	58.1 (28.8, 87.4)	83.4 (54.2, 112.5)	87.2 (56.8, 117.5)

MCBC: maximal tolerable cystometric bladder capacity or until voiding/leaking begins, or at 40 cm H_2O.
N: all subjects who received at least 1 dose and provided baseline MCBC values.
Source: 1047 Clinical Study Report Table 9, and Review by Yun Tang

As mentioned in Section 6.1.2 Financial Disclosure, an investigator receiving compensation in excess of $25,000 contributed (b) (6) subjects to Study 1047. Those (b) (6) subjects were randomized to receive Toviaz 8 mg during the 12 Week Efficacy phase. And analysis omitting these (b) (6) subjects showed continued improvement from baseline in MCBC in the Toviaz treatment

groups, with little change in the MCMC results, as shown in Table 6.

Table 6. Change from Baseline in Maximum Cystometric Bladder Capacity (mL) at Week 12-omitting subjects (b) (6).

MCBC (mL) -Mean Baseline and Change from Baseline to Week 12			
	Toviaz 4 mg	Toviaz 8 mg	Oxybutynin XL
N	41	(b) (4)	38
Baseline (mean)	195.1	174	164.1
Change from Baseline LS mean (95% CI)	58.1 (28.8, 87.4)	77 (47, 107)	87.2 (56.8, 117.5)

Source: Review by Yun Tang

Analyses of the primary endpoint were carried out for age and weight subpopulations, as shown in the following tables.

Efficacy, based on the primary efficacy endpoint, was also demonstrated for the age subgroups of children 6-11 years old, and 12-17 years old.

Table 7. Efficacy Results – Primary Endpoint by Age (FAS)

MCBC (mL) -Mean Baseline and Change from Baseline to Week 12			
	Toviaz 4 mg	Toviaz 8 mg	Oxybutynin XL
6-11 years old			
N	27	24	24
Change from Baseline LS mean (95% CI)	49 (9, 85)	87 (48, 126)	83 (43, 123)
12-17 years old			
N	14	17	14
Change from Baseline LS mean (95% CI)	74 (24, 135)	78 (31, 124)	95 (42, 148)

Source: Review by Yun Tang

Efficacy by weight group (>25kg – 35 kg; >35kg), based on the primary efficacy endpoint, is shown in Table 8 below.

Table 8. Efficacy Results-Primary Endpoint by Weight Group

MCBC (mL) -Mean Baseline and Change from Baseline to Week 12			
	Toviaz 4 mg	Toviaz 8 mg	Oxybutynin XL
> 25kg-35 kg			
N	13	13	13

Change from Baseline LS mean (SD)	47.2 (43.6)	53.2 (64.7)	79.3 (110.2)
> 35 kg			
N	21	27	22
Change from Baseline LS mean (SD)	76.0 (103.3)	102.0 (105.3)	110.3 (114.1)

Source: Sponsor Integrated Summary of Efficacy Table 38.

(b) (4)

Reviewer's comment: Based on the efficacy results shown in Tables 8 and 9, and PK modeling, the Sponsor originally proposed the following doses: Toviaz 4 mg in pediatric patients 6 years of age and older weighing (b) (4) to 35 kg, and Toviaz 8 mg in pediatric patients 6 years of age and older weighing > 35 kg. The reviewer is referred to previous sections of this review and to the ClinPharm review for discussion of final dose selection considerations.

(b) (4)

Data Quality and Integrity

According to the Sponsor all study sites were initiated during a sponsor/investigator meeting or at a site visit by the sponsor or designated representative. Each site was provided with instructional manuals to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data. The Sponsor states that the study was monitored through routine center visits. At these visits, study procedures were reviewed, case report form/data collection tool data were compared to original clinical records, data queries were resolved, and protocol deviations were discussed with the investigator. Compliance oversight leaders performed on-site and remote oversight to assess monitoring effectiveness and to ensure compliance with the study protocol by investigational sites according to ICH/GCP, applicable standard operating procedures and local regulation. Quality assurance audits were performed at 21 centers.

Efficacy Results – Secondary and other relevant endpoints

The secondary efficacy endpoints included additional urodynamic measures and patients' e-diary symptom endpoints including urinary urgency and urge incontinence measures, as well as measures of voided urine and bladder catheterization volumes.

Reviewer's comment: The Sponsor provided results and analyses for multiple secondary endpoints. While we considered all results of all secondary efficacy endpoints, in this section, we provide results and analyses only for selected secondary endpoints.

The following are the additional urodynamic parameters analyzed by the Sponsor. The items shown in bold font have been selected for additional discussion in this section.

1. Detrusor pressure at maximum bladder capacity
2. **Presence of IDC**
3. **Bladder volume at first IDC**
4. **Bladder compliance** (Δ volume/ Δ detrusor pressure)
5. Mean number of micturitions/24 hrs.
6. Mean number of catheterizations/24 hrs.
7. Mean number of micturitions and catheterizations combined/24 hrs.
8. **Mean number of incontinence episodes/24 hrs.**
9. Mean urgency episodes/24 hrs. if applicable (only for sensate subjects)
10. Mean volume voided per micturition
11. **Mean volume per catherization**

Detrusor pressure at maximum bladder capacity: Treatment with Toviaz 4 and Toviaz 8 mg resulted in decreases from baseline to Week 12 in detrusor pressure at maximum bladder capacity. Mean change from baseline for Toviaz 4 mg and 8 mg was
-2.9 and -1.6, respectively.

Table 10. Efficacy Results-Detrusor Pressure at Maximum Bladder Capacity

Detrusor pressure at maximum bladder capacity (cmH_2O)			
	Toviaz 4 mg (N=41)	Toviaz 8 mg (N=41)	Oxybutynin (N=38)
Baseline	26.5	27.2	23.6
Change from baseline (95% CI)	-2.9 (-7.6, 1.9)	-1.6 (-6.3, 3.1)	-2.4 (-7.3, 2.5)

N is the number of patients who took at least one dose and had valid endpoint data at baseline.
Source: 1047 Clinical Study Report Table 11.

Reviewer's Comment: We note that for all three treatment arms, the confidence intervals for mean changes from baseline in detrusor pressure at maximum volume included zero (0). We approach the statistical interpretation of these secondary endpoint data with caution because they are descriptive data only.

Presence of IDC: At Week 12, all study arms showed a numeric decrease in presence of IDC for subjects who had IDC at baseline. Fewer than 5% of subjects in any treatment arm worsened from baseline to Week 12.

Table 11. Efficacy Results-Presence of IDC

Shift Table: Presence of IDC at Baseline and at Week 12							
		Toviaz 4 mg (N=41)		Toviaz 8 mg (N=41)		Oxybutynin (N=38)	
	Presence of IDC?	***Yes***	***No***	***Yes***	***No***	***Yes***	***No***
Baseline	**Yes**	18 (44)	9 (22)	18 (44)	18 (44)	18 (47)	14 (37)
	No	2 (5)	12 (29)	1 (2)	4 (10)	0	6 (16)

N is the number of patients who took at least one dose and had valid endpoint data at baseline.
Source: Review by Yun Tang

Bladder volume at first IDC: Treatment with both Toviaz 4 and Toviaz 8 mg resulted in increases from baseline to Week 12 in bladder volume at first IDC.

Table 12. Efficacy Results-Bladder volume at first IDC

Bladder volume at first IDC (mL) at Week 12			
	Toviaz 4 mg (N=26)	Toviaz 8 mg (N=36)	Oxybutynin (N=32)
Baseline	89	89	77
Change from Baseline (95% CI)	31 (2.4, 58.6)	26 (2.2, 49.9)	41 (16, 67)

N is the number of patients who took at least one dose and had endpoint data > 0 at baseline.

Source: Review by Yun Tang

Bladder compliance (Δ volume/ Δ detrusor pressure): Treatment with both Toviaz 4 and Toviaz 8 mg resulted in numerical increases from baseline to Week 12 in bladder compliance.

Table 13. Efficacy Results-Bladder compliance

Bladder compliance (mL/cmH_20) at Week 12			
	Toviaz 4 mg (N=40)	Toviaz 8 mg (N=41)	Oxybutynin (N=38)
Baseline	13.8	10.1	14
Change from Baseline (95% CI)	6.4 (-0.5, 13.3)	5.4 (-1.5, 12.3)	11 (4, 18)

N is the number of patients who took at least one dose and had endpoint data > 0 at baseline.
Source: Review by Yun Tang

Reviewer's Comment: We note that for the two Toviaz treatment arms, the confidence intervals for mean changes from baseline in detrusor pressure at maximum volume included zero (0). We approach the statistical interpretation of these secondary endpoint data with caution because they are descriptive data only.

Mean number of micturitions/24 hrs.: Treatment with Toviaz 4 and 8 mg resulted in decreases in the mean number of micturitions per 24 hrs. These data are not shown here. (At baseline, the mean number of micturitions per 24 hours ranged from 3.51 to 3.75 across treatment arms.)

Mean number of catheterizations/24 hrs.: Treatment with Toviaz 4 and 8 mg and oxybutynin resulted in decreases from baseline to Week 12 in the mean number of catheterizations per 24 hours. These data are not shown here. (At baseline, the mean number of catheterizations per 24 hours ranged from 3.73 to 4.24 across treatment arms.)

