March 29, 2019

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Citizen Petition

The undersigned submits this petition under 21 C.F.R. 10.30 to request the Commissioner of Food and Drugs amend 21 CFR § 216.23 and add oxitriptan (also known as 5-hydroxytryptophan or 5-HTP) to the list of substances that can be used in compounding under section 503A of the FD&C Act (21 U.S.C. 353a) (referred to as ''the 503A Bulks List'' or ''the list'') and permit continued compounding of oxitriptan for patients with tetrahydrobiopterin deficiency until oxitriptan is added to the list.

A. Action Requested

We request that the Commissioner amend the regulation 21 CFR § 216.23 (bulk drug substances that can be used to compound drug products in accordance with section 503A of the Federal Food, Drug, and Cosmetic Act) to include oxitriptan on the 503A Bulks List and to allow continued compounding of oxitriptan for the treatment of tetrahydrobiopterin deficiency diseases in the interim.

In a proposed rule published on December 16, 2016, FDA evaluated oxitriptan as a treatment for depression and insomnia. Data supporting the efficacy of oxitriptan for depression are limited, and there is no evidence to support long-term efficacy of oxitriptan for the treatment of this chronic disease. Regarding the use of oxitriptan to treat insomnia, the clinical trials examining insomnia were too poorly designed and/or executed to assess efficacy.

On February 19, 2019, FDA published a final rule whereby the FDA placed six bulk drug substances on the list. This final rule also identified four bulk drug substances that FDA has considered and is not including on the list. Oxitriptan was one of the four substances that was not included on the list. The effective date of the rule was March 20, 2019. As a result of FDA's action, drugs compounded with oxitriptan will not qualify for the 503A exemptions and cannot be used in compounding under section 503A of the FD&C Act.

FDA did not review information for the use of oxitriptan in the treatment of tetrahydrobiopterin deficiency. Compounded oxitriptan has been prescribed for many years for the treatment of patients with tetrahydrobiopterin deficiency disease. It is essential that oxitriptan be permitted to be compounded for patients with tetrahydrobiopterin deficiency until oxitriptan is added to the list.

B. Statement of Grounds

There is a long history of use of compounded oxitriptan for the treatment of diseases resulting from tetrahydrobiopterin deficiency. The first successfully reported use of oxitriptan to compensate neurotransmitter deficiency in dihydropteridine reductase (DHPR) deficiency occurred in 1975.[1] Neurotransmitter replenishment with oxitriptan should be reserved for experts specialized in the management of disorders of biopterin metabolism. Established dosing guidelines for oxitriptan in the treatment of DHPR deficiency do not currently exist, although dosing based on experts personal experiences are documented in the scientific literature. Oxitriptan should be prescribed at low starting doses, divided into three daily administrations, and progressively advanced under strict monitoring. Starting doses of oxitriptan 1-2 mg/kg/day has been evaluated for the treatment of DHPR deficiency.[2] Monitoring should encompass physical exam to detect the minimal dose required to relieve specific symptoms or biochemical laboratory analysis of neurotransmitter metabolites.[1] Adverse reactions due to oxitriptan dose escalation have mainly presented as diarrhea, vomiting, mydriasis, and tachycardia.[3,4] The severity of DHPR deficiency is closely related to the impairment of aromatic amino hydroxylation and folate homeostasis, resulting on neonatal hyperphenylalaninemia, biogenic amine deficiency, and tetrahydrofolate depletion. A combination of therapies addressed to the correction of these metabolic derangements has to be promptly applied after diagnosis, to avoid irreversible brain damage and worsening of prognosis.[2] Oxitriptan therapy is a component of the therapies to correct the metabolic derangements of DHPR deficiency and no treatment alternative exists to replace oxitriptan. Oxitriptan is a required therapeutic treatment for patients with DHPR deficiency.

6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency, an autosomal recessive genetic disorder, is one of the causes of malignant hyperphenylalaninemia due to tetrahydrobiopterin deficiency. PTPS deficiency not only causes hyperphenylalaninemia, but also is responsible for defective neurotransmission of monoamines because of malfunctioning tyrosine and tryptophan hydroxylases, all are tetrahydrobiopterin-dependent hydroxylases. Patients effected with PTPS appear normal at birth, however will typically present with developmental delay and abnormal movements within the first few months of life.[2] When left untreated, the deficiency causes neurological signs at age 4 or 5 months, although clinical signs are often obvious from birth. The principal symptoms include psychomotor retardation, tonus disorders, convulsions, drowsiness, irritability, abnormal movements, hyperthermia, hypersalivation and difficulty swallowing. The goal of treatment is to control hyperphenylalaninemia by dietary restriction of phenylalanine or tetrahydrobiopterin administration, and to restore neurotransmitter homeostasis by oral administration of amine precursors L-dopa and oxitriptan.[5] The doses usually given are L-dopa/carbidopa: 5-10 mg/kg body weight(bw) /day and oxitriptan: 5-10 mg/kg bw/ day. However, doses can vary, and indeed have to be adapted to each individual. Neurotransmitter doses are usually divided into three equal portions during the day. However, diurnal fluctuations are often observed and require changes in the schedule of drug administration. The optimal dose should be adjusted to the requirements of each patient with monitoring for adverse effects and the possible disappearance of neurological symptoms when they exist.

