DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 022030

WRITTEN REQUEST – AMENDMENT 3

Pfizer, Inc.
Attention: Monique J. Carter, M.S., R.A.C.
Director, Pfizer Global Regulatory Affairs
500 Arcola Road
Collegeville, PA 19426-3982

Dear Ms. Carter:

Please refer to your correspondence dated April 30, 2019, requesting changes to FDA's November 14, 2011, Written Request for pediatric studies for fesoterodine fumarate.

We have reviewed your proposed changes and are amending the below-listed sections of the Written Request. All other terms stated in our Written Request issued on November 14, 2011, and as amended on May 19, 2014, and October 3, 2016, remain the same. (Text added is underlined. Text deleted is strikethrough.)

> *Timeframe for submitting reports of the study:* Reports of the above study must be submitted to the Agency on or before January 28, 2021~~June 30, 2020~~. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study report is submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the report of the study at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

For ease of reference, a complete copy of the Written Request, as amended, is attached to this letter.

Reports of the studies that meet the terms of the Written Request dated November 14, 2011, as amended by this letter and by previous amendments dated May 19, 2014, and October 3, 2016, must be submitted to the Agency on or before January 28, 2021, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, clearly mark your submission **"SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"**

in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter.

In accordance with section 505A(k)(1) of the Act, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following:

- the type of response to the Written Request (i.e., complete or partial response);
- the status of the application (i.e., withdrawn after the supplement has been filed or pending);
- the action taken (i.e., approval, complete response); or
- the exclusivity determination (i.e., granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

If you have any questions, please call Nenita Crisostomo, Regulatory Health Project Manager, at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Complete Copy of Written Request as Amended

COPY OF THE AMENDED WRITTEN REQUEST

BACKGROUND:
These studies investigate the potential use of fesoterodine in the treatment of pediatric patients aged 6 – 17 years with symptoms of detrusor overactivity associated with a neurological condition (e.g. spina bifida), hereafter referred to as neurogenic detrusor overactivity (NDO).

Neurological conditions can affect lower urinary tract function in pediatric patients. The principal neurologic lesions that affect lower urinary tract function may be classified as acquired or congenital in origin, with the vast majority of bladder dysfunction in children related to neural tube defects, most commonly myelomeningocele. NDO is associated with involuntary contractions of the detrusor muscle, defined as detrusor overactivity, which occur as the bladder fills. Detrusor overactivity is diagnosed by cystometric evaluation.

The outcome of upper urinary tract function is related to detrusor and urethral sphincter function. In some pediatric patients, dyssynergistic dysfunction exists, wherein detrusor and urethral sphincter contraction is uncoordinated (detrusor-sphincter dyssynergia) resulting in high intravesical pressures, vesicoureteric reflux, and ultimately renal damage. In children with myelodysplasia with detrusor-sphincter dyssynergia, there is a risk of upper urinary tract (UUT) deterioration and renal damage. In atonic dysfunction, there is a lack of detrusor and (usually) sphincter activity, which results in a low pressure bladder generally protecting the urinary tract, but incontinence then becomes a problem.

Treatment of NDO in children depends on presentation, underlying cause, and the risk of deterioration in function of both upper and lower urinary tract. Clean intermittent catheterization (CIC) is first line therapy for bladder emptying in children with areflexic bladders and high post-void residual urine volume, and may be combined with antimuscarinic therapy in specific populations, e.g., patients with high pressure bladders.

Antimuscarinic drugs are the cornerstone of pharmacotherapy in the pediatric NDO population, and have been shown to improve intravesicular pressure, and decrease symptoms. Of these, only oxybutynin is approved for use in children, and is available as a once a day extended release (XL) tablet, as well as an immediate release tablet. Although effective, oxybutynin use has been limited by the known antimuscarinic side effect profile. Other treatments such as alpha blockers, anxiolytics, tricyclic antidepressants, intravesical oxybutynin, onabotulinumtoxinA injection, electrical stimulation and biofeedback, may also be used, although safety and efficacy have not been reliably demonstrated. Given the limited choice available there is an unmet need for alternative treatments in children with NDO.

Fesoterodine is an antimuscarinic drug available as a prolonged release (PR) tablet formulation, and is approved at doses of 4 mg and 8 mg once daily for the treatment of overactive bladder in adults; it is currently not approved for use in the pediatric population.

Fesoterodine functions as a prodrug of 5-hydroxymethyltolterodine (5-HMT). After oral administration, fesoterodine cannot be detected in plasma, as it is rapidly and extensively hydrolyzed by nonspecific esterases to 5-HMT, which is the principal active moiety responsible for the antimuscarinic effects of fesoterodine. 5-HMT is also the principal active moiety for tolterodine.

Therefore, studies to establish the PK, safety, tolerability and efficacy of fesoterodine in the pediatric NDO population are justified.