Thus, Toviaz 4 and 8 mg and oxybutynin resulted in decreases from baseline to Week 12 in the mean number of micturitions and catheterizations combined per 24 hours. (At baseline, the mean number of micturitions or catheterizations combined per 24 hours ranged from 4.72 to 5.37 across treatment arms.)

Mean number of incontinence episodes/24 hrs.: Treatment with Toviaz 4 and Toviaz 8 mg resulted in decreases from baseline to Week 12 in the mean number of incontinence episodes per 24 hours. These data are shown in table 14 below. (At baseline, the mean number of incontinence episodes per 24 hours ranged from 2.68 to 3.12 across treatment arms.)

Table 14. Efficacy Results-Mean number of incontinence episodes per 24 hours

Mean Number of Incontinence Episodes per 24 Hours at Week 12			
	Toviaz 4 mg (N=33)	Toviaz 8 mg (N=33)	Oxybutynin (N=35)
Mean Baseline (SD)	2.8 (1.8)	2.7 (1.5)	3.1 (2.4)
Mean Week 12 (SD)	2.4 (1.6)	1.9 (1.5)	2.0 (1.5)
Mean CFB at Week 12 (SE)	-0.5 (0.2)	-0.9 (0.2)	-1.0 (0.2)
95% CI of mean CFB	(-0.9, 0)	(-1.4, -0.4)	(-1.5, -0.6)

N is the number of patients who took at least one dose and had endpoint data > 0 at baseline.
Source: Review by Yun Tang

Mean urgency episodes/24 hrs. if applicable (only for sensate subjects): Treatment with Toviaz 4 and 8 mg and oxybutynin resulted in decreases from baseline to Week 12 in the mean number of urgency episodes per 24 hours. These data are not shown here. (At baseline, the mean number of urgency episodes per 24 hours ranged from 2.01 to 2.73 across treatment arms.)

Mean volume voided per micturition: Treatment with Toviaz 4 and 8 mg and oxybutynin resulted in numerical increases from baseline to Week 12 in the mean volume voided per micturition. These data are not shown here. (At baseline, the mean volume voided per micturition ranged from 101.96 to 173.51 mL across treatment arms.)

Mean volume per catherization: Treatment with Toviaz 4 and 8 mg and oxybutynin resulted in increases from baseline to Week 12 in the mean volume per catheterization. These data are shown in Table 15 below. (At baseline, the mean volume per catheterization ranged from 118.16 to 147.80 mL across
treatment arms.)

Table 15. Efficacy Results-Mean volume voided per catheterization

Mean volume voided per catheterization (mL) at Week 12			
	Toviaz 4 mg (N=36)	Toviaz 8 mg (N=32)	Oxybutynin (N=28)
Baseline	148	118	118
Change from baseline (95% CI)	29 (-1, 60)	47 (15, 20)	46 (11, 81)

N is the number of patients who took at least one dose and had endpoint data > 0 at baseline.
Source: Review by Yun Tang

Dose/Dose Response

For a thorough discussion of dose selection and dose response the reader is referred to the Clinical Pharmacology review. In brief, the observed plasma concentrations of 5-HMT in fesoterodine-treated subjects increased proportionally with fesoterodine 4 and 8 mg doses when administered as Toviaz tablets. Based on the primary efficacy endpoint and some secondary efficacy endpoints, Toviaz 8mg appeared to provide a larger treatment effect than Toviaz 4 mg.

Durability of Response

Study 1047 assessed urodynamics at baseline and at Week 12. Therefore, durability of response beyond Week 12 was not measured. There may be indirect evidence of response provided by the paucity of drop-outs seen during the safety extension phase. One subject in the Toviaz 4mg arm and two subjects in the Toviaz 8 mg arm discontinued with "insufficient clinical response" as the reason. Drugs in the class do not show waning of effect.

Persistence of Effect

The reader is referred to the previous section, entitled "Durability of Response."

Additional Analyses Conducted on the Individual Trial

Population PK modeling was conducted in Study 1047. For a discussion of those data and analyses, the reader is referred to the Clinical Pharmacology review.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Efficacy is supported by study 1047 alone. Therefore, this section is not applicable to this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Because the overall study population was small (n=124) and included very small numbers of subjects from different racial subgroups, efficacy in various racial subgroups of pediatric patients with NDO is unknown.

7.2.2. Other Relevant Benefits

Toviaz adds an additional once daily oral option for the treatment of NDO in pediatric patients.

7.3. Integrated Assessment of Effectiveness

Through the achievement of both the primary and several secondary endpoints, substantial evidence of effectiveness has been demonstrated for Toviaz for the treatment of pediatric patients with NDO ages 6 to 17 years. Study 1047 demonstrated mean increases in MCBC at 12 weeks of 58.1 mL for Toviaz 4 mg and 83.4 mL for Toviaz 8 mg. Both these increases are clinically meaningful.

Although caution is advised when comparing efficacy results across studies, the improvement in mean MCBC observed for Toviaz in Study 1047 is comparable to/or exceeds those of the currently approved first-line oral therapies. For example, oxybutynin syrup, the mean MCBC change from baseline (230 mL) to 24 weeks (279 mL) was 49 mL, for solifenacin oral suspension, the mean MCBC change from baseline (224 mL) to 24 weeks (279 mL) was 55 mL, and for mirabegron oral suspension and tablets, the mean increase in MCBC from baseline (188 mL) to 24 weeks (275 mL) was 87 mL.

Clinical meaningful benefit is supported by secondary efficacy analyses, which showed improvements in several urodynamic parameters including decrease in detrusor pressor at maximum bladder capacity, decrease in the number of involuntary detrusor contractions (IDC) at Week 12 compared to baseline, and increase in bladder volume at first IDC.

These findings support the applicants proposed indication. For a discussion of dose selection for different weight categories, including the differences between the Sponsor's original proposals and the final agreed-upon labeled dosing instruction for different weight categories, the reader is referred to prior sections of this review and to the Clinical Pharmacology review.

Of note, Study 1047 incorporated an active comparator, oxybutynin chloride XL. Although formal statistical comparative analyses with oxybutynin were not appropriate for the design of this study, informal comparisons were conducted and provide supportive information about efficacy and safety of Toviaz tablets relative to a widely used drug for the indication.

Finally, Study 1047 does not provide information about durability of efficacy beyond 12 weeks. Study 1109 followed a small number of Japanese subjects (n=11) for 52 weeks. However, we note that only 2 subjects in Study 1109 were enrolled in Cohort 1, providing insufficient data for efficacy analyses and conclusion regarding durability of efficacy.

8. Review of Safety

Safety Summary
There was sufficient exposure to Toviaz to conduct a safety assessment for the indication. Toviaz was generally well tolerated in pediatric patients. The safety profile of Toviaz in pediatric patients with NDO is consistent with the safety profile of Toviaz in adults. There are no new or unresolved safety issues.

8.1. Safety Review Approach

The Sponsor's pediatric clinical development program included a Phase 2 PK study (1066) in patients with NDO and OAB symptoms and a Phase 3 study in patients with NDO (1047), and a long-term safety study (1109).

Our primary safety review focused on Study 1047 Cohort 1. We also reviewed safety data for both cohorts from study 1047, as well as the long -term extension study 1109, and the dose-ranging study, Phase 2 1066. (Refer to Table 2. Listing of Clinical Trials Relevant to this sNDA in Section 5.1.**)**

8.2. Review of the Safety Database

The Safety Analysis Set was defined as all subjects who received at least one dose of study medication at any time during the study (ie, in either study phase). (The Sponsor also defined an Active Comparator Safety Set, a Safety Extension Phase Safety Set, and an Overall Study Safety Set. These definitions are listed in Table 16.)

Table 16. Safety Analysis Sets

Active Comparator Safety Set	All subjects who received at least 1 dose of study medication during the Active Comparator Phase.	Safety
Safety Extension Phase Safety Set	All subjects who received at least one dose of study medication during the Safety Extension Phase.	Safety
Overall Study Safety Set	Subjects who were randomized to Toviaz during the Active Comparator Phase and received at least 1 dose of study medication during both phases of the study.	Safety
Safety Analysis Set	All subjects who received at least 1 dose of study medication at any time during the study.	Safety

The Applicant pooled safety data reported for 95 total subjects with NDO administered Toviaz 4 and 8 mg tablets QD, AEs from clinical studies of Toviaz conducted in these subjects were pooled as follows: data from Cohort 1 of Study 1047 (Active Comparator Phase; N = 84) were pooled with data from subjects with NDO in Study 1066 (N = 11). As subjects in Study 1066 were administered both Toviaz 4 and 8 mg tablets QD, data from an individual subject in Study 1066 could be pooled with data from subjects in both the Toviaz 4 and 8 mg tablets QD arms in Study 1047. Clinical laboratory evaluations, vital signs, physical findings, and other data were not pooled and were evaluated instead using individual study data.

8.2.1. Overall Exposure

The Applicant and FDA agreed to the size of the safety population in pre-sNDA meetings. In total, 131 pediatric patients aged ≥ 6 years with NDO were treated with Toviaz in clinical trials (the Phase 2 and Phase 3 studies).

