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Via Electronic Mail (commissioner@fda.hhs.gov) and U.S. Mail

February 21, 2024

The Honorable Robert M. Califf, M.D. Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Commissioner Califf:

It has been nearly four years since the U.S. Food and Drug Administration (FDA) strengthened existing warnings regarding the mental and behavioral health side effects of asthma and allergy drug montelukast (brand name Singulair) by imposing a black box warning, the strictest and most serious warning given to medications.[1] Since that decision in March 2020, the prevalence of tragic adverse mental health events, including aggression, depression, and suicide, continue to be widely reported, and disproportionately so for pediatric patients.[2] Of the estimated 12 million people prescribed the medication, an estimated 1.6 million are children.[3] The effects of montelukast on children are of particularly urgent concern in light of the national youth mental health crisis plaguing our State[4] and the subsequent strain on our health care system.[5] It is

[1] U.S. Food & Drug Admin., Drug Safety Communication, FDA requires Boxed Warning About Serious Mental Health Side Effects for Asthma and Allergy Drug Montelukast (Singulair) (Mar. 4, 2020), https://www.fda.gov/drugs/drug-safety-and-availability/fda-requires-boxed-warning-about-serious-mental-health-side-effects-asthma-and-allergy-drug [hereinafter FDA Drug Safety Communication].
[2] *See* Dan Levine et al., *A Son Died, His Parents Tried to Sue. How U.S. Courts Protect Big Pharma*, REUTERS (June 26, 2023), https://www.reuters.com/investigates/special-report/usa-lawsuits-merck-singulair/; *see also* Christina Jewett & Benjamin Mueller, *The F.D.A. Warned an Asthma Drug Could Induce Despair. Many Were Never Told*, N.Y. TIMES (Jan. 9, 2024), https://www.nytimes.com/2024/01/09/health/fda-singulair-asthma-drug-warning.html; Sci. Advisory Bd., Nat'l Ctr. for Toxicological Rsch., *Public Testimonials of the Montelukast (Singulair) Side Effects Support and Discussion Group Members*, U.S. FOOD & DRUG ADMIN. (May 18-19, 2022), https://www.fda.gov/media/158517/download [hereinafter *Public Testimonials*].
[3] Jewett & Mueller, *supra* note 2.
[4] *See AAP-AACAP-CHA Declaration of a National Emergency in Child and Adolescent Mental Health*, AM. ACAD. OF PEDIATRICS, https://www.aap.org/en/advocacy/child-and-adolescent-healthy-mental-development/aap-aacap-cha-declaration-of-a-national-emergency-in-child-and-adolescent-mental-health/ (last updated Oct. 19, 2021).
[5] *See, e.g.*, Stephen Stock et al., *Children Languish in Emergency Rooms Awaiting Mental Health Care*, CBS NEWS (Feb. 28, 2023), https://www.cbsnews.com/news/emergency-rooms-children-mental-health/; Amy Wimpey Knight

therefore time again for the FDA to act. The New York Office of the Attorney General writes to encourage the FDA to address the dangers of montelukast, particularly to the most vulnerable population—minor children—and protect all patients from these heartbreaking, unintended side effects.

Reports of Severe Mental and Behavioral Risks, Especially in Minors

The mental and behavioral health injuries this medication has inflicted over the course of its twenty-five year history on the market has been extensively documented in adverse event reports and studies demonstrating a correlation between montelukast usage and the development of neuropsychiatric disorders. The FDA has stayed abreast of this research: from 2008, it has communicated its drug safety reviews of montelukast (Singulair) to the public,[6] and in 2014, the FDA's Nonprescription Drugs Advisory Committee rejected an application for brand name Singulair medication to be approved for over-the-counter (OTC) use based on clinical data and adverse event reporting.[7] Most recently, in 2019 the FDA convened a panel of outside experts[8] and conducted a comprehensive review of available clinical trial safety data, post-marketing adverse event reporting, and reviews of the published medical literature prior to issuing its black box warning highlighting the mental and behavioral health risks of montelukast use.[9]

Data accumulated since the 2020 black box warning suggest that the neuropsychiatric dangers posed by montelukast are consistent with these prior findings, and are, in fact, much greater for children than for adults.[10] A 2022 retrospective cohort study investigated more than 72,000 adult asthma patients and 82,500 allergy patients on montelukast and found that in the subsequent year these patients had greater rates of generalized anxiety disorder, insomnia, and

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et al., *The Youth Mental Health Emergency Isn't Over. Government Must Act Now*, U.S. NEWS & WORLD REP. (Oct. 19, 2023), https://www.usnews.com/news/health-news/articles/2023-10-19/the-youth-mental-health-emergency-isnt-over-government-must-act-now.

[6] *See, e.g.*, U.S. Food & Drug Admin., Healthcare Professional Sheet, Follow-up to the March 27, 2008 Communication about the Ongoing Safety Review of Montelukast (Singulair) (Jan. 13, 2009), https://wayback.archive-it.org/7993/20170406045731/https:/www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm079523.htm.