A placebo-controlled study is not being conducted for NDO patients 6 – 17 years of age because there is an approved product for treatment of NDO in this pediatric population, and it would not be appropriate to randomize some patients to placebo. Efficacy will be established in pediatric patients by comparing each patient's baseline with post-treatment cystometric capacity. Supportive efficacy data will be provided from a comparison between fesoterodine and an active control, oxybutynin in subjects >25 kg.

To obtain needed pediatric information on fesoterodine, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

NONCLINICAL STUDIES:

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

CLINICAL STUDIES:

An open label, active control, randomized study with a 12-week safety extension phase evaluating the efficacy, PK, safety and tolerability of fesoterodine in pediatric neurogenic detrusor overactivity subjects aged 6 – 17 years. Subjects >25 kg will be studied and analyzed as a separate cohort to those weighing ≤25 kg. Each patient will serve as his/her own control.

Use of Extrapolation and Implementation of Timelines

Efficacy in 6 to 17 year olds cannot be extrapolated from adults and will be determined by the study outlined above in the Written Request (WR).

OBJECTIVE OF EACH WEIGHT-DEFINED COHORT:

Cohort 1 To evaluate the safety and efficacy, and population PK, following fesoterodine treatment in neurogenic detrusor overactivity subjects aged 6 – 17 years and >25 kg. In addition, to contextualize the benefit/risk of fesoterodine, the efficacy and tolerability of fesoterodine will be compared to an active-control, oxybutynin.

Cohort 2 To assess the efficacy, safety and tolerability of fesoterodine in neurogenic detrusor overactivity subjects aged 6 – 17 years and ≤25 kg.

The dosing of lighter subjects is dependent on the availability of an age-appropriate Beads-in-Capsule formulation.

PATIENTS TO BE STUDIED:

Age group and weight-defined cohorts in which the study is performed:

Cohort 1: Pediatric neurogenic detrusor overactivity subjects aged 6 – 17 years and weight >25 kg.

Cohort 2: Pediatric neurogenic detrusor overactivity subjects aged 6 – 17 years and weight ≤25 kg.

Number of patients to be studied:

Cohort 1: Approximately 99 patients evaluable for primary analysis.

Cohort 2: Approximately 50 patients evaluable for primary analysis.

Representation of Ethnic and Racial Minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

STUDY ENDPOINTS:

Pharmacokinetic Endpoints:

The pharmacokinetic endpoints will include population pharmacokinetic analysis-derived estimates for absorption rate constant, apparent oral clearance and volumes of distribution of 5-HMT in pediatric NDO patients of ages 6 – 17 years who weigh >25 kg (Cohort 1) or ≤25 kg (Cohort 2). Sparse PK samples will be collected at steady state at each dose level (Week 4).

Primary Endpoint

- Maximum cystometric capacity, defined as maximal tolerable cystometric capacity, until voiding or leaking begins, or at a pressure of ≥40 cm H_20.

Important Secondary Endpoints

- Detrusor pressure at maximum bladder capacity.
- Presence of involuntary detrusor contractions (IDC).
- Bladder volume at first IDC.
- Bladder compliance.

Voiding Diary-based Endpoints

- Mean number of micturitions and/or catheterizations/24 hrs.
- Mean number of incontinence episodes/24 hrs.
- Mean urgency episodes/24 hrs if applicable (only for sensate subjects).
- Mean volume voided per micturition or mean volume per catheterization.

Measures of Compliance

- Assessment at clinic visits of returned medication by counts of remaining tablets to assess percentage concordance with expected use. An electronic dosing log will also be used to assess daily medication dosing.

Safety Endpoints

For both Cohort 1 and Cohort 2, after the initial 12 weeks of the study, there will be an additional 12- week safety-extension phase.

Safety outcomes must include:

- Adverse events, including monitoring of targeted events including, but not limited to:
    - Anticholinergic effects such as dry mouth, dry eyes and constipation
    - CNS effects such as behavioral changes (e.g., aggression), decreased cognitive function, headache, seizures, somnolence
    - Visual effects such as accommodation disorder, blurred vision, and amblyopia
- Monitoring of the following:
    - Visual acuity and accommodation
    - Neuropsychiatric testing (cognitive function) by the Child Behavior Check List (CBCL) and Grooved Pegboard Test (GPT)
    - Vital signs, including heart rate, in the context of age-appropriate norms
    - Laboratory evaluations of clinical chemistry and hematology in the context of age-appropriate norms, with particular reference to liver function tests and renal chemistry
    - Urinary tract infection, as evidenced by urinalysis, with urine microscopy, culture and sensitivity
    - Post-void residual urine volume in subjects not performing CIC, or with >1 urinary tract infection (UTI) during the studies
    - Physical Examination and weight

All safety data will be evaluated with descriptive statistics.

Method, Frequency and Duration of Monitoring

Monitoring by the sponsor will take place twice each month for these events, and a quarterly review of cumulative events will also be performed.

All adverse events must be monitored until symptom resolution or until the condition stabilizes.

The following adverse events must be captured when spontaneously reported:

- All adverse events regardless of causality will be recorded and reported.