Table 17. All pediatric subjects with NDO exposed to Toviaz

Safety Database for the Toviaz Pediatric sNDA Individuals exposed to any Toviaz in this development program for the indication under review N= 131 (N is the sum of all available numbers from the columns below)		
Clinical Trial Groups	Toviaz 4 mg (n= 69)	Toviaz 8 mg (n= 73)
Study 1047[1]	58	62
Study 1066 [2]	11	11

[1]The numbers for Study 1047 include subjects who took oxybutynin in the efficacy phase and took Toviaz in the safety phase.
[2]Study 1066 was a cross-over study. All subjects received both doses of Toviaz, so a total of 11 subjects took both doses of Toviaz in Study 1066.

Table 18. All pediatric subjects taking at least one dose of fesoterodine

Safety Database for fesoterodine Individuals exposed to at least one dose of fesoterodine in the pediatric development program for fesoterodine (includes both NDO and OAB)				
Clinical Trial Groups	4 mg tab (n= 79)	8 mg tab (n=82)	2 mg BIC (n=28)	4 mg BIC (n=29)
1047 Cohort 1	58	62	(b) (4)	
1047 Cohort 2	---	---		
1109[5]	0	2		
1066 (11 NDO + 10 OAB)	21	20		

[1] *Study drug* means the drug being considered for approval.
[2] to be used in product's labeling
[3] If placebo arm patients switch to study drug in open label extension, then the sample n should count those patients only once; do not count

twice patients who go into extension from randomized study drug arm
[4] Include n in this row only if patients exposed to the study drug for indication(s) other than that in the marketing application have been included in the safety database under review.
[5]Study 1109 was an extension of Study 1047. No additional subjects were added.

Table 19. Duration of exposure to Toviaz*

	Number of patients with NDO exposed to Toviaz for:			
Dosage	>= 1 dose	>= 12 weeks	>= 24 weeks	>= 12 months
4 mg	N= 69	N= 48	N= 30	N=0
8 mg	N= 73	N= 60	N= 36	N=2

*Study 1047 contributed 84 subjects and was of 24 weeks duration. Study 1066 contributed 11 subjects and was of 8 weeks duration. Study 1109 enrolled subjects from Study 1047 for a total of 12 months of exposure to Toviaz.

8.2.2. Relevant characteristics of the safety population:

Safety analyses were done primarily on Cohort 1 of Study 1047. Details of relevant characteristics of the safety population can be found in **Demographic and Baseline Characteristics** under Section 6.1.2.

8.2.3. Adequacy of the safety database:

The extent of the safety database was determined by the relative infrequency of this condition in the population, especially in the United States. There is no reason to expect region-based differences in the underlying etiologies contributing to NDO, in the clinical management of NDO, nor race-based differences in drug exposure or pharmacology for Toviaz tablets in the pediatric NDO population. Therefore, the data in this this program, which included predominantly non-US patients, and did not represent the US population racially, can be generalized to pediatric patients of diverse races with NDO in the US, and does not raise concerns regarding the adequacy of the safety database.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The overall quality of the submission was good. The information was well-organized and readily located. However, the following deficiencies were identified:

- No children weighing ≤ 25 kg received Toviaz 4 mg tablets. Therefore, safety assessments for Toviaz tablets for this weight cohort are lacking.

  Reviewer's comment: [redacted] (b) (4)

- Ophthalmologic testing lacked necessary refractive error testing, and suffered from other problems in testing technique, rendering the collected data uninterpretable.

- Neuropsychiatric (cognitive) testing was done using the Childhood Behavior Checklist (CBCL) and the Grooved Pegboard Test (GPT). These tests have been widely employed in clinical and epidemiological studies in both adults and school age children. However, these scales alone do not adequately evaluate cognition. For example, they measure only a relatively circumscribed array of cognitive domains.

8.3.2. Categorization of Adverse Events

The Sponsor's process for recording, coding and categorizing AEs, as well as their approach to safety analyses were reasonable and appropriate. Adverse events (AE)s were reported spontaneously. The Sponsor categorized adverse events as Tier 1 and Tier 2.
Tier 1 were adverse events of special interest (AESI), which included, but were not limited to, the following: anticholinergic events (e.g., constipation, dry eyes, dry mouth); CNS effects such as behavioral changes (e.g., aggression), decreased cognitive function, headache, seizures, and somnolence; and visual effects (e.g., accommodation disorder, blurred vision, and amblyopia).
Tier 2 events were those that were identified in at least 4 subjects in any treatment arm. In Cohort 1, these were constipation, diarrhea, dry mouth, headache, influenza, nasopharyngitis, urinary incontinence, UTI, and viral upper respiratory tract infection.

8.3.3. Routine Clinical Tests

Details of the routine clinical testing, including various clinical laboratory tests, are reviewed in the related sections of this review, and this testing was adequate.

8.4. Safety Results

For Study 1047 during the Active Comparator Phase, treatment emergency adverse events (TEAE)s were reported for 61.9% of subjects in the Toviaz 4 mg arm, 47.6% of subjects in the Toviaz 8 mg arm, and 75.0% of subjects in the oxybutynin arm. The following sections provide summary information on deaths, serious adverse events, discontinuations due to AEs, commonly reported TEAEs, laboratory results, and special safety tests.

8.4.1. Deaths

No deaths were reported.

8.4.2. Serious Adverse Events

For Study 1047 Cohort 1, a total of 12 serious adverse events (SAEs) were reported in 8 (6.5%) subjects. Of these, 7 were reported in subjects assigned to Toviaz 4 mg, 4 were reported in subjects assigned to Toviaz 8 mg, and 1 was reported in a subject assigned to oxybutynin. 6 subjects experienced SAEs during the efficacy phase; 2 experienced SAEs during the safety extension phase. No SAEs were considered treatment-related by the investigator. A table of SAEs reported in subjects in Studies 1047, 1066, and 1109, and selected SAE case narratives are presented below.

For Study 1066, 1 subject experienced an SAE while taking Toviaz 8 mg. The event was considered likely treatment-related.

For Study 1047 Cohort 2, assigned to the new fesoterodine BIC formulation, a total of 7 SAEs were reported for 5 subjects. Of these, 4 SAEs were reported in subjects assigned to fesoterodine BIC 2 mg, and 3 SAEs were reported in subjects assigned to fesoterodine BIC 4 mg. No SAEs reported in Cohort 2 subjects were considered treatment-related by the investigator.

For Study 1109, no SAEs were reported for either of the two subjects who participated in Cohort 1. One SAE was reported for the one of the 10 subjects who participated in Cohort 2. This SAE of UTI in a subject assigned to fesoterodine BIC 2 mg was reported as a single occurrence in Study 1047, and was reported again during Study 1109.

Table 20. SAEs reported in Studies 1047, 1066 and 1109

SOC Preferred Term	1047-Cohort 1	1047-Cohort 2	1109	1066
Overall				
Cardiac Disorders				
Gastrointestinal Disorders				
Constipation				(b) (6) 8mg
Peritonitis	(b) (6) 4mg			
Peritonitis		(b) (6) 4mgBIC		
Appendicitis	4mg			
Appendicitis				
Infections and Infestations				
Acute Pyelonephritis	8mg			
Acute Pyelonephritis	oxy			
Dengue Fever		4mgBIC		
Epididymitis	8mg			
Urinary Tract Infection	4mg			
Urinary Tract Infection		2mgBIC	(b) (6)	
Urinary Tract Infection		4mgBIC		
Viral Infection	8mg			
Injury, Poisoning and Procedural Complications				
Animal Bite		2mgBIC		
Musculoskeletal and Connective Tissue Disorders				
Epiphysiolysis	4mg			
Reproductive System and Breast Disorders				
Ovarian Cyst	8mg			
Skin and Subcutaneous Tissue Disorders				
Cellulitis				
Condition Aggravated				
Decubitus Ulcer				

Narratives for selected Cohort 1 SAEs

The following SAE case narratives are provided as reasonably reflective of the SAEs reported in Cohort 1.

Case (b) (6) involves an 11-year-old male, taking Toviaz 8 mg, who developed pyelonephritis of moderate severity. The subject developed a fever and "symptomatic urinary tract infection" on Day 125 and was hospitalized. On Day 126 laboratory test results showed C-reactive protein (CRP) of 62.9 mg/L (normal range [NR]: 0 - 8 mg/L), neutrophil count of 95.5% (NR: 40% − 74%), and white blood cell (WBC) count of 26.21 × 103/mm3 (NR: 4.0 − 10.8 × 103/mm3); urinalysis showed 612.3 WBC/HPF (NR: <16.6/HPF). The subject was treated with acetaminophen, ceftriaxone, diclofenac, meropenem, netilmicin sulfate, tramadol hydrochloride, TrophAmine (amino acids NOS), dextrose and sodium chloride. The study drug was permanently discontinued on Day 125 in response to the event of acute pyelonephritis, and to the subject's mother's refusal to continue treatment. The acute pyelonephritis was considered resolved on Day 135. The subject was discharged from the hospital, and from the study on this day. No concomitant medications were ongoing at the time of the SAE. Concomitant non-drug treatment ongoing at the time of the SAE included bladder catheterization (since an unknown date). In the opinion of the Investigator, there was not a reasonable possibility that the acute pyelonephritis was related to the study drug. The Investigator attributed the pyelonephritis to clean-intermittent catheterization.
Reviewer's comment: Antimuscarinic drugs, can cause urinary retention, which could increase the risk of UTI. However, the Clinical Review Team agrees that bladder catheterization posed a risk for UTI and pyelonephritis. The SAE of pyelonephritis may be related to treatment with Toviaz, but any causal relationship is confounded by the pre-existing condition of bladder catheterization.