In addition, my clinical experience with this disease has been:

- Four patients have been treated with oxitriptan at Summit Health Pharmacy since 2014

- Patient 1 (DOB 12/2004) initiated oxitriptan therapy at Summit Health Pharmacy February 2014. Small dose adjustments have occurred since we started dispensing the prescribed oxitriptan compounded suspension. The dose has increased once based on the patient's physical exam and/or biochemical laboratory values. The initial dose of 0.9 mg/kg/dose administered three times a day was prescribed and the current dose is 0.57mg/kg/dose given three times a day. The patient's weight for age was 3rd percentile in 2014 and has increased to just below 25th percentile in 2019. Patient has received a mitochondrial cocktail mix since 2012 when we initially became involved in their care.

- Patient 2 (DOB 3/2003) initiated oxitriptan therapy May 2003 and transitioned care to Summit Health Pharmacy July 2014 for a diagnosis of 6-pyruvoyl-tetrahydropterin synthase (PTPS) deficiency. Small dose adjustments have occurred since we started dispensing the prescribed oxitriptan compounded capsules. The dose has changed on 4 occasions based on the patient's physical exam and/or biochemical laboratory values. The initial dose of 1.75 mg/kg/dose administered three times a day was prescribed and the current dose remains 1.75mg/kg/dose given three times a day. The patients' weight for age was 50th percentile in 2014 and has decreased to 25th percentile in 2019. Patient is additionally prescribed sapropterin and carbidopa/levodopa compounded capsules. Treating physician Dr Joseph Melvin DO, JD communicated "Without this life sustaining medication (5HTP) patient would experience deficits in all activities of daily living".

- Patient 3 (DOB 7/1999) initiated oxitriptan therapy at Summit Health Pharmacy December 2014. Small dose adjustments have occurred since we started dispensing the prescribed oxitriptan compounded capsules. The dose has changed on 4 occasions based on the patient's physical exam and/or biochemical laboratory values.

- Patient 4 (DOB 3/2011) initiated oxitriptan therapy at Summit Health Pharmacy September 2016 for a diagnosis of DHPR deficiency. Small dose adjustments have occurred since we started dispensing the prescribed oxitriptan compounded suspension. The dose has changed on three occasions based on the patient's physical exam and/or biochemical laboratory values. The initial dose of 0.8 mg/kg/dose administered three times a day was prescribed and the current dose is 1.07mg/kg/dose given three times a day. The patient's weight for age was below 3rd percentile in 2016 and has increased to just below 75th percentile in 2019. Patient is additional prescribed compounded leucovorin and carbidopa/levodopa suspensions, Phenex-2 oral powder, Compleat Pediatric reduced calorie, Elecare Jr nutritional supplements, and sapropterin oral powder.

-A fifth patient has not received therapy at Summit Health Pharmacy but was submitted by Dr Can Ficicioglu MD, PhD for inclusion in the petition. Patient 5 (DOB: 08/2012) was detected through newborn screening due to elevated phenylalanine (phe) level and started on a phe restricted diet. Confirmatory testing revealed abnormal urine pterins. Due to this finding and associated symptoms, patient was diagnosed with PTPS deficiency. Patient was started on BH4 supplementation which decreased patient's Phe levels. The physician was

able to increase patient protein intake in the diet. Patient was also started on compounded carbidopa/levodopa and oxitriptan oral suspensions. Patient needs multiple doses of each medication throughout the day. Patient is additionally prescribed compounded selegiline and sapropterin oral tablets for solution.

C. Environmental Impact

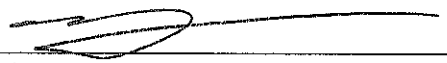
We claim a categorical exclusion under 21 CFR 25.30 (i) from the environmental assessment because the requested action involves corrections and technical changes in regulations which ordinarily do not require the preparation of an EA or an EIS.

D. Economic Impact

The following information is to be submitted upon request by the Commissioner following review of the petition: A statement of the effect of requested action on: (1) Cost (and price) increases to industry, government, and consumers; (2) productivity of wage earners, businesses, or government; (3) competition; (4) supplies of important materials, products, or services; (5) employment; and (6) energy supply or demand.)

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.


(Signature)

Vincent Canzanese Rph (Name of petitioner)

Summit Health Pharmacy Inc. (Mailing address)

3400 Edgmont Ave Brookhaven, PA 19014

(610) 872-5418 (Telephone number)

1. Bartholome´ K, Byrd D. L-dopa and 5-hydroxytryptophan therapy in phenylketonuria with normal phenylalanine-hydroxylase activity. Lancet 1975;2: 1042–1043.
2. Ponzone, A. , Spada, M. , Ferraris, S. , Dianzani, I. and de Sanctis, L. Dihydropteridine reductase deficiency in man: From biology to treatment. Med. Res. Rev. 2004;24: 127-150.
3. Ponzone A, Ferrero GB, Guardamagna O, Ferraris S, Curtius HC, Blau N. Screening and treatment in tetrahydrobiopterin deficiency. In: Curtius HC, Ghisla S, Blau N, editors. Chemistry and biology of pteridines. Berlin: Walter de Gruyter; 1990: 393–401.
4. Ponzone A, Biasetti S, Guardamagna O, Ferraris S. Terapia dei difetti di tetraidrobiopterina. In: Nicola P, Ponzone A, Cerutti F, editors. Juvenile diabetes, hyperammoniemias, hyperphenylalaninemias. Milan:Masson S.p.A.; 1988. pp 275–284.
5. Longo N. Disorders of biopterin metabolism. J Inherit Metab Dis. 2009;32(3):333–342.