A Data Monitoring Committee (DMC) must be included because the study is being performed in children, a potentially fragile population. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf.

KNOWN DRUG SAFETY CONCERNS AND MONITORING:

A set of Targeted Medical Events for active monitoring are included in the Safety Review Plan for fesoterodine. These include events associated with:

- URINARY RETENTION: Identified as an important potential risk for antimuscarinic compounds

- LIVER ENZYME ELEVATION: Identified as an important potential risk. Isolated cases of liver enzyme elevations in the Phase 2 and Phase 3 adult trials

- COGNITIVE FUNCTION IMPAIRMENT: Identified as an important potential risk for antimuscarinic compounds

- ANTIMUSCARINIC CLASS EFFECT: Identified as a potential risk for antimuscarinic compounds

- ADVERSE EVENTS OBSERVED WITH TOLTERODINE: Events noted in the Adverse Events and Post-marketing Surveillance sections of the tolterodine labels

- SEVERE CUTANEOUS ADVERSE REACTIONS: Identified as a potential risk for antimuscarinic compounds

- BEHAVIORAL CHANGES: Behavioral changes were seen with tolterodine in pediatrics

Monitoring of Targeted Medical Events by the sponsor will take place twice each month, and a quarterly review of cumulative events will also be performed.

Extraordinary results: In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case,

you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

DRUG INFORMATION

- Dosage form

  Prolonged Release Tablet (fesoterodine fumarate, 4 mg & 8 mg) - commercial adult formulation (NDA 22-030) for use in children >25 kg (Cohort 1).

  Beads-in-Capsule (fesoterodine fumarate, projected doses of 2 mg & 4 mg) - capsule can be administered intact or by opening the capsule and using the beads as a sprinkle, for use in children ≤25 kg (Cohort 2).

  The Beads-in-Capsule formulation remains under development. Prior to starting dosing of ≤25 kg subjects, in-vitro testing (dissolution and in-use stability) to support the two proposed administrative methods, swallowing the capsule whole and sprinkling the beads on media, will be carried out. A modified bead in capsule prototype will also be evaluated in adults for relative bioavailability and food effects prior to starting dosing of ≤25 kg subjects; the intention is that the final Beads-in-Capsule formulation will demonstrate pharmacokinetics and bioavailability similar to the adult formulation without a pronounced food effect.

- Route of administration
  Oral

- Regimen
  Fesoterodine is to be taken once daily.

Use an age-appropriate formulation in the study described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

In accordance with section 505A(e)(2), if

1. you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);

2. the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and

3. you have not marketed the formulation within one year after the Agency publishes such notice.

The Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age-appropriate formulation may be conducted in adults.

STATISTICAL INFORMATION, INCLUDING POWER OF STUDY(IES) AND STATISTICAL ASSESSMENTS:

Cohort 1

- **Sample size:** Enroll sufficient subjects to ensure approximately 33 evaluable subjects per group. Thirty-three patients in each fesoterodine dose group will provide 90% power to detect a mean change from baseline of 70 mL in the primary endpoint at a 2-sided 5% level of significance assuming a standard deviation of 120 mL. The pairwise comparisons between each dose of fesoterodine and oxybutynin are considered descriptive and therefore are not required to have 90% power.

- **Statistical Methods:** Calculate the mean change from baseline to week 12 in the primary endpoint for each treatment group and associated standard error, 95% confidence interval and p-value. Calculate the means and 95% confidence intervals for the differences between each fesoterodine dose group and oxybutynin to assess the comparability of fesoterodine and oxybutynin. The primary analysis population should include all subjects who have been randomized and received at least one dose of study medication and have provided baseline primary endpoint data. Use descriptive statistics to evaluate safety data.

Cohort 2

- **Sample size:** Enroll sufficient subjects to ensure approximately 25 evaluable subjects per group. Twenty-five patients per fesoterodine dose group will provide an estimate of a 2-sided 95% confidence interval for the change from baseline in the primary endpoint of approximately ± 55 mL around the point estimate for the mean, with approximately 80% coverage probability, assuming a standard deviation of 120 mL.

- **Statistical Methods:** Calculate the mean change from baseline to Week 12 for the primary endpoint for each treatment group and associated standard error and 95%

confidence interval. The primary analysis population should include all subjects who have been randomized and received at least one dose of study medication and have provided baseline primary endpoint data. Use descriptive statistics to evaluate safety data.

Labeling that may result from the study: You must submit proposed pediatric labeling to incorporate the findings of the study. Under section 505A(j) of the Act, regardless of whether the study demonstrate that fesoterodine is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study. Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study.

Format and types of reports to be submitted: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications at http://www.fda.gov/Cder/guidance/7087rev.htm

Timeframe for submitting reports of the study: Reports of the above study must be submitted to the Agency on or before January 28, 2021. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study report is submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you

are advised to submit the report of the study at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

Response to Written Request: Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric study will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study. If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed. Furthermore, if you agree to conduct the study, but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

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/

JULIE G BEITZ
06/27/2019 05:38:33 PM