Case (b) (6) involves a 7-year-old male, taking Toviaz 4 mg, who developed UTI of moderate severity and abdominal pain. His past medical history included bladder hypertrophy, bladder catheterization, and urinary tract infection. On Day 20, the subject underwent urinalysis at a local hospital, which showed white blood cell (WBC) count of 30-49/HPF (normal range: 0-5/HPF), urine leukocyte esterase of 250 Leu/ μ L (2+), and urine sediment-Bacilli: 1913.7/ μ L (2+). The subject was hospitalized for UTI on the same day. No action was taken with the study drug due to the event. The subject was treated with acetaminophen, cefazolin, amoxicillin/clavulanic acid, and gentamycin. After treatment, he was afebrile; urine culture grew Citrobacter koseri >100000. Blood culture had no growth. On Day 24, the subject's condition was stable; the event of urinary tract infection was considered resolved and he was discharged from the hospital.
This subject also experienced an AE of decubitus ulcer on his right foot from Day 21 to Day 62, and another SAE of cellulitis, which began on Day 63, and worsened on Day 64, at which time it was reported as an SAE.
In the opinion of the Investigator, there was not a reasonable possibility that the urinary tract infection was related to the study drug. In the opinion of the Investigator, there was not a reasonable possibility that the cellulitis was related to the study drug.
Reviewer's comment: Antimuscarinic drugs, can cause urinary retention, which could increase the risk of UTI. However, the Clinical Review Team agrees that this subject with a past history of

bladder catheterization and UTI, was at increased risk for UTI. The SAE of UTI may be related to treatment with Toviaz, but any causal relationship is confounded by the pre-existing condition of bladder catheterization. The narrative implies, but does not specify, that the cellulitis resulted from progression of the subject's foot ulcer. We agree that the SAEs of decubitus ulcer and cellulitis were not related to treatment with Toviaz.

Case (b) (6) involves a 13-year-old male, taking Toviaz 4 mg, who developed the SAEs of appendicitis and peritonitis. The subject developed constipation (mild severity) on Day 1, which resolved on Day 21. No treatment was reported. On Day 55 the subject developed the SAEs of appendicitis and peritonitis (severe severity), which resolved on Day 60. No details regarding lab tests or treatment were provided. In the opinion of the Investigator, there was not a reasonable possibility that the appendicitis or peritonitis were related to the study drug. *Reviewer's comment: Antimuscarinic drugs, can cause constipation, which could increase the risk of appendicitis. However, this subject's constipation resolved 34 days prior to his SAE of appendicitis. No additional information regarding the SAEs of appendicitis and peritonitis was provided, other than that they both resolved within 5 days. It is not possible to assess causality.*

Selected Narratives for SAEs arising in Study 1047 Cohort 2

The following SAE case narratives are provided as reasonably reflective of the SAEs reported in Cohort 2.

Case (b) (6) involves a 10-year-old female, taking the new fesoterodine BIC formulation 4 mg, who developed the SAEs of appendicitis and peritonitis. On Day 5 the subject developed abdominal pain, nausea, vomiting (all of moderate severity), and diarrhea (of mild severity). On Day 7 the study drug was temporarily stopped due to these AEs. On Day 11, the subject was diagnosed with the SAE of appendicitis and peritonitis, and was hospitalized. On the same day her lab test results showed leukocytes of 12.61 × 109/L (normal range not specified) and a surgery was performed. The subject was treated with intravenous (IV) paracetamol, IV amoxicillin/clavulanate, and metamizole (Novalgin). On Day 18 the events of abdominal pain, nausea (Investigator causality-not related), vomiting (Investigator causality-not related), diarrhea (Investigator causality-not related), appendicitis (Investigator causality-not related), and peritonitis (Investigator causality-not related) resolved, and the subject was discharged from the hospital. The study drug was restarted on Day 24. The subject completed the study and received the last dose of the study drug on Day 177. In the opinion of the Investigator, there was not a reasonable possibility that the appendicitis was related to the study drug. *Reviewer's comment: Antimuscarinic drugs, can cause constipation, which could increase the risk of appendicitis. However, given the background rate of constipation and of appendicitis in children with NDO and in 10-year-olds in general, it is not possible to assess causality.*

Case (b) (6) involves a 6-year-old male, taking the new fesoterodine BIC formulation 2 mg, who developed the SAE of urinary tract infection. His past medical history includes vesicoureteric reflux and NDO. On Day 18, the subject had nausea and fever. On Day 20, lab tests showed WBC (blood) of 13350/ μ L and WBC (urine) of 220.3/high power field (HPF)(NR: 0.0-4.9/HPF). The subject was hospitalized on that day and treated with intravenous antibiotics (not specified). On Day 22, during the course of the above treatment, the subject developed a decubitus ulcer (mild severity), for which a dressing was applied. On Day 27, the subject was discharged from the hospital on cefalexin. On Day 32, he had an outpatient medical visit at which time the events of UTI and decubitus ulcer were considered resolved. Concomitant non-drug treatments ongoing at the time of the SAE included bladder catheterization. The subject completed the study and received the last dose of the study drug on Day 182. In the opinion of the Investigator, there was not a reasonable possibility that the UTI was related to the study drug.
Reviewer's comment: Antimuscarinic drugs, can cause urinary retention, which could increase the risk of UTI. However, the Clinical Review Team agrees that bladder catheterization posed a risk for UTI, and that the any causal relationship is confounded by the pre-existing condition of bladder catheterization.

Case (b) (6) involves a 6-year-old female, taking the new fesoterodine BIC formulation 4 mg, who developed the SAE of UTI (two occurrences). Her past medical history included vesicoureteric reflux and neurogenic bladder. On Day 46, the subject had fever and UTI (moderate severity) and was hospitalized. She was treated with oral cefixime 200 mg twice a day. No action was taken with the study drug due to this event. On Day 52, the urine culture was positive for *Serratia fonticola*. She was started on intravenous (IV) meropenem 480 mg three times a day. The event of UTI (first occurrence) resolved on Day 62. The subject was discharged from the hospital on an unknown date. On Day 127, the subject again developed UTI of moderate severity, and was subsequently hospitalized. She continued treatment with cefaclor and was additionally treated with IV cefotaxime. No action was taken with the study drug due to this event. The event of UTI (second occurrence) resolved without sequelae on Day 130) and the subject was discharged from the hospital on an unknown date. Concomitant medications ongoing at the time of the SAEs of UTI included cefaclor as a prophylaxis for UTI. Concomitant non-drug treatment ongoing at the time of the SAEs included bladder catheterization for voiding dysfunction. The subject completed the study and received the last dose of fesoterodine on Day 177. In the opinion of the Investigator, there was not a reasonable possibility that either UTI was related to the study drug.
Reviewer's comment: Antimuscarinic drugs, can cause urinary retention, which could increase the risk of UTI. However, the subject had the pre-existing condition of bladder catheterization, which poses a risk for UTI. Furthermore, although a history of previous UTI is not provided, the fact that the subject was receiving antibiotic UTI prophylaxis suggests that she was known to be at risk for UTI. It's the opinion of the Clinical Review Team that any causal relationship is confounded by the subject's pre-existing conditions.

Narrative for Study 1066 SAE

Case (b) (6) involves a 15-year-old female, taking Toviaz 8 mg, who developed the SAE of constipation. Her past medical history included neurogenic bowel and constipation. On Day 30 the dose of Toviaz was escalated from 4 mg to 8 mg. On Day 48, the subject developed upper abdominal pain of mild severity and vomiting of mild severity. These were treated with milk of molasses enema and saline enema, and the events resolved that day. On Day 51, she presented to the emergency department with chills, muscle aches, and constipation. Her basic metabolic panel, complete blood count, and urinalysis were normal. Abdominal x-ray on the same day showed gas and large amount stool in colon. The subject was started on intravenous (IV) fluid and polyethylene glycol electrolyte solution (Golytely) via nasogastric tube. Subsequently, on the same day, the subject was admitted to the inpatient department for "clean out". Toviaz was temporarily interrupted from Day 51 to Day 52, as the subject was hospitalized with nasogastric tube and was unable to take the drug. The subject was treated with IV ondansetron for nausea and was put on a clear liquid diet. On Day 52, after 4 L of Golytely, she had a repeat abdominal x-ray which showed improvement, but stool was still present. The subject continued treatment with macrogol and ibuprofen; and was additionally treated with dextrose and sodium chloride injection, metoclopramide, and soft soap enemas. The enemas were clearer on Day 53. Repeat x-ray showed improvement, but stool was still present. Nonetheless, the event of constipation was considered resolved on Day 53, and the subject was discharged home on polyethylene glycol and saline/soap suds enemas. The study drug was restarted on the same day. On Day 55 the subject also experienced the AE of hematochezia of mild severity. In the opinion of the investigator, there was a reasonable possibility that constipation was related to study drug. In the opinion of the investigator, there was not a reasonable possibility that the upper abdominal pain was related to the study drug but was considered to be due to "other illness-constipation." In the opinion of the investigator, the hematochezia was not related to the study drug.