[7] Larry Hand, *FDA Panel Rejects OTC Use of Montelukast (Singulair Allergy)*, MEDSCAPE (May 2, 2014), https://www.medscape.com/viewarticle/824583?form=fpf#vp_1.

[8] *See September 27, 2019: Meeting of the Pediatric and Drug Safety and Risk Management Committees*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/advisory-committees/advisory-committee-calendar/september-27-2019-meeting-pediatric-and-drug-safety-and-risk-management-committees-09272019 (last updated Nov. 8, 2019).

[9] Amy Biehl, Safety Evaluator, Off. of Surveillance & Epidemiology, Ctr. for Drug Evaluation & Rsch., Neuropsychiatric Events Associated with Montelukast: Postmarketing Experience, Presentation at the Meeting of the Pediatric and Drug Safety and Risk Management Committees (Sept. 27, 2019), available at https://www.fda.gov/media/131184/download; U.S. Food & Drug Admin., FDA Briefing Document, Neuropsychiatric Events with Use of Montelukast in Pediatric Patients (Sept. 27, 2019), https://www.fda.gov/media/131035/download; *see also* Katherine Clarridge et al., *A Boxed Warning for Montelukast: The FDA Perspective*, 7 J. Allergy & Clinical Immunology: Pract., 2638 (2021).

[10] *See* Joanna Thompson, *Asthma Drug Still Being Prescribed to Kids Despite Potential Mental Health Risks*, SCI. AM. (Jan. 19, 2024), https://www.scientificamerican.com/article/asthma-drug-still-being-prescribed-to-kids-despite-potential-mental-health-risks/#:~:text=Montelukast%20remains%20one%20of%20the,cross%20the%20blood%2Dbrain%20barrier.

prescriptions for antidepressants compared to those not prescribed montelukast.[11] Likewise, a recently published prospective cohort study found that neuropsychiatric events were reported in 62.4% of patients with asthma who were between the ages of 3-18 years.[12] Similarly, a recent comprehensive review of the literature found that behavioral and psychiatric disorders were commonly reported in children taking montelukast in case reports and drug safety studies.[13]

Moreover, anecdotal reports submitted to the FDA since 2020 spotlight the extreme side effects experienced by people taking montelukast, particularly children.[14] One parent described how their 14-year-old daughter's "neuropsychic and physical symptoms slowly worsened [while on montelukast]. . . . She spent increasing amounts of time in my bed due to nightmares, she became fearful that she would be murdered in her bed and she took to sleeping with a knife under her pillow."[15] Another described learning that her daughter prescribed montelukast for exercise-induced asthma at age 13 had "attempted to take her own life 6 times over a period of around 2-3 years, since starting this drug."[16] A family member of one 10-year-old described how "[f]or an entire year, my family was on suicide watch for a 10-year-old boy who screamed daily in fits of anger, sadness, and depression 'I want to DIE' 'Just KILL ME' 'I'm so stupid and I don't want to live anymore' 'My brain is telling me I'm dumb and I don't deserve to live' Kicking. Hitting. Screaming. Hiding under covers in fits of tears."[17] Many more such heart-wrenching stories are found in these testimonials submitted to the FDA. They reveal that these families were not informed by their health care providers of the risks associated with the use of this drug and that the written warnings provide insufficient notice.

Furthermore, the mental and behavioral health side effects of montelukast have especially dangerous consequences for teens and children under the age 18 due to the reduced availability of pediatric mental health resources. Nearly 20% of children aged 3 through 17 have a mental, emotional, developmental, or behavioral health condition (depression, anxiety problems, or behavioral or conduct problems), and of those children, nationwide, 40% do not receive treatment or counseling.[18] The lack of any specific warning, restriction, or contraindication for pediatric patients is extremely concerning and requires swift action.

The Current Black Box Warning is Insufficient

As you are fully aware, in response to these reports and studies the FDA has required the addition of warnings to the product label that originally contained no warnings regarding neuropsychiatric events. In 2009, the FDA required the inclusion of a "precaution" on the drug

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[11] Tapio Paljarvi et al., *Analysis of Neuropsychiatric Diagnoses After Montelukast Initiation*, JAMA NETWORK OPEN, May 24, 2022, at 1.
[12] Oznur Yilmaz Bayer et al., *Neuropsychiatric Adverse Drug Reactions Induced by Montelukast Impair the Quality of Life in Children with Asthma*, 59 J. ASTHMA 580 (2020).
[13] Chris Wai Hang Lo et al., *Neuropsychiatric Events Associated with Montelukast in Patients with Asthma: A Systematic Review*, EUR. RESPIRATORY REV., July 13, 2023, at 15.
[14] *Public Testimonials*, *supra* note 2.
[15] *Id*. at 11.
[16] *Id*. at 19.
[17] *Id*. at 44.
[18] U.S. DEP'T OF HEALTH & HUMAN SERVS., AGENCY FOR HEALTHCARE RSCH. & QUALITY, AHRQ PUB. NO. 22(23)-0030, 2022 NATIONAL HEALTHCARE QUALITY AND DISPARITIES REPORT 73 (Oct. 2022), https://www.ncbi.nlm.nih.gov/books/NBK587182/pdf/Bookshelf_NBK587182.pdf.