Reviewer's comment: The Clinical Review Team agrees that the SAE of constipation is possibly related to treatment with Toviaz. Constipation is a known potential side effect of muscarinic antagonists. Although the subject had an underlying history of neurogenic bowel and constipation, her current exacerbation occurred shortly after an increase in Toviaz dose. Since we consider constipation as possibly related, we also consider the AE of upper abdominal pain possibly related to the study drug, as it resolved with treatment for constipation. Since constipation can be a cause of hematochezia, we also consider the AE of hematochezia as possibly related to the study drug.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Study 1047

AEs leading to permanent study discontinuation were reported in 9 subjects in Study 1047. Of these, 6 subjects were in Cohort 1 (all taking Toviaz) and 3 subjects were in Cohort 2 (all taking the new fesoterodine BIC formulation). AES leading to discontinuation are listed in the table below.

Table 21. Discontinuations due to AEs in Study 1047

Subject ID	Age/Sex	MedDRA (v.22.xx) Preferred Term (investigator's verbatim term)	Dose	Last Dose Day	Onset/Stop Day	Outcome	Relationship to Study Drug*
Subjects taking Toviaz tablets							
(b) (6)	7/M	Urinary incontinence (Increased urinary leakage)	4 mg tablet	85	24/85	ongoing	Possible
	12/M	Medication error (medication error)	4 g (supposed to be 8 mg)	128	87,94/128	NA	Not related
	10/M	Fatigue (Tiredness)	4 mg tablet	98	63/177	resolved	Possible
	9/M	Epiphysiolysis (Epiphysiolysis of the distal tibia)	4 mg tablet	65	66/66	resolved	Not related
	11/M	Pyelonephritis acute (acute pyelonephritis)	8 mg tablet	125	125/135	resolved	Not related
	16/F	Product dispensing error (Drug was not dispensed)	8 mg tablet	45	45/45 (?86)	NA	Not related
Subjects taking the new fesoterodine BIC formulation							
(b) (6)	6/F	Hypertonic bladder (NDO progression)	2 mg BIC	106	106/106 (d/c'd on 120)	unknown	Not related. Related to underlying disease
	9/M	Tachycardia (Tachycardia)	2 mg BIC	80	81/88	resolved	Related
	13/M	Dyspnea (intermittent shortness of breath)	2 mg BIC	15	11/15	resolved	Related

*As assessed by the investigator.

The following case narratives are provided as reasonably reflective of the AEs leading to discontinuation that were reported in Study 1047.

Case (b) (6) involves a 7-year-old male, taking Toviaz 4 mg, who developed urinary incontinence, leading to study discontinuation. Other AEs included UTI and constipation. His past medical history included constipation and urinary incontinence, for which he had a permanent catheter placed. On Day 17 the subject was diagnosed with UTI (moderate severity). He was treated with ciprofloxacin, Omnicef (cefdinir), Rocephin (ceftriaxone), Tylenol (paracetamol), Naprosyn (naproxen), and sodium chloride. No action was taken with the study drug due to this event. The urinary tract infection resolved on Day 29. On Day 24, the subject experienced urinary incontinence of moderate severity. No treatment was reported for this event. On Day 28, the subject experienced constipation and diarrhea both of moderate severity. The subject continued treatment with Senokot (Senna glycoside) and was additionally treated with Miralax (polyethylene glycol 3350). No action was taken with the study drug at this time. The study drug was permanently discontinued in response to the event of urinary incontinence, with the last dose taken on Day 85. The subject was discontinued from the study on the same day. In the opinion of the Investigator, there was a reasonable possibility that the urinary incontinence and constipation were related to the study drug.
Reviewer's comment: The patient has a past history of urinary incontinence, requiring placement of a permanent catheter. The SAE of incontinence began during a UTI. These preexisting diagnoses are confounding. There is insufficient detail to assess causality.

Case (b) (6) involves a 12-year-old male, taking Toviaz 4 mg (who was supposed to be on 8 mg), who discontinued due to the AE of medication error. During the efficacy phase, the patient was assigned to oxybutynin, which was not increased as per protocol from 5 mg to 10 mg. On Day 87, he began Toviaz for the safety extension phase. He was assigned to Toviaz 8 mg, but was never titrated up from the 4 mg starting dose. Additional AEs included 2 occurrences of UTI (Days 73-80, and Days 87-101), dry mouth (Day 101), and aggression (Day 124). The aggression resolved on Day 142, 14 days after the last dose of study drug. Concomitant medications ongoing at the time of the AEs included glycopyrrolate (an anticholinergic). The study drug was permanently discontinued due to the event of medication error (failing to increase Toviaz to 8 mg) with the last dose of Toviaz 4 mg taken on Day 128. The subject was discontinued from the study due to medication error without associated adverse event on Day 142. In the opinion of the Investigator, there was not a reasonable possibility that both the occurrences of UTI were related to the study drug (oxybutynin). In the opinion of the Investigator, there was a reasonable possibility that aggression and dry mouth were related to the study drug (Toviaz).
Reviewer comment: This case includes three medication errors described in this narrative: Failure to reach to proper dose of oxybutynin, failure to reach the proper dose of Toviaz, and ongoing treatment with the anticholinergic drug, glycopyrrolate. The study drug was stopped 4

days after the onset of aggression, and it may be that the AE of aggression also contributed to discontinuation from the study. Causality determination with the UTI and aggression events is confounded by patient's background medical condition and his concomitant medications. See additional discussion of this case in Section 8.5.2, Cognitive Function.

Case (b) (6) involves a 10-year-old male on Toviaz 4 mg who developed fatigue**,** restlessness, and weight increased, all of moderate severity on Day 63. No further detail on his symptoms was provided. He discontinued the study on Day 98 due to the event of fatigue. Other AEs included headache, toothache, abdominal pain. In the opinion of the Investigator, there was a reasonable possibility that the fatigue was related to the study drug.
Reviewer comment: Antimuscarinic drugs have been associated with fatigue. Although fatigue is a symptom that can have many causes, it is plausible that Toviaz contributed to this AE. For additional discussion of this case, see Section 8.5.2, Cognitive Function.

Case (b) (6) involves a 6-year-old female on fesoterodine BIC 2 mg, who developed hypertonic bladder of moderate severity. (On Day 15-17 mild dizziness -considered related)
Reviewer's comment: The subject had urodynamic studies on Day 106, the day she received the diagnosis of hypertonic bladder, providing more confidence in the diagnosis of detrusor hyperreflexia. We agree with the investigator that this may represent inadequate treatment of the patient's underlying detrusor hyperreflexia.

Case (b) (6) involves a 9-year-old male on fesoterodine BIC 2 mg, who developed tachycardia. The subject's medical history included constipation, spinal cord operation, pyelonephritis, spinal cord lipoma and paraparesis. The subject took no other concomitant medications. On Day 81 the subject was diagnosed with tachycardia (mild severity) and supraventricular extrasystoles (moderate severity). The subject was monitored by Holter monitor, but no treatment was reported. The subject was discontinued from the study drug (last dose Day 80). The events of tachycardia and supraventricular extrasystoles resolved on Day 88. In the opinion of the Investigator, there was a reasonable possibility that the tachycardia was related to the study drug.
Reviewer's comment: Toviaz has been associated with increases in HR in adults and pediatric patients in Study 1047. Resolution of the tachycardia 8 days after cessation of fesoterodine is consistent with a causal relationship. Final product labeling will inform prescribers about the risk of (b) (4) associated with Toviaz.

Case (b) (6) involves a 13-year-old male on fesoterodine BIC 2 mg, who developed dizziness and dyspnea (both of mild severity) on Day 11. Both AEs worsened to moderate severity on Day 15, and then resolved on the same day, which was the day of the subject's last dose of fesoterodine. The subject took no other concomitant medications. The subject was discontinued from the study on day 19, 4 days after the last dose of study drug. In the opinion

of the Investigator, there was a reasonable possibility that the dizziness and dyspnea were related to the study drug.
Reviewer's comment: There is insufficient detail to assess causality.

Study 1066
No discontinuations due to AEs were reported for Study 1066. However, one subject withdrew from the study after experiencing several AEs. A case narrative for this subject is provided below.

Case (b) (6) involves a 17-year-old, generally healthy female with idiopathic OAB on Toviaz 4 mg, who developed dry eye, dry mouth (both of mild severity) on Day 1. On Day 4, she developed constipation (moderate severity), which resolved on Day 7. On Day 15, the subject developed upper abdominal pain (mild severity). On Day 24, the subject developed a UTI (mild severity). She missed doses of study drug on Days 15, 17, 24, 25, and 28. The subject was no longer willing to participate in the study and discontinued from the study with the last dose of the study drug taken on Day 29. The events of dry eye, dry mouth, upper abdominal pain, and urinary tract infection were considered resolved on Day 29. In the opinion of the Investigator, there was a reasonable possibility that dry mouth and dry eye were related to the study drug. In the opinion of the Investigator, there was not a reasonable possibility that constipation, upper abdominal pain and UTI were related to the study drug.
Reviewer's comment: The types of events that were reported, the timing of the subject's discontinuing the study drug relative to the events, and her subsequent withdrawal from the study after a series of AEs, is consistent with a dropout due to AEs.

8.4.4. Significant Adverse Events

The following AEs were predefined as AEs of special interest (AESI):

- Anticholinergic effects, such as dry mouth, dry eyes and constipation
- CNS effects, such as behavioral changes (e.g., aggression), decreased cognitive function, headache, seizures, and somnolence
- Visual effects, such as accommodation disorder, blurred vision, and amblyopia
- UTI
- Increased post-void residual urine volume

The Sponsor monitored for these AESI. These types of events have been discussed previously in this review and are discussed further in Section 8.5, Analysis of Submission-Specific Safety Issues.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

The most commonly reported adverse reactions in study 1047 were diarrhea, UTI, dry mouth, constipation, abdominal pain, nausea, weight increase and headache.

The table below lists the adverse reactions reported at an incidence greater than or equal to 2% in either group administered Toviaz 4 mg or Toviaz 8 mg, or administered oxybutynin chloride XL 10 mg, in the efficacy phase of Study 1047.

Table 22. Adverse Reactions Reported in ≥2% of Subjects in the 12-Week Efficacy Phase of Study 1047

Preferred term	Toviaz 4 mg (N=42) %	Toviaz 8 mg (N=42) %	Oxybutynin (N=40) %
Diarrhea	11.9	7.1	2.5
Urinary tract infection	9.5	2.4	10.0
Dry mouth	7.1	9.5	27.5
Constipation	7.1	7.1	12.5
Abdominal pain[†]	7.1	4.8	10.0
Nausea	4.8	2.4	5.0
Weight increased	4.8	0	2.5
Headache	4.8	7.1	12.5
Incontinence[°]	2.4	4.8	10.0
Vomiting	0	0	5.0
Pyelonephritis	0	0	5.0

[†]Includes abdominal pain and abdominal pain upper
[°]Includes incontinence and urinary incontinence
Source: Study 1047 report and product label

8.4.6. Laboratory Findings

Analysis of routine clinical laboratory parameters provided no evidence of influence of therapy with Toviaz tablets or fesoterodine BIC on hematology or chemistry test results. No "Hy's Law" cases were reported. No trends in change from baseline in urinalysis were observed.

8.4.7. Vital Signs

Increases from baseline in mean heart rate (HR) were reported for both doses of Toviaz in Study 1047. At Weeks 4 and 12, the increases from baseline in the mean HR for patients treated with Toviaz 4 mg who had at least one follow-up measurement were 4 and 5.5 beats per minute, respectively. At Weeks 4 and 12, the increases from baseline in the mean HR for patients treated with Toviaz 8 mg who had at least one follow-up measurement were 10.4 and 8.9 beats per minute, respectively. At 24 weeks, increases from baseline in the mean HR for patients who initially received Toviaz 4 mg or 8 mg or subsequently transitioned from active comparator to Toviaz 4 mg or 8 mg were 4.7 beats per minute and 7.3 beats per minute, respectively. Increases in HR were generally greater with Toviaz 8 mg than Toviaz 4 mg doses. Compared to oxybutynin, Toviaz use resulted in HR increases leading to a greater proportion of pediatric patients with HRs above the 99th percentile for age. The HR increasing effect of Toviaz was most pronounced in patients less than 12 years of age receiving Toviaz 8 mg. A mild AE of "heart rate increased" was reported for 1 subject in the Toviaz 8 mg arm. The AE was considered related to study treatment by the investigator, and the subject completed the study. The increases in HR observed in Study 1047 with Toviaz 4 mg and 8 mg dosing were not associated with symptoms and did not result in Toviaz discontinuation.

Subjects showed no clinically significant change in mean blood pressure.

8.4.8. Electrocardiograms (ECGs)

EKGs were only performed at screening, but not on-treatment.

8.4.9. QT

QT studies were not conducted.

8.4.10. Immunogenicity

Immunogenicity studies were not conducted.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Visual Acuity and Accommodation

At the Division's request, the Sponsor conducted tests of visual acuity and ocular accommodation in Study 1047 to detect adverse effects of Toviaz on those measurements.

Review of the ophthalmological testing in study 1047 by our OND ophthalmology consultant revealed numerous problems with missing information, including the lack of measurement of refractive error. The lack of key information renders the available data not helpful in detecting an adverse effect of Toviaz on ophthalmological tests. For a number of reasons, establishing causality between Toviaz and ophthalmological adverse effects is difficult. The incidence of myopia in childhood is common, due to the natural growth of the eye. However, absent data on the refractive error, it is not possible to distinguish between myopia, astigmatism and other causes of decreased distance visual acuity. Reduction of accommodative potential may manifest as decreased distance visual acuity. Pharmacologically, muscarinic antagonists can cause accommodation problems and dry eyes, which could manifest as visual problems. It is plausible that some of these cases could be due to effects of Toviaz, but the available information is insufficient to draw that conclusion. The following narratives provide brief information on all cases of ophthalmological adverse events reported in the Toviaz pediatric development program. Some of the cases suggest a causal relationship, including four of the cases below that either had resolution of symptoms on cessation of the drug or an increase in symptoms with increase in dose.

Study 1047

Case (b) (6) involved a 10-year-old female, taking Toviaz 4 mg, who developed worsening myopia on Day 166. The subject had worn eyeglasses for myopia for several years. The subject's last dose of Toviaz was Day 166, and she completed the study on this day. The myopia was ongoing at the time of study completion. In the opinion of the Investigator, there was a reasonable possibility that the worsening myopia was related to the study drug.
Reviewer's comment: Not assessable.

Case (b) (6) involved a 13-year-old male, taking Toviaz 4 mg, who developed myopia of mild severity on Day 97. The last dose of Toviaz was on Day 168. On Day 169 the subject underwent ophthalmologic testing. The myopia was ongoing at the time of study completion. In the opinion of the Investigator, there was not a reasonable possibility that the myopia was related to the study drug.
Reviewer's comment: Not assessable.

Case (b) (6) involved a 6-year-old female, taking Toviaz 8 mg, who developed myopia of mild severity on Day 31. She began wearing eyeglasses on Day 62, and the myopia resolved on that day. In the opinion of the Investigator, there was not a reasonable possibility that the headache and myopia were related to the study drug.
Reviewer's comment: Resolution of the subject's myopia with eyeglasses, makes it unlikely to be treatment-related.

Case (b) (6) involved an 8-year-old male, taking Toviaz 4 mg in the Safety extension phase. The subject developed myopia of moderate severity on Day 25 while taking oxybutynin 10 mg

in the active comparator phase. Oxybutynin was discontinued due to myopia on Day 41. The myopia improved to mild severity. The subject continued the study on Day 63, beginning Toviaz 4 mg. He completed the study and took his last dose of Toviaz on Day 160. The event of myopia was considered resolved on that day. In the opinion of the Investigator, there was a reasonable possibility that the myopia was related to the study drug (oxybutynin).
Reviewer's comment: The improvement in severity of the myopia from moderate to mild with cessation of oxybutynin, suggests oxybutynin as the cause. However, Toviaz may also have contributed, since the AE persisted while on this drug, and resolved once off. The independent role of Toviaz in the patient's mild myopia in this case is impossible to discern.

Case (b) (6) involved a 9-year-old female, taking Toviaz 8 mg in the safety extension phase. After taking oxybutynin in the efficacy phase, the subject began Toviaz on Day 89. On Day 162, one day after the last dose of study drug, the subject experienced myopia of mild severity, which was ongoing at the time of study completion. In the opinion of the Investigator, there was not a reasonable possibility that the myopia was related to the study drug.
Reviewer's comment: Onset of the AE on Day 162, after study drug cessation makes it unlikely that Toviaz caused this AE.

Case (b) (6) involved an 8-year-old female, taking Toviaz tablets 4 mg, who developed accommodation disorder of mild severity on Day 95. This subject had also developed constipation (mild) on Day 25, and headache (severe) on Day 56. Toviaz was temporarily stopped from Day 95 to Day 99 due to the headache and accommodation disorder. The accommodation disorder resolved on Day 178, 1 day after the last dose of the study drug. (The constipation resolved on Day 83, and headache resolved on Day 144.) In the opinion of the Investigator, there was a reasonable possibility that the constipation, headache, and accommodation disorder were related to the study drug.
Reviewer's comment: Resolution of the patient's mild accommodation disorder after cessation of Toviaz (a positive de-challenge) suggests a possible causal link with Toviaz, though it is not possible to draw a definitive conclusion on causality in this case.

Case (b) (6) involved a 10-year-old male, taking Toviaz tablets 4 mg, who developed blurred vision of mild severity on Day 170. The subject received the last dose of the study drug on Day 183. The event of blurred vision was ongoing at the time of the last available report. In the opinion of the Investigator, there was not a reasonable possibility that the blurred vision was related to the study drug.
Reviewer's comment: The available case information is sparse. Unable to assess.

Case (b) (6) involved an 8-year-old male, who developed visual impairment (the investigator term was "worsening near vision of left eye,") of mild severity on Day 86. The event of visual impairment resolved on Day 171, one (1) day after the last dose of the study drug. The

patient's past medical history included dry eye. In the opinion of the Investigator, there was a reasonable possibility that the visual impairment was related to the study drug.
Reviewer's comment: This narrative does not provide much detail. However, resolution of the AE with cessation of the drug suggests a possible causal link with Toviaz.