label warning of the potential for neuropsychiatric injuries, including "agitation, aggression, anxiousness, dream abnormalities and hallucinations, depression, insomnia, irritability, restlessness, suicidal thinking and behavior."[19] The current March 2020 warning emphasizes the neuropsychiatric side effects that had been listed on the label since 2009, including "agitation, aggression, depression, sleep disturbances, suicidal thoughts and behavior (including suicide)," placed in a black bordered text box with an all caps title in bold typeface stating "Warning: Serious Neuropsychiatric Events." In addition, health care providers must give montelukast patients a medication guide so that they can learn more about the medication, its side effects, and use.[20] In its March 2020 press release regarding the change, the FDA noted that "many health care professionals and patients/caregivers are not aware of the risk."[21] Unfortunately, this still remains the case four years later. As seen in the testimonials to the FDA, many caregivers remain uninformed of these serious side effects and were not informed by their health care providers.[22] It appears that health care providers, including psychiatrists, pediatricians, pharmacists, as well as children's caregivers, remain either unaware of these possible dangers or the severity of their potential effects.[23]

Moreover, while the current warning notes that the "benefits of [montelukast] may not outweigh the risks in some patients" and "reserve[s]" the use of montelukast for those with allergies that did not respond to alternative treatments, no other change was made to its indication for use in patients with asthma nor were any contraindications provided for pediatric patients. Accordingly, montelukast remains FDA-approved for the treatment of asthma in children 1 year and older, and for the treatment of allergies in children 6 months and older.[24] A recent study has shown that after the imposition of the FDA's black box warning, reports of certain adverse behavioral and mental health events for adolescents increased.[25] We believe the benefit-risk considerations have changed since the FDA's evaluation in 2020 of montelukast, and the recent alarming reports warrant more stringent protections for pediatric patients.

The FDA Should Take Urgent Action

It is the responsibility of the FDA to implement new safety labeling changes based on new safety information, including information from adverse events reporting systems and

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[19] *Asthma Drugs Get 'Precaution' Labeling for Possible Psychiatric Side Effects*, ABC NEWS (June 12, 2009), https://abcnews.go.com/Health/Healthday/story?id=7828143&page=1 (quoting the original FDA press release, which is no longer available).
[20] *See* Medication Guide, Singulair, ORGANON (2021), https://www.organon.com/product/usa/pi_circulars/s/singulair/singulair_mg.pdf.
[21] FDA Drug Safety Communication, *supra* note 1.
[22] *Public Testimonials*, *supra* note 2.
[23] *See* Anita Wagner et al., *FDA Drug Prescribing Warnings: Is the Black Box Half Empty or Half Full?* 15 PHARMACOEPIDEMIOLOGY & DRUG SAFETY 369 (2006) (finding significant variability in the consistency in which black box warnings were heeded by health care providers).
[24] *See* U.S. Food & Drug Admin., Medical Product Safety Information, Singulair (montelukast) and All Montelukast Generics: Strengthened Boxed Warning - Due to Restricting Use for Allergic Rhinitis (Mar. 4, 2020), https://www.fda.gov/safety/medical-product-safety-information/singulair-montelukast-and-all-montelukast-generics-strengthened-boxed-warning-due-restricting-use.
[25] Samer Abdelkader et al., *The Impact of Montelukast's Black Box Warning on Pediatric Mental Health Adverse Event Reports*, 28 J. PEDIATRIC PHARMACOLOGY & THERAPEUTICS 704 (2023).

analysis of existing information.[26] The New York Attorney General's Office therefore respectfully asks the FDA to take immediate action to prevent further unnecessary health risk to patients in our State related to the use of montelukast.

The FDA has a wide variety of regulatory tools at its disposal and should prioritize providing more adequate warnings to the public by considering the following actions on an accelerated timeline:

1) issuing a new Drug Safety Communication stating that the FDA is evaluating the risks of using montelukast in children under the age of 18 for asthma and allergic rhinitis;

2) sending a Dear Health Care Provider letter to physicians, pharmacists, and other health care providers emphasizing montelukast's safety risks to minors and urging providers to consider other FDA-approved medications for asthma or allergic rhinitis in children under the age of 18 years;

3) conducting a review of all available information to determine whether the risk from use of montelukast clearly outweighs any therapeutic benefit in children and warrants a *contraindication* warning that montelukast should not be used in children under 18; and

4) evaluating whether any other interventions may be necessary to ensure that the potential benefits of montelukast use in children for the treatment of both asthma and allergic rhinitis outweigh the risks, such as requiring the imposition of risk evaluation and mitigation strategies (REMS).

I welcome any information you may wish to provide on any actions you are planning related to evaluating montelukast and its use in minor patients. I appreciate the FDA's attention to this important matter.

Respectfully submitted,

Darsana Srinivasan
Chief, Health Care Bureau

[26] 21 U.S.C. § 355(o)(4).