Case (b) (6) involved a 6-year-old male, taking fesoterodine BIC 2 mg, who on Day 27 (upon discharge after hospitalized for UTI) developed strabismus of mild severity. On Day 32 he developed astigmatism of mild severity. The subject completed study 1047, and entered study 1109, receiving the last dose of fesoterodine on Day 182. Astigmatism and strabismus were ongoing at the time of study completion. In the opinion of the Investigator, there was not a reasonable possibility that the astigmatism and strabismus were related to the study drug.
Reviewer's comment: The events reported do not suggest a causal relationship.

Case (b) (6) involved an 8-year-old female, taking fesoterodine BIC 4 mg, who developed worsening myopia on Day 115. The subject had previously been wearing eyeglasses for myopia. The myopia was ongoing at study completion on Day 168. In the opinion of the Investigator, there was not a reasonable possibility that the worsening myopia was related to the study drug.
Reviewer's comment: As described, the event in the case appears consistent with background disease progression.

Case (b) (6) involved a 6-year-old male, taking fesoterodine BIC 4 mg, who developed myopia of mild severity on Day 92. The subject completed Study 1047 on Day 166 and entered Study 1109. The subject began wearing eyeglasses on Day 257. Myopia was ongoing at the time of study completion. In the opinion of the Investigator, there was not a reasonable possibility that the myopia was related to the study drug.
Reviewer's comment: There is insufficient information in this case to assess causality. For the reported event, the roles of fesoterodine vs. background condition are unclear.

Study 1066
Case (b) (6) involved an 11-year-old male, taking Toviaz 4 mg, who developed the AE of "vision blurred" of moderate severity on Day 32. On this day, Toviaz had been escalated from 4 mg to 8 mg (per study protocol). The subject completed the study and received the last dose of the study drug on Day 62. The event of vision blurred was ongoing as of the last available report. In the opinion of the Investigator, there was a reasonable possibility that the event of vision blurred was related to the study drug.
Reviewer's comment: The timing of the AE coincided with the dose increase, suggesting a causal relationship. Events of myopia, accommodation disorder and blurred vision will be included in labeling.

Study 1109
Case (b) (6) involved a 6-year-old male, taking fesoterodine BIC 2 mg, who developed allergic conjunctivitis of mild severity on Day 183. He was treated with epinastine hydrochloride, and the allergic conjunctivitis resolved on Day 186. In the opinion of the Investigator, there was not a reasonable possibility that the event of conjunctivitis allergic was related to the study drug.
Reviewer's Comment: Allergic conjunctivitis and dry eye (a known side effect of muscarinic antagonists) may share a clinical presentation with ocular pruritus and injection. However, resolution of the subject's symptoms with a topical antihistamine while still taking Toviaz, argues against Toviaz as a cause.

8.5.2 Cognitive Function

While a direct relationship between antimuscarinics and cognitive dysfunction has not been established, the Sponsor nonetheless monitored for cognitive function adverse events in the Toviaz pediatric development program.

There were five reports of cognitive or behavioral changes in Studies 1047, 1066, and 1109. Case narratives are provided below. All AEs were described as "of mild severity," and all subjects recovered. Subjects in Study 1047 underwent testing with the Childhood Behavior Checklist (CBCL) and the Grooved Pegboard Test (GPT). Both of these measures have been widely employed as cognitive endpoints in clinical and epidemiological studies in both adults and school age children. That said, these scales – even when administered together - measure only a relatively circumscribed array of cognition. The CBCL is largely a behaviorally-focused measure that relies on the observations of a child's parent. The GPT, on the other hand, does provide some direct assessment of cognitive performance although primarily in the motor domain. The results from the CBCL and GPT in Study 1047 did not suggest an adverse effect of Toviaz. Furthermore, there is no widely established neuropsychological profile of anticholinergic-induced cognitive impairment in either children or adults. Based on the information provided, and in agreement with our consultant from the Division of Neurology 1, there is insufficient information to attribute or exclude Toviaz as causative in the following reported events.

Study 1047-Cohort 1
Case (b) (6) involves a 13-year-old female, with spina bifida and cauda equina syndrome resulting in neurogenic detrusor overactivity. The verbatim AE term is "*cognitive disturbance*," which was coded to the AE term "*cognitive disorder*." The event, described as mild, non-serious, occurred on study day 22 and resolved on study day 156. Toviaz was continued and no treatment was given in response to the event. The subject completed the study and received the last dose of the study drug on study day 165. No further information was reported concerning this event. There was no deterioration in either the Childhood Behavior Checklist or

Grooved Pegboard Test scores. In the opinion of the Investigator, there was a reasonable possibility that the cognitive disorder was related to the study drug.
Reviewer's comment: The subject's symptoms are vague. The cognitive testing tools used are neither sensitive nor specific. The case is unassessible.

Case (b) (6) involves a 12-year-old male, with a medical history including spina bifida with ventriculoperitoneal (VP) shunts in the right cervical area, lower external contractures and weakness, small left kidney with pelviectasis, decubitus ulcers, tibia and fibula fractures and facial acne. The verbatim AE term was "aggressive behavior" coded to PT "aggressive behavior," which was reported by the child's mother. The event was described as mild in severity and started 30 days after beginning therapy with Toviaz 4mg. The event resolved 18 days later. (Of note, study drug was stopped 4 days after the onset of the AE. The reason for stopping the drug was "medication error"—the subject had been on a lower dose than the dose to which he was randomized.) The Child Behavior Checklist and Grooved Pegboard Test results showed increases in aggressive behavior at Week 24, which corresponds to the time of the reported AE. The investigator assessed the event as possibly related to Toviaz.
Reviewer's comment: There is insufficient detail in this case to assess causality.
This case is also discussed in Section 8.4.3 Dropout and/or Discontinuations due to Adverse Events.

Case (b) (6) involves a 10-year-old male, with a medical history including talipes, meningomyelocele and paraparesis. On study day 63, the subject experienced *fatigue*, *restlessness*, and weight increased, all of moderate severity. No treatment was reported. The study drug was discontinued on study day 98 due to the event of fatigue. The events of fatigue, restlessness, and weight increased resolved on Day 177. No concomitant medications were ongoing at the time of these AEs. The investigator assessed the events as possibly related to Toviaz.
Reviewer's comment: There is insufficient detail in this case to assess causality.
This case is also discussed in Section 8.4.3 Dropout and/or Discontinuations due to Adverse Events.

Study 1047 Cohort 2
Case (b) (6) involves a 6-year-old male, with a medical history including sacral agenesis and constipation. The verbatim AE term reported was "*behavior modification*," which was coded to PT "*behavior disorder*." The event started on study day 75 and resolved 122 days later. He received consultation from a psychologist on study days 118, 128 and 135, and the event was considered resolved on study day 197, which was the last day of the study. The event was assessed as mild in severity and possibly related to fesoterodine beads-in-capsule (BIC) 2 mg. No action was taken with fesoterodine. No further information concerning the nature of the event was provided. The Child Behavior Checklist showed an increase in the Delinquent Rule-Breaking Behavior T score of 10 points at Week 12, but otherwise the scores remained stable

throughout the study. There were no notable changes in the results of the Grooved Pegboard Test. In the opinion of the Investigator, there was a reasonable possibility that the behavior disorder was related to the study drug.
Reviewer's comment: There is insufficient detail in this case to assess causality.

Study 1066
Case (b) (6) involves a 9-year old male, with a medical history including spina bifida, sacral myelomeningocele and tethered cord. Other medical history included neurogenic bowel, cecostomy, seasonal allergy, nasal fracture and latex allergy. The investigator's verbatim AE term was "intermittent inattentive behavior," which was coded to "disturbance in attention," occurring on Day 2 of the study. The event was described as mild in severity, no treatment was provided, and no action was taken with the study drug (Toviaz 4 mg). The event of disturbance in attention resolved on study day 5. It was assessed as not related to Toviaz, and the principle investigator deemed the event to be consistent with the subject's behavior history. No further information was provided. The subject completed the study (which called for a dose increase to Toviaz 8 mg on Day 30) and received the last dose of the study drug on Day 50. Cognitive Behavior Checklist and Grooved Pegboard scores were not conducted in the Phase 2 study 1066.
Reviewer's comment: This subject's symptoms resolved after three days, and did not recur during the subsequent 45 days, despite an increase in dose of Toviaz. It is unlikely that Toviaz caused this AE.

8.5.3 Post-Void Residual Volume

Post-void residual volume (PVR) was assessed in subjects not performing clean-intermittent-catheterization, and in any subject who experienced more than one UTI. For subjects not performing clean-intermittent-catheterization, PVR was measured at Screening, Baseline, Week 4, Week 12, and Week 24. At Weeks 4, 12, and 24, the mean increases from baseline for Toviaz 4 mg were 5.4, 25.6, and 11.5 mL respectively. At Weeks 4, 12, 24, the mean increases from baseline for Toviaz 8 mg were -7.3, -4, and 11.6 mL respectively. The sample sizes were small in both arms, ranging from 4 to 7.
Reviewer's comment: The small sample sizes make interpretation difficult. While no obvious clinically meaningful increase for baseline was observed, there is insufficient data to quantify the risk. Increase in post-void residual is a known risk for Toviaz use in adults with OAB, however, there is insufficient data to assess the risk in children with NDO.

8.6. Safety Analyses by Demographic Subgroups

Study 1047 was not adequately powered to reach conclusions regarding the safety in demographic subgroups. Post-hoc subgroup analysis of 2 weight subgroups (>25 to ≤35 kg and >35 kg) was performed, and did not reveal a pattern of notable differences in AE incidence rates for either of the Toviaz dose groups, as is shown in the table below.

However, as previously discussed in Section 8.4.7. Vital Signs, analysis of increases in heart rate by age subgroup did show a more pronounced increase above the 99th percentile in patients less than 12 years of age receiving Toviaz 8 mg.

Table 23. Adverse Reactions Reported in ≥2 Subjects in Any Treatment/Weight Group in the 12-Week Efficacy Phase of Study 1047

Preferred term	Weight > 25 to ≤ 35 kg		Weight >35 kg	
	Toviaz 4 mg (N=17) %	Toviaz 8 mg (N=14) %	Toviaz 4 mg (N=25)	Toviaz 8 mg (N=28)
Diarrhea	11.8	7.1	12.0	7.1
Urinary tract infection	17.6	7.1	4.0	0
Dry mouth	0	0	12.0	14.3
Constipation	11.8	0	4.0	10.7
Abdominal pain	5.9	0	0	3.6
Nausea	0	7.1	8.0	0
Headache	5.9	7.1	4.0	7.1
Incontinence°	5.9	14.3	0	0

°Includes incontinence and urinary incontinence
Source: Sponsor Integrated Summary of Safety Table 22.

8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies included in this submission.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No new carcinogenicity studies were conducted for this efficacy supplement.

8.8.2. Human Reproduction and Pregnancy

There were no pregnancies during the study.

8.8.3. Pediatrics and Assessment of Effects on Growth

Study 1047 did not assess height. Effects on growth were not assessed.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No issues with drug abuse potential, withdrawal or rebound have been reported. In Study 1047 there were 2 reports of overdose. Subject (b) (6) assigned to Toviaz 4 mg, and subject (b) (6) assigned to fesoterodine BIC 2 mg. No details of these cases were provided. Overdosage with Toviaz can result in severe anticholinergic effects. Treatment should be symptomatic and supportive. In the event of overdosage, ECG monitoring is recommended.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The Sponsor submitted the Periodic Adverse Drug Experience Report (PADER) for the time period from November 01, 2019 to October 31, 2020, which contained an analysis of postmarketing data and adverse events, and a review of the published literature. The analysis revealed no additional safety data from the completed pediatric clinical studies (1047, 1066, 1109). There was only one spontaneous report of pediatric use of Toviaz (off-label use for enuresis in an 11-year-old girl), for which the patient had not yet begun treatment at the time of the report. The review of published literature from May 16, 2020 through January 4, 2021 did not identify any new references of relevance.

8.9.2. Expectations on Safety in the Postmarket Setting

There are 14 years of postmarket experience with Toviaz, which was approved for use in the E.U. in 2007, and in the United States in 2008. As of October 2020, approximately 4.3 million adult patients have received Toviaz. The Sponsor estimates 14,919 patient-years of off-label use in patients under 16 years-old. Based on the experience of Toviaz in adults with OAB, and the comparability of Toviaz systemic exposure between adult and pediatric patients, we do not anticipate additional safety issues in the postmarket setting for Toviaz in pediatric patients.

8.9.3. Additional Safety Issues From Other Disciplines

There were no additional safety issues from other disciplines.

8.10. Integrated Assessment of Safety

The safety assessment is based on the Phase 3 study 1047, as well as the Phase 2 study 1066, and the long-term extension study 1109. Data from these three studies was analyzed separately given differences in study design and drug formulation.

In regard to the patient exposure and demographics in the three studies provided in this submission:

- 141 pediatric patients aged ≥ 6 years (131 with NDO; 10 with symptoms of OAB) received Toviaz tablets in clinical trials (Phase 2 and 3 studies).
- An additional 57 pediatric patients aged ≥ 6 years received the new fesoterodine beads-in-capsule formulation.
- In study 1047, the duration of treatment with Toviaz for the majority of patients in Cohort 1 was 91 to 180 days, with a mean treatment duration of 175 days, with equal duration for subjects assigned to 4 mg and 8 mg doses of Toviaz.

In regard to deaths, SAES, and TEAEs leading to discontinuations in the major clinical studies:

- There were no deaths reported in the development program.
- In study 1047 Cohort 1, a total of 12 serious adverse events (SAEs) were reported in 8 (6.5%) subjects. SAEs included appendicitis, peritonitis, epididymitis, UTI, viral infection, epiphysiolysis, ovarian cyst, decubitus ulcer, and cellulitis. None of these SAEs appear to be drug-related.
- In study 1066, 1 subject experienced the SAE of constipation, which was considered likely treatment-related.
- In Study 1047 Cohort 2, which tested the new fesoterodine BIC formulation, a total of 7 SAEs were reported for 5 subjects. SAEs included appendicitis, peritonitis, dengue fever, UTI, and animal bite. None of these SAEs appear to be drug-related.
- In study 1109, one SAE was reported for a subject assigned to the new fesoterodine BIC formulation, however, this SAE had occurred during study 1047.
- In study 1047 Cohort 1, TEAEs leading to discontinuation occurred in 6 subjects (7.1%). TEAEs leading to discontinuation included urinary incontinence, medication error, fatigue, epiphysiolysis, pyelonephritis, and product dispensing error. None of these TEAEs were clearly treatment-related.

In regard to commonly reported TEAEs:

- In study 1047 Cohort 1, TEAEs reported by ≥ 2% of patients were diarrhea, UTI, dry mouth, constipation, abdominal pain, nausea, weight increased, headache, and incontinence. UTI TEAEs were thought to reflect the high annual incidence of UTI in

pediatric patients with NDO practicing CIC. Incontinence AEs are likely not related to treatment with Toviaz.

In regard to TEAEs of special interest and special safety issues:

- Ophthalmological AEs, including myopia, accommodation disorder and blurred vision, were reported in 8 of 131 (6.1%) of subjects in Study 1047 Cohort 1 (both efficacy and safety extension phases) and Study 1066. Study 1047 suffered from deficiencies in ophthalmologic testing, rendering the ophthalmologic test data not helpful in establishing causality. Study 1066 did not include ophthalmologic testing. It is plausible that some of these cases could be due to effects of Toviaz. The ophthalmological AEs did not result in discontinuation of Toviaz in any patient. These events will be included in product labeling.
- Increases from baseline in mean heart rate (HR) were reported for both doses of Toviaz in Study 1047. At Weeks 4 and 12, the increases from baseline in the mean HR for patients treated with Toviaz 4 mg who had at least one follow-up measurement were 4 and 5.5 beats per minute, respectively. At Weeks 4 and 12, the increases from baseline in the mean HR for patients treated with Toviaz 8 mg who had at least one follow-up measurement were 10.4 and 8.9 beats per minute, respectively. At 24 weeks, increases from baseline in the mean HR for patients who initially received Toviaz 4 mg or 8 mg or subsequently transitioned from active comparator to Toviaz 4 mg or 8 mg were 4.7 beats per minute and 7.3 beats per minute, respectively. Increases in HR were generally greater with Toviaz 8 mg than Toviaz 4 mg doses. Compared to oxybutynin, Toviaz use resulted in HR increases leading to a greater proportion of pediatric patients with HRs above the 99th percentile for age. This was most pronounced in patients less than 12 years of age receiving Toviaz 8 mg. A mild AE of “heart rate increased” was reported for 1 subject in the Toviaz 8 mg arm. The AE was considered related to study treatment by the investigator, and the subject completed the study. The increases in HR observed in Study 1047 with Toviaz 4 mg and 8 mg dosing were not associated with symptoms and did not result in Toviaz discontinuation. The mean increases in HR will be included in product labeling.
- An adverse effect of Toviaz on cognitive function could not be discerned from the cognitive tests that were performed or from the potentially relevant AE reports.

9. Advisory Committee Meeting and Other External Consultations

There were no issues that required advice from an FDA Advisory Committee and an Advisory Committee meeting was not held for this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Labeling discussions were held with the entire review team on April 22 and 28, 2021 and May 5, 10 and 24, 2021. The Division's edited labels (PI and PPI) were conveyed to the Sponsor on May 17, 2021. The Sponsor accepted the Division PI edits and returned the PI document on May 25, 2021. Several minor division edits were conveyed to the Sponsor on and May 28, 2021. After another round of minor edits with Sponsor, a third FDA-edited label was conveyed on June 8, 2021. Thus, at the time this Clinical review was finalized, while final labeling had not been agreed-upon, the majority of labeling discussions with Sponsor had been completed with success.

10.2. Nonprescription Drug Labeling

Toviaz is available by prescription only.

11. Risk Evaluation and Mitigation Strategies (REMS)

There was no reason to require a REMS for this product, and none was requested.

12. Postmarketing Requirements and Commitments

Neither a postmarketing requirement nor commitment is needed for this product.

13. Appendices

13.1. Financial Disclosure

Covered Clinical Study (Name and/or Number): A0221047

Was a list of clinical investigators provided:	Yes X☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 328		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 3 Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in Study: _____ Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes X☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

AGIUA I HEATH
06/10/2021 04:26:17 PM

MARK S HIRSCH
06/10/2021 04:35:35 PM
I